Decentralised Procedure

Public Assessment Report

Copaxone 40 mg/ml Injektionslösung in einer Fertigspritze

Glatiramer acetate

DE/H/5283/004/DC

(former UK/H/0453/004/DC)

Applicant: Teva Pharmaceuticals Ltd.

Date: 07.12.2017

This module reflects the scientific discussion for the approval of Copaxone 40 mg/ml Injektionslösung in einer Fertigspritze. The procedure was finalised on 4th December 2014.

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Copaxone 40 mg/ml Injektionslösung in einer Fertigspritze
Name of the drug substance (INN name):	Glatiramer acetate
Pharmaco-therapeutic group (ATC Code):	L03AX13
Pharmaceutical form(s) and strength(s):	Solution for injection in prefilled syringe; 40 mg/ml
Reference Number(s) for the Decentralised Procedure	DE/H/5283/004/DC (former UK/H/0453/004/DC)
Reference Member State:	DE (former UK)
Concerned Member States:	AT, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK
Applicant (name and address)	Teva Pharmaceuticals Ltd. Ridings Point, Whistler Drive Castleford, West Yorkshire WF10 5HX United Kingdom

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States agreed to grant a marketing authorisation (MA) for the medicinal product Copaxone 40 mg/ml Injection. This application was submitted using the Decentralised Procedure (DCP) with the UK as Reference Member State (RMS) and Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain and Sweden as Concerned Member States (CMSs).

Copaxone 40 mg/ml Injection (PL 10921/0026) is a prescription-only medicine (POM), indicated for the treatment of relapsing forms of multiple sclerosis (MS). Copaxone is not indicated in primary or secondary progressive MS.

This is an application for a known active substance made under Article 8(3) of Directive 2001/83/EC, as amended, as a line-extension of Copaxone 20 mg/ml solution for injection, pre-filled syringe (PL 10921/0023), which was authorised to Teva Pharmaceutical Limited in the UK on 07 April 2003. The line-extension reflects an application for a new dosing regimen, and strength of the active substance, for Copaxone in the prevention of relapses in patients with relapsing forms of Multiple Sclerosis. The current posology for PL 10921/0023 is a daily injection of Copaxone 20 mg/mL, whereas the new posology for PL 10921/0026 introduces an injection of Copaxone 40 mg/ml three times a week to allow better tolerability of the injections. The original grant of a marketing authorisation for Copaxone 20 mg/ml solution for injection, pre-filled syringe (PL 10921/0023) was a line-extension of Copaxone Injection 20 mg powder and solvent for solution for injection (PL 10921/0019), reflecting a new pharmaceutical form. Copaxone Injection 20 mg powder and solvent for solution for injection was authorised to Teva Pharmaceuticals Limited in the UK on 09 August 2000.

Multiple Sclerosis (MS) is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. It is generally assumed that MS is mediated by some kind of autoimmune process, possibly triggered by infection, and superimposed upon a genetic predisposition. 80-85% of the patients present a form known as relapsing-remitting MS (RRMS), which is characterised by unpredictable acute episodes of neurological dysfunction (clinical attacks or relapses) followed by variable recovery and periods of clinical stability. Within 10 years, more than 50% of these patients develop secondary progressive MS (SPMS), with sustained deterioration with or without relapses. Patients with relapsing MS, including both RRMS and SPMS with superimposed relapses, are the common target for current treatments. About 15% of the patients develop primary progressive MS (PPMS) from the beginning, and together with relapses it is called progressive relapsing MS (PRMS). Relapses include acute inflammatory focal lesions, whereas progression reflects the occurrence of demyelination, axonal loss and gliosis.

The mechanism by which the active substance of Copaxone 40 mg/ml Injection – glatiramer acetate – exerts its effects in patients with MS is not fully understood. It is thought, however, to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis (EAE); a condition induced in several animal species through immunisation against central nervous system derived material containing myelin, and often used as an experimental animal model of MS. Studies in animals and in MS patients suggest that upon administration of glatiramer acetate, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

No new non-clinical studies were conducted in support of this line-extension application, since the pharmacodynamic, pharmacokinetic and toxicological properties of glatiramer acetate are well-known.
The applicant has submitted the data from three clinical studies to support this application: a pivotal study and two supportive studies. A certificate of compliance with Good Clinical Practice (GCP) guidelines is provided in the clinical study reports.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS and CMSs considered that this application could be approved at the end of procedure (Day 210) on 04 December 2014. After a subsequent national phase, a licence was granted in the UK on 08 January 2015.

After changing the RMS, Germany is the new RMS. The former procedure number was UK/H/0453/004/DC.

II. QUALITY ASPECTS

II.1 Introduction

Copaxone 40 mg/ml Injection is formulated as a clear solution for injection, free of visible particles. The excipients present are mannitol and water for injections.

The solution for injection is presented in a pre-filled syringe, consisting of a 1 ml long colourless type I glass syringe barrel with staked needle, a blue plastic plunger rod, a rubber plunger stopper and a needle shield. Copaxone 40 mg/ml Injection is available in packs containing 3 or 12 pre-filled syringes of 1 ml solution for injection, or in a multipack containing 36 (3 packs of 12) pre-filled syringes of 1 ml solution for injection.

II.2 Drug substance

Glatiramer acetate

USAN:	Glatiramer acetate
Chemical name:	L-glutamic acid, polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt)
Molecular formula:	Poly [L-Glu$^{13-15}$, L-Ala$^{39-46}$, L-Tyr$^{8.6-10}$, L-Lys$^{30-37}$]. n(CH_3CO_2H); n=15 to 24 units of acetic acid moieties per 100 amino acid residues
Average molecular weight:	5,000 - 9,000 daltons
Appearance:	White to slightly yellowish lyophilised material.
Solubility:	Soluble in water, insoluble in acetone.

Glatiramer acetate is not the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.
Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.
Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.
Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal product

Pharmaceutical development

The objective of the pharmaceutical development was the achievement of a safe and efficacious dosage form for subcutaneous administration of glatiramer acetate three times per week.
The excipients used in the manufacture of the 40 mg/ml presentation (PL 10921/0026) are the same as those used for the already marketed 20 mg/ml presentation (PL 10921/0023). These are controlled in accordance with requirements of their respective current Ph. Eur. monographs.
Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.
None of the excipients are of animal/human origin.
No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product

Satisfactory batch formulae have been provided for manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated for manufacture of production-scale batches and is satisfactory.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from production-scale batches that comply with the release specification. Confirmation has been provided from the applicant that the reference standards used for the testing of the 40 mg/ml (PL 10921/0026) presentation will be identical to those used for the currently marketed 20 mg/ml presentation (PL 10921/0023). This is acceptable.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a proposed shelf-life of 2 years with the following storage conditions:
'Keep the pre-filled syringes in the outer carton, in order to protect from light. Store in a refrigerator (2-8°C). Do not freeze. If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once, for up to one month. After this one month period, if the Copaxone pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2-8°C).'

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended for this application.

III. NON-CLINICAL ASPECTS

No new non-clinical studies were conducted in support of this line-extension application since the pharmacodynamic, pharmacokinetic and toxicological properties of glatiramer acetate are well-known. As glatiramer acetate is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. The dossier for the original application included written summaries and tabulated data providing complete documentation of the non-clinical studies conducted to support the application. Since that time, the applicant states that no additional non-clinical safety studies were conducted by the applicant with the parenteral formulation of Copaxone (glatiramer acetate for subcutaneous injection). However, the applicant has conducted a thorough review of relevant non-clinical information that was published since the original application, and has incorporated this information in the present non-clinical overview.

There are no major non-clinical objections to the grant of a national licence for Copaxone 40 mg/ml

solution for injection, pre-filled syringe.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant's clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate.

IV.2 Pharmacokinetics

No new study data was submitted, which is acceptable.

IV.3 Pharmacodynamics

No new study data was submitted, which is acceptable.

IV.4 Clinical efficacy

The clinical data for this application consists of a pivotal study (Study A) and two supportive studies, Studies B and C. Study A evaluated the proposed product at the proposed regimen (40 mg/ml three times a week, i.e. 120 mg a week) over 12 months, with an open label extension. This study was placebo controlled and did not include a comparison with the currently approved dosing regimen (20 mg/ml daily injection, i.e. 140 mg a week). Studies B and C investigated daily injections of glatiramer acetate 40 mg/ml versus daily injections of glatiramer acetate 20 mg/ml.

Pivotal study (Study A)

A multinational (20 countries), multicentre (136 sites), randomized, parallel-group study performed in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) to assess the efficacy, safety and tolerability of glatiramer acetate (GA) injection 40 mg, administered three times a week (TIW) compared to placebo in a double-blind design.

The study consisted of 3 phases:

- Screening phase: up to 1 month.
- Placebo-Controlled (PC) Phase: 12 months of GA 40 mg or matching placebo, administered TIW by subcutaneous injection.
- Open-label (OL) Extension: All subjects were offered the opportunity to continue treatment with GA 40 mg administered TIW, until this dose strength would be commercially available for the treatment of RRMS subjects or until the development of this GA dose regimen would be stopped by the Sponsor.

Patients experiencing a relapse were re-consented prior to restarting test medication.

Subject inclusion and exclusion criteria

Subjects were included in the study if the following criteria were met:

- Subjects must have had a confirmed and documented multiple sclerosis (MS) diagnosis as defined by the revised McDonald criteria, with a relapsing-remitting disease course.
- Subjects must have been ambulatory with an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 in both screening and baseline visits.
- Subjects must have experienced one of the following:
  - At least one documented relapse in the 12 months prior to screening, or
  - At least two documented relapses in the 24 months prior to screening, or
  - One documented relapse between 12 and 24 months prior to screening with at least one documented T1-gadolinium (Gd) enhancing lesion on magnetic resonance imaging (MRI) performed within 12 months prior to screening.
- Subjects must have been 18 to 55 years of age, inclusive.

The main criteria for exclusion were: progressive forms of MS; use of experimental/investigational drugs, immunosuppressive agents or cytotoxic agents within the 6 months prior to screening; use of natalizumab or any other monoclonal antibodies, or cladribine within 2 years prior to screening; previous treatment with immunomodulators (including interferon β 1a and 1b, and intravenous [IV]

immunoglobulin) within 2 months prior to screening; previous use of GA or any other glatiramoid; chronic (more than 30 consecutive days) systemic (IV, per os [PO] or intramuscular [IM]) corticosteroid treatment within 6 months prior to screening visit; previous total body irradiation or total lymphoid irradiation; a known history of sensitivity to Gd, inability to successfully undergo MRI scanning, or known drug hypersensitivity to mannitol; clinically significant or unstable medical or surgical condition, which may include hepatic, renal or metabolic diseases, systemic disease, acute infection, current malignancy or recent history (5 years) of malignancy, major psychiatric disorder, history of drug and/or alcohol abuse and allergies; endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI).

Both treatment groups were comparable with respect to baseline demographics, MS disease characteristics and MRI parameters. 97.6 % of the study population was Caucasian, 67.9 % were females. Mean age of study population was 37.6 years. Mean time from first symptoms was 7.7 years and the majority of subjects had 1 or 2 relapses in the 2 years prior to screening. Baseline EDSS score was approximately 2.7, which is relatively low on a scale of 0 to 10 (9 meaning patient confined to bed).

Results

Approximately 1350 patients were planned to be enrolled, and to be randomised in a 2:1 ratio to the two treatment arms. The total number randomised was 1404 (943 on GA 40 mg TIW and 461 on placebo).

Randomisation was not stratified on any variables. 6.7% of patients in the placebo group and 8.9 % in the GA group did not complete the placebo-controlled phase of the study.

The most common single reason for early discontinuation was withdrawal of consent: 17 subjects (3.7 %) in the placebo group and 34 subjects (3.6 %) in the GA 40 mg TIW group. The second most common reason was due to adverse events (AEs): 6 subjects (1.3 %) in the placebo group and 29 subjects (3.1 %) in the GA 40 mg TIW group. One subject in the placebo group died during the placebo-controlled PC phase of the study.

Primary endpoint: The total number of confirmed relapses during the 12-month double blind placebo-controlled treatment phase.
A relapse was defined as the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities lasting at least 48 hours, and immediately preceded by an improving neurological state of at least 30 days from onset of previous relapse.
This criterion is different from the clinical definition of relapse: ‘at least 24 hours duration of symptoms’. Since the ‘in-study’ relapse definition had to be supported by an objective neurological evaluation (see next paragraph), a neurological deficit had to sustain long enough to eliminate pseudo-relapses.

An event was counted as a relapse only when the subject's symptoms were accompanied by observed objective neurological changes, consistent with at least one of the following:

- An increase of at least 0.5 in the EDSS score, as compared to previous evaluation.
- An increase of one grade in the actual score of 2 or more of the 7 Functional Systems (FS), as compared to previous evaluation.
- An increase of 2 grades in the actual score of one FS as compared to the previous evaluation.

Although the duration of the study is not fully in line with the Draft guideline on the clinical evaluation of medicinal products for the treatment of MS (EMA/CHMP/771815/2011, Rev 2), results of the principal analysis of the primary endpoint - the total number of confirmed relapses during the 12-month double-blind PC treatment phase - demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo: the risk ratio (95% confidence interval [CI]) was 0.656 [0.539; 0.799], reflecting a 34.4% reduction in total number of relapses in the GA 40 mg TIW group ($p<0.0001$).

Secondary Endpoints:
1. *The cumulative number of new/enlarging T2 lesions at Months 6 and 12*: the analysis demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo; the risk ratio [95% CI] was 0.653 [0.546; 0.780], reflecting a 34.7% reduction in the cumulative number of new/enlarging T2 lesions in the GA 40 mg TIW group (p<0.0001).

2. *The cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12*: the analysis demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo; the risk ratio [95% CI] was 0.552 [0.436; 0.699], reflecting a 44.8% reduction in the cumulative number of enhancing lesions on T1-weighted images in the GA 40 mg TIW group (p<0.0001).

3. *The percentage change in brain volume from baseline to Month 12 (indicative of brain atrophy)*: the analysis did not demonstrate a statistically significant treatment effect of GA 40 mg TIW over placebo; the adjusted mean difference [95% CI] was -0.061 [-0.154; 0.033, p=0.2058] (p=0.2058).

Relapse-Related Exploratory Endpoints:
- *Time to first confirmed relapse during the PC phase*: a favourable effect for GA 40 mg TIW over placebo was demonstrated with a 39.4% reduction in the hazard for first relapse during the PC phase (p<0.0001).
- *Proportion of relapse-free subjects during the PC phase*: a favourable effect for GA 40 mg TIW over placebo was demonstrated with almost a 2-fold increase in the odds of being relapse-free during the PC phase (p<0.0001).
- *The total number of severe relapses defined as confirmed relapses requiring hospitalization and/or IV Steroids during the PC Phase*: a favourable effect for GA 40 mg TIW over placebo was demonstrated with a 35.6% reduction in the total number of confirmed severe relapses during the PC phase (p<0.0001). (A post-hoc subgroup analysis of the primary endpoint was undertaken with a modified definition of 'severe relapse'. Severe relapse was re-defined as 'patients who had at least 1 relapse in the year prior to screening and had at least 9 T2-hyperintense lesions or at least 1 Gadolinium-enhancing lesion in cranial MRI. The results did not identify any specific additional sub-group).

TABLE A: Primary Endpoint and Robustness Analysis

Endpoint Analyses		Treatment Effect: GA 40 mg vs. Placebo		
		ITT Population	CO Population	EV Population
Total No. of Confirmed Relapses: Negative Binomial Regression (Principal Model)	Risk Ratio [95% CI]	0.656 [0.539; 0.799]	0.619 [0.505; 0.759]	0.617 [0.499; 0.763]
	P-value	<0.0001	<0.0001	<0.0001
Total No. of Confirmed Relapses: Negative Binomial Regression (Unadjusted)	Risk Ratio [95% CI]	0.669 [0.546; 0.821]	0.636 [0.514; 0.786]	0.628 [0.503; 0.784]
	P-value	0.0001	<0.0001	<0.0001
Total No. of Confirmed Relapses: Quasi-Likelihood (Over-Dispersed) Poisson Regression	Risk Ratio [95% CI]	0.657 [0.553; 0.780]	0.623 [0.522; 0.744]	0.621 [0.517; 0.746]
	P-value	<0.0001	<0.0001	<0.0001
Individual Annualized Relapse Rate: ANCOVA	Adjusted Mean Difference	-0.166 [-0.262; -0.070]	-0.178 [-0.253; -0.102]	-0.173 [-0.249; -0.097]
	P-value	0.0007	<0.0001	<0.0001
Individual Annualized Relapse Rate: Wilcoxon's test	NA	NA	NA	NA
	P-value	<0.0001	<0.0001	<0.0001

ITT Population - Intent-to-Treat population, which included all randomised subjects.

CO Population - Completers analysis population, which included all randomised subjects who completed the PC phase

EV Population - Evaluable analysis population, which included all subjects in the CO population without any major protocol violations.

NA - Not applicable

Disability-Related Exploratory Endpoints

Disability-related endpoints were exploratory only. FS and EDSS were assessed based on a slightly modified neurological examination compared to the one described by Kurtzke. The study employed Neurostatus, a standardised neurological examination and assessment of the Kurtzke EDSS to quantify disability in seven FS.

The following table presents the values of the primary and secondary outcome measures for the intent-to-treat population.

Outcome Measure	Adjusted Mean Estimates		P-Value
	Copaxone (40 mg/ml) (N=943)	Placebo (N=461)	
Annualized relapse rate (ARR)	0.331	0.505	p<0.0001
Absolute Risk Difference[a] (95% confidence intervals)	-0.174 [-0.2841 to -0.0639]		
Cumulative number of new/enlarging T2 lesions at Months 6 and 12	3.650	5.592	p<0.0001
Rate ratio[b] (95% confidence intervals)	0.653 [0.546 to 0.780]		
Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12	0.905	1.639	p<0.0001
Rate ratio[b] (95% confidence intervals)	0.552 [0.436 to 0.699]		

[a] Absolute risk difference is defined as the difference between the adjusted mean ARR of GA 40 mg TIW and adjusted mean ARR of Placebo

[b] Absolute risk difference is defined as the difference between the adjusted mean ARR of GA 40 mg TIW and adjusted mean ARR of Placebo

Addendum: Open-label extension (ongoing)

This is an open-label extension hence efficacy data are only for information. There was a sustained effect in the reduction of relapses after 3 years with GA 40 mg TIW. In addition the effect on MRI variables or disability progression was in favour of the group who had received GA for 36 months (early-start) as compared to the group that had received GA for 24 months only (delayed-start).

Safety

The overall incidence of adverse events (AEs) was higher in the GA 40 mg TIW group (72.1% [680 subjects]) compared to the placebo group (61.6% [284 subjects]). General disorders and administration site conditions were reported in 10.0% of the patients in the placebo group and 43.1 % in the GA 40 mg TIW group. The most common AEs reported in the GA 40 mg TIW group were in the categories of injection site reactions (ISR) and immediate post-injection reactions (IPIRs).

The most commonly reported AEs (other than ISR and IPIRs), reported by ≥ 2% of subjects in the GA 40 mg TIW group, and with an incidence higher than placebo by ≥ 1%, were (in no particular order): nasopharyngitis, influenza-like illness, respiratory tract infection viral, pyrexia, nausea and chills. Adverse events were higher in patients switching from placebo to active treatment in the open-label phase (delayed start).

The AEs reported in this study by GA-treated subjects are consistent with the known AE profile of glatiramer acetate.

Study B

A multinational, multicenter, randomised, parallel-group, double-blind (DB) study to compare the efficacy, tolerability and safety of glatiramer acetate injection 40 mg/ml to that of glatiramer acetate injection 20 mg/ml, administered once daily by subcutaneous injection in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS)

RRMS (McDonald criteria 2005) eligible subjects were equally randomised into one of the two treatment arms: either GA 40 mg or GA 20 mg administered subcutaneously, once daily, for treatment duration of up to 12 months, followed by an open-label (OL) phase of treatment with a daily injection of GA 40 mg for 12 months. The objectives of the study were to compare GA 40 mg to GA 20 mg for efficacy, as determined by the rate of confirmed relapses during the DB phase, as well as MRI-related parameters, tolerability, and safety. Scheduled visits at the sites for the DB phase were performed at screening, baseline, months 1, 2, 3, 6, 9, 12 (end of DB phase), and months 15, 18, 21, and 24 of the OL phase.

Of the 1155 subjects randomised to study treatment, 1024 subjects completed the DB phase and 1005 subjects (98.1%) continued treatment with GA 40 mg in the OL phase (482 subjects in the original GA 40 mg group and 523 subjects initially randomised to GA 20 mg).
Premature termination from the DB phase was reported for 52 subjects (8.9%) on GA 20 mg and 79 subjects (13.9%) on GA 40 mg. The main reasons for termination were due to AEs (GA 20 mg: 28/586 subjects [4.8%]; GA 40 mg: 51/569 [9.0%]) and consent withdrawal (GA 20 mg: 10/586 subjects [1.7%]; GA 40 mg: 12/569 [2.1%]). One subject died in a traffic accident and 5 subjects (0.4%) withdrew due to pregnancy. Following the results of the DB phase in which the primary endpoint was not reached, 891 subjects (88.7%) terminated due to Teva's decision to terminate the OL phase. Termination due to AEs was reported for 30 subjects (3.0%) in the OL phase.

The study included 828 females (71.7%) and 327 males (28.3%). The mean (SD) age was 36.34 (8.99) years, and the majority of subjects were Caucasian (1100/1155 subjects; 95.2%). Mean (SD) BMI was 25.3 (5.5) kg/m^2. The two treatment groups were comparable with respect to baseline demographic variables. Overall, the mean (SD) time from MS diagnosis was 6.6 (6.4) years, and the mean (SD) number of exacerbations recorded in the 2 years prior to screening was 2.0 (1.0) years. Baseline MS disease characteristics and MRI measures were comparable for the two treatment groups.

Efficacy

Principal analysis was undertaken on relapse rate during the DB phase, using Quasi-Likelihood (over-dispersed) Poisson Regression, adjusted to the exposure in the DB phase, with prior 2-year relapse rate, and baseline EDSS score, and country as covariates. The results did not demonstrate a statistically significant difference between the dose groups. The analysis yielded a RR (Rate Ratio) [95%CI] of the 40 mg dose over the 20 mg dose of: 1.0732 [0.8799, 1.3090]; p-value=0.4859.

Because the primary endpoint did not achieve significance, testing of the secondary endpoints did not ensure preservation of the overall type-I error.

Safety

Overall incidence was calculated as the percent of subjects reporting a specific adverse event (AE) at least once, out of the total number of subjects. Incidence rate (IR) was calculated as the incidence adjusted for group exposure to study drug, and expressed in terms of 100 subject-years. The overall incidence (%) and IR of AEs was comparable in both the GA 20 mg and GA 40 mg treatment groups (85.2%, IR = 90.9 vs. 86.1%, IR = 95.6, respectively) during the DB phase. A slightly higher incidence and IR were reported in the OL phase for subjects initially randomised to GA 20 mg who switched to GA 40 mg (55.4%; IR=97.9) compared to those who were on GA 40 mg in both phases (52.7%; IR = 92.1).

The most common AEs in both study phases were related to injection site (IS) reactions, and symptoms associated with Immediate Post-Injection Reactions (IPIRs).

Double-blind phase: generally, severe IS reactions were reported in similar incidence in both groups, except for IS mass which had 6 severe cases on GA 40 mg compared to one case on GA 20 mg. IS mass was the leading cause for early termination due to AEs in the GA 40 mg group, 14 subjects in the GA 40 mg group (2.5%; IR = 2.7) vs. 2 subjects in the GA 20 mg group (0.3%; IR = 0.4). One subject on GA 20 mg vs. 6 subjects on GA 40 mg had a change from baseline in QTcB (heart-rate corrected QT interval, in accordance with Bazett' function) greater than 60 msec during the DB phase. None of these changes reached a level of QTcB >500 msec. Fifty-one (9.0%; IR=9.9) subjects on GA 40 mg vs. 28 subjects (4.8%; IR = 5.1) subjects on GA 20 mg terminated the DB phase of the study due to AEs. AEs of IS reactions, IPIR symptoms, skin reactions and oedemas were the most common AEs leading to early termination.

Adverse events were clearly higher in patients switching from GA 20mg to GA 40 mg in the open-label phase (delayed start).

Study C

A multi-center, randomised, double-blind parallel group study comparing a new higher dose formulation of glatiramer acetate (GA) 40 mg to the currently marketed 20 mg formulation in Relapsing Remitting Multiple Sclerosis (RRMS) patients.

Eligible subjects were equally randomized into one of the two treatment arms, either GA 20 mg or GA 40 mg. Both doses were administered subcutaneously, once daily, for treatment duration of 36 weeks.

Results

Efficacy

The total number of T1-Gd enhanced lesions measured on the Intent-to-treat (ITT) cohort showed a 38% reduction in favour of GA 40 mg as compared to GA 20 mg in the cumulative number of Gd-enhancing lesions at months 7, 8 and 9 (p= 0.0898). *Post-hoc* analysis demonstrated that this advantage was apparent as early as 3 months following study randomization, showing a significant reduction of 52% in favour of the 40 mg dose as compared to 20 mg (p-value=0.0051).

Analyses of confirmed relapses were performed on the ITT cohort. The mean (± SD) number of confirmed relapses on-study was 0.52 ± 0.59 for subjects on GA 20 mg and 0.30 ± 0.59 for subjects on GA 40 mg. The mean annualized number of confirmed relapses was 0.81 ± 0.98 on 20 mg as compared to 0.49 ± 1.1 on 40 mg.

Safety

The overall incidence of Immediate Post-Injection Reactions (IPIRs) on 40 mg was 32.6% (mostly moderate) compared to 22.7% (mostly mild) on 20 mg. All events resolved with no sequelae. This incidence is consistent with GA 20 mg experience. The largest difference between the groups with regards to IPIR symptoms (flushing, palpitations, tachycardia, dyspnoea and chest pain) was in palpitations; 10.9% for subjects on GA 40 mg compared to 2.3% for subjects on GA 20 mg.

Analysis across trials

a) In the absence of head-to head data, the applicant originally provided **comparative historical data** regarding Annualized Relapse Rate (ARR) in studies where GA 20 mg once a day was used:

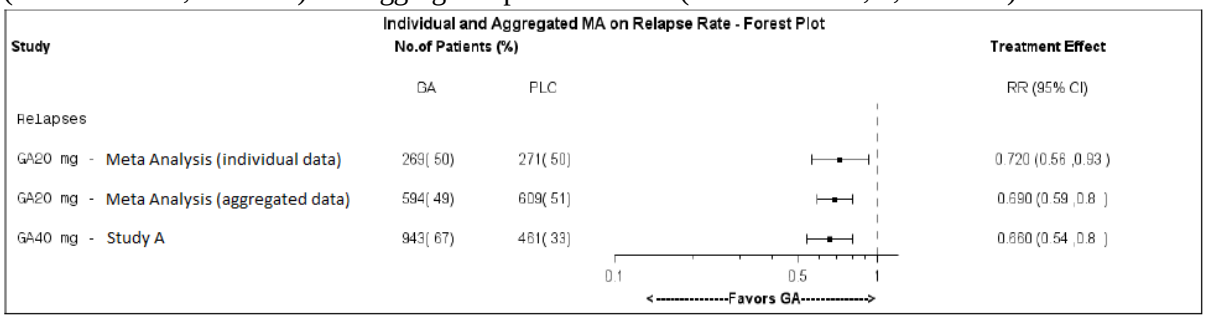
- Study D was a 2-year study of oral Tecfidera vs placebo, with GA as a comparator (2007-2011, non-TEVA sponsored)
- Study E was a large 2-year study in treatment-naïve patients with GA vs. interferon beta-1b without placebo-arm (2003-2008, non-TEVA sponsored)
- Study B (20 mg/ml daily, 2006-2008, TEVA sponsored)
- Study A (40 mg/ml TIW)

Studies A, B, D and E: GA Annualized Relapse Rate

	Annualized Relapse Rate (ARR)			
	Study A GA 40 mg TIW	**Study B GA 20 mg/day**	**Study E GA 20 mg/day**	**Study D GA 20 mg/day**
Estimate (95% CI)	0.33 (0.28-0.39)	0.30 (0.26-0.35)	0.34 (0.28-0.42)	0.29 (0.23-0.35)

b) Meta-analysis

Studies A and D and three further placebo-controlled studies from the ClinicalTrials.gov database (studies F, G and H) were used in a meta-analysis to look at relapse rate using both individual data (from studies F, G and H) and aggregated published data (from studies D, F, G and H).



The data regarding relapse rate is favourable to GA 40 mg TIW.

c) Pooled data

Hazard ratio of GA vs. placebo of the time to first relapse from a Cox regression model (adjusted for baseline EDSS and number of relapses prior to screening) were derived from pooling the individual data of three placebo-controlled studies with 20 mg GA daily (namely, Studies F, G and H, which were the pivotal studies used to support the licence application for Copaxone 20 mg, powder and solvent for solution for injection, PL 10921/0019). This data was compared with the corresponding hazard ratio derived from the GALA study with 40 mg TIW.

Time to First Relapse Analysis: Hazard Ratio, p-value and CI Compared to Placebo of the Individual Studies, Pooled GA 20 mg Daily Studies and Study A, GA 40 mg TIW

GA Dose and Regimen	**Hazard Ratio**	**p-value**	**95% CI**
Study F (N=50)	0.445	0.043	0.203, 0.975
Study G (N=251)	0.777	0.099	0.576, 1.048
Study H (N=239)	0.829	0.322	0.571, 1.202
Pooled 20 mg daily (Studies F, G and H (N=540)	0.745	p=0.009	0.597, 0.930
Study A 40 mg TIW (N=1,404)	0.643	p<0.0001	0.524, 0.789

d) The applicant also provided data from a **predictive model** using EDSS at baseline, number of previous relapses, age, and gender, Gd-enhancing lesions at baseline, volume of T2 lesions or time from diagnosis. Predicted ARR for a typical patient receiving GA 40 mg TIW was roughly comparable to that with daily GA 20 mg.

IV.5 Clinical safety

In support of the safety data in the proposed GA 40 mg/ml TIW SmPC, relevant observations are presented in this section. Safety analysis is focused on data from RRMS patients who participated in Study A in which placebo or GA 40 mg/ml was administered three times a week. Safety data for other doses and regimens, (GA 20 mg/ml a day and 40 mg/ml a day), derived from the completed Studies B and C, are presented within this document for comparison purposes. Thus, GA 40 mg/ml TIW is compared directly to placebo TIW, and indirectly to daily doses of GA 20 mg/ml and 40 mg/ml.

For the analysis of safety data, two cohorts were defined:

1. A **double-blind (DB) phase cohort** comprising four groups of subjects with RRMS from Studies A, B and C (i.e. placebo, 40 mg/ml TIW, 40 mg/ml a day and 20 mg/ml a day);
2. An **open-label (OL) phase cohort** comprising four groups of subjects with RRMS from the OL phase of Studies A and B (there was no OL phase in Study C).

All subjects received GA 40 mg/ml (daily in Study B or TIW in Study A) during the OL phase of their respective studies. These groups were designated as 'early start' (ES) if the subjects had received GA 40 mg/ml (either daily or TIW) during the DB phase, or 'delayed start' (DS) if subjects had received GA 20 mg/day or placebo TIW during the DB phase and had not started GA 40 mg/ml (either daily or TIW) until the OL phase.

The overall incidence of subjects reporting AEs during the DB phase was lower in the TIW dose groups (both GA 40 mg and placebo) compared to the daily dose groups (GA 40 mg/day and GA 20 mg/day). A total of 72.1% subjects in the GA 40 mg TIW group and 61.6% subjects in the placebo TIW group reported AEs, compared to 86.2% and 87.2% in the GA 20 mg/day and GA 40 mg/day groups, respectively.

The System Order Class (SOC) with the highest incidence of subjects reporting AEs in all three GA dose groups was 'General Disorders and Administration Site Conditions', and this incidence was noticeably lower in the GA 40 mg TIW group (43.1%) compared to the daily dosage groups (63.2% in the GA 20 mg/day group and 67.2% in the GA 40 mg/day group); only 12.1% of subjects in the Placebo TIW group had AEs in this SOC; this difference relates to ISRs reported among the GA subjects and is consistent with the known AE profile of GA. ISR was the High-Level Term (HLT) with the highest incidence of subjects reporting AEs in all three GA dose groups, and this incidence was noticeably lower in the GA 40 mg TIW group (35.5%) compared to the daily dosage groups (59.2% in the GA 40 mg/day group and 57.5% in the GA 20 mg/day group). The second highest incidence was reported for the SOC 'Infections and infestations' with a high incidence of upper respiratory tract infections in all groups (including placebo).

The incidence of subjects reporting AEs in all other SOCs and HLT was generally lower in the GA 40 mg TIW group compared to both the GA 20 mg/day group and the GA 40 mg/day group.

DB Phase Cohort: Summary of Adverse Events

Preferred Term/Grouped AEs n (%) of subjects	Studies B and C		Study A	
	GA 20 mg/ml/day (N=630)	GA 40 mg/ml/day (N=615)	Placebo TIW (N=461)	GA 40 mg/ml TIW (N=943)
All AEs	543 (86.2)	536 (87.2)	284 (61.6)	680 (72.1)
Treatment-related AEs	424 (67.0)	440 (72.0)	71 (15.0)	450 (48.0)
Serious AEs	26 (4.1)	26 (4.2)	21 (4.6)	42 (4.5)
Deaths	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Withdrawal due to AEs	31 (4.9)	57 (9.3)	6 (1.3)	29 (3.1)

The incidence of subjects who discontinued due to AEs in the DB phase groups was higher in the GA daily dose groups (9.3% and 4.9% subjects on GA 40 mg/day and GA 20 mg/day, respectively) compared to the GA 40 mg TIW (3.1% subjects) and placebo TIW (1.3% subjects) groups.

The only AEs which led to early discontinuation in ≥1% of subjects in the GA 40 mg/day, GA 20 mg/day or GA 40 mg TIW groups were: IS erythema (1.8%, 0.6% and 0.3%, respectively), IS pain (1.0%, 0.6% and 0.4%, respectively), and dyspnoea (1.1%, 0.8% and 0.1%, respectively).

The most common AEs leading to early discontinuation in the DB phase cohort were ISR and/or IPIR symptoms. The most common AE, after ISRs and IPIRs, which led to early termination, was swelling face; this was reported by 0.8% subjects in the GA 40 mg/day group and 0.5% subjects in the GA 20 mg/day group.

No new safety signal was identified from the 36-month data from Study A or from the post-marketing data in the US (28 January 2014 until 31 August 2014).

Study A – Extension data - Frequency and Incidence of Adverse Events Occurring for at least 5% of Subject by System Organ Class, High Level Term and Preferred Term

STUDY A			Delayed Start (N=419, Subject Years=831.4)				Early Start (N=834, Subject Years=2554.8)				All (N=1253, Subject Years=3386.2)			
			No. of Reports	No. of Subjects	% of Subjects	Event Rate per 100 Subject Years	No. of Reports	No. of Subjects	% of Subjects	Event Rate per 100 Subject Years	No. of Reports	No. of Subjects	% of Subjects	Event Rate per 100 Subject Years
System Organ Class	High Level Term	Preferred Term												
-ALL	-ALL	-ALL	1220	285	68.0	146.7	4405	665	79.7	172.4	5625	950	75.8	166.1
System Organ Class	High Level Term	Preferred Term												
General Disorders And Administration Site Conditions	Injection Site Reactions	Injection Site Erythema	119	106	25.3	14.3	368	229	27.5	14.4	487	335	26.7	14.4
		Injection Site Pain	59	54	12.9	7.1	122	100	12.0	4.8	181	154	12.3	5.3
		Injection Site Pruritus	26	25	6.0	3.1	74	55	6.6	2.9	100	80	6.4	3.0
		Injection Site Swelling	25	25	6.0	3.0	84	44	5.3	3.3	109	69	5.5	3.2
Infections And Infestations	Influenza Viral Infections	Influenza	26	22	5.3	3.1	81	57	6.8	3.2	107	79	6.3	3.2
	Upper Respiratory Tract Infections	Nasopharyngitis	71	50	11.9	8.5	258	137	16.4	10.1	329	187	14.9	9.7
		Upper Respiratory Tract Infection	39	28	6.7	4.7	99	73	8.8	3.9	138	101	8.1	4.1
	Urinary Tract Infections	Urinary Tract Infection	29	24	5.7	3.5	107	75	9.0	4.2	136	99	7.9	4.0
Musculoskeletal And Connective Tissue Disorders	Musculoskeletal And Connective Tissue Pain And Discomfort	Back Pain	25	20	4.8	3.0	100	74	8.9	3.9	125	94	7.5	3.7
Nervous System Disorders	Headaches Nec	Headache	47	30	7.2	5.7	227	112	13.4	8.9	274	142	11.3	8.1

There was no increased risk of QTc prolongation in Study A as compared to the pooled data from Studies B and C. Chest pain and palpitations were analysed as part of the IPIR analysis for Study A and pooled Studies B and C, and the comparison with the proposed product was favourable.

The lower incidence of chest pain and palpitations seen in Study A compared to previous studies might be related to the lower incidence of IPIR reporting in Study A and may be a result of the lower injection frequency, when compared to the previous studies with daily injections.

This was demonstrated in Study J; an open-label, randomised, multi-center, parallel-arm study to assess the safety and tolerability of GA 40 mg/ml TIW compared to 20 mg/ml daily subcutaneous injections in subjects with relapsing-remitting MS. The primary endpoint was the rate of injection related adverse events in either treatment population. In this study the annualized rate of IPIRs for the GA 40 mg/mL TIW group was approximately half that of the rate for GA 20 mg/ml daily group.

The applicant also noted that there could be a lower reporting of adverse events in Study A as compared to what took place with Studies B and C due to a familiarity of the investigators with the immediate post injection reaction (IPIR) phenomenon.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Copaxone 40 mg/ml Injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns

IMPORTANT IDENTIFIED RISKS	• Immediate post injection reaction • Injection site reactions (excluding necrosis and atrophy) • Injection site necrosis and atrophy • Hypersensitivity • Benign neoplasms of the skin and soft tissues *(new)* • Convulsions *(new)* • Anxiety *(new)*
IMPORTANT POTENTIAL RISKS	• Liver injury • Glomerulonephropathies *(new)*
MISSING INFORMATION	• Paediatric patients (below 18 years of age) • Elderly patients • Pregnant or breastfeeding women • Patients with renal or hepatic impairment

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Immediate post injection reaction	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Injection site reactions (excluding necrosis and atrophy)	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Injection site necrosis and atrophy	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Hypersensitivity	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Benign neoplasms of the skin and soft tissues	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Convulsions	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Anxiety	The adverse events identified with Copaxone use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
IMPORTANT POTENTIAL RISKS		
Liver injury	The adverse events associated with Copaxone following post marketing use have been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Glomerulonephropathies	The adverse event was associated	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	with Copaxone in non-clinical studies but was not seen in humans. It has been highlighted in the product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW. Monitoring of renal function in patients with renal impairment is recommended.	
MISSING INFORMATION		
Paediatric patients (under 18 years of age)	Missing information is highlighted in product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Elderly patients	Missing information is highlighted in product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Pregnant and breast feeding women	Missing information is highlighted in product literature for Copaxone 20 mg/mL and Copaxone 40 mg/mL TIW	None
Patients with renal or hepatic impairment	Due to the potential risk of glomerulonephropathies, which was not seen in humans but the possibility of it cannot be excluded, monitoring of renal function in patients with renal impairment is recommended.	None

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Copaxone 20 mg/0.5 ml Solution for Injection, Pre-filled Syringe.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The proposed new presentation of Copaxone 40 mg/ml injection is twice as concentrated to deliver double the dose three times a week, with a minimum of 48 hours between injections. This new formulation is identical to the Copaxone 20 mg/ml solution for injection, pre-filled syringe (PL 10921/0023) but for the concentration, and the weekly dose will be 120 mg as opposed to the currently approved 140 mg.

The reduced injection schedule is aimed at reducing the common side effects seen with Copaxone injections, such as injection site reactions. No new non-clinical data have been presented.

A pivotal study and two supportive studies were performed to evaluate the proposed product at the proposed dosing regimen.

Quality

The quality of the product is acceptable and no concerns have been identified.

Efficacy

In Study A, the total number of confirmed relapses during the 12-month double-blind PC treatment phase demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo: the risk ratio [95% confidence interval, CI] was 0.656 [0.539; 0.799], reflecting a 34.4% reduction in total number of relapses in the GA 40 mg TIW group ($p<0.0001$). The absolute risk difference is -0.174 [95% CI, -0.2841 to -0.0639].

Comparison in terms of efficacy between GA 20 mg/ml daily and GA 40 mg/ml TIW can only be historical, as no direct comparison is available. The applicant has submitted a number of analyses, i.e. from individual studies, prediction modelling, pooled data or using meta-analysis methodology. Across the data presented there is no clear signal that the new proposed regimen would be less effective than daily injections of 20 mg/ml on relapse rate.

It is agreed that none of the studies specifically looked at disability and that the 36-month data from Study A is reassuring.

Safety

The safety data with the new proposed regimen is overall favourable when compared to that of daily injections with GA 20 mg/ml. Injections three times a week seem to lead to a reduction in injection site reactions and immediate post injection reactions when looking at data across studies. There is no new safety signal with the proposed formulation.

Conclusion

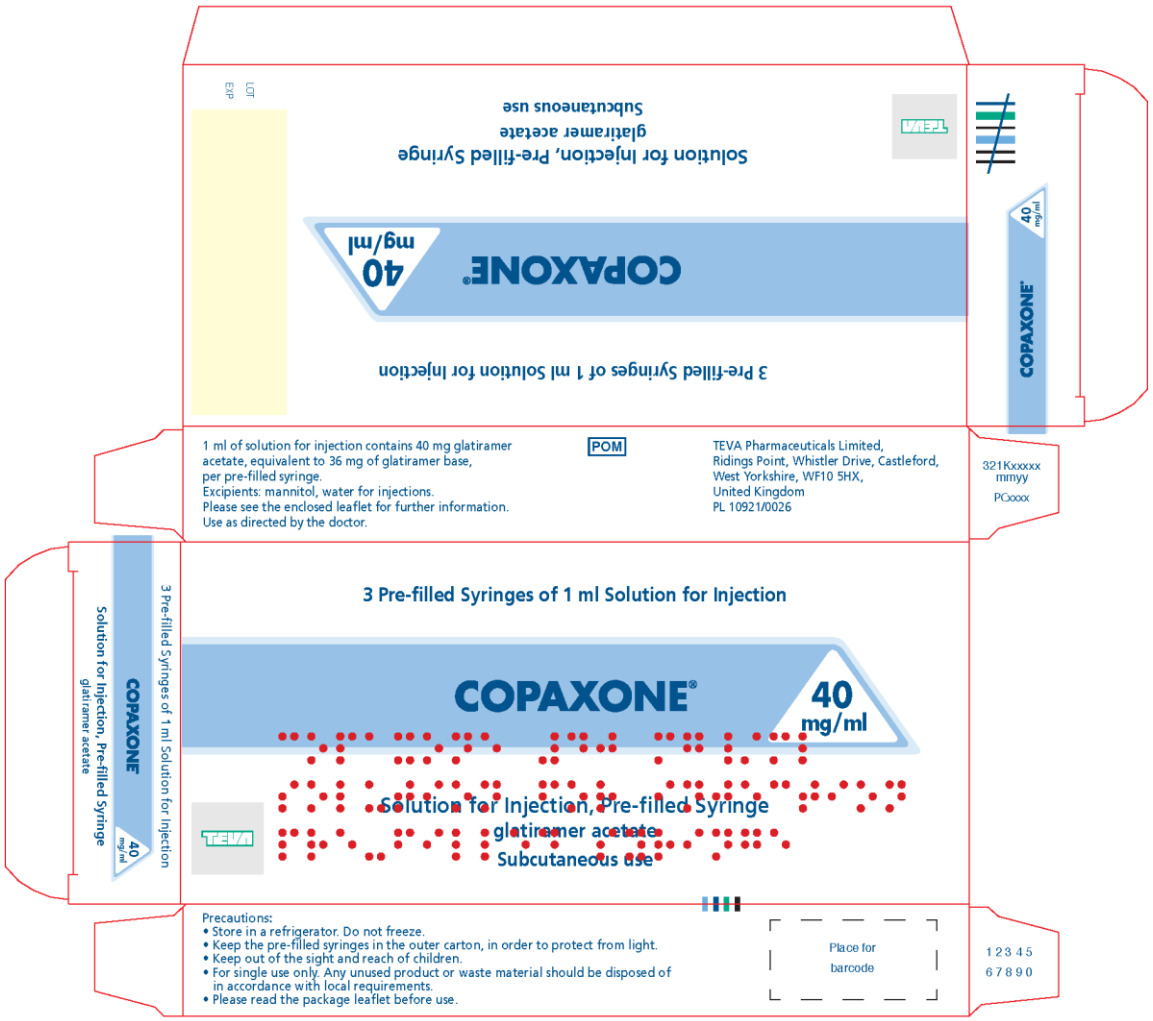
This is a line-extension of an already marketed product and the treatment with Copaxone 40 mg/ml injection has been shown to be superior to placebo on relapses and secondary endpoints. Furthermore, the tolerability with the new injection is favourable. The benefit/risk for this application is, therefore, considered positive.

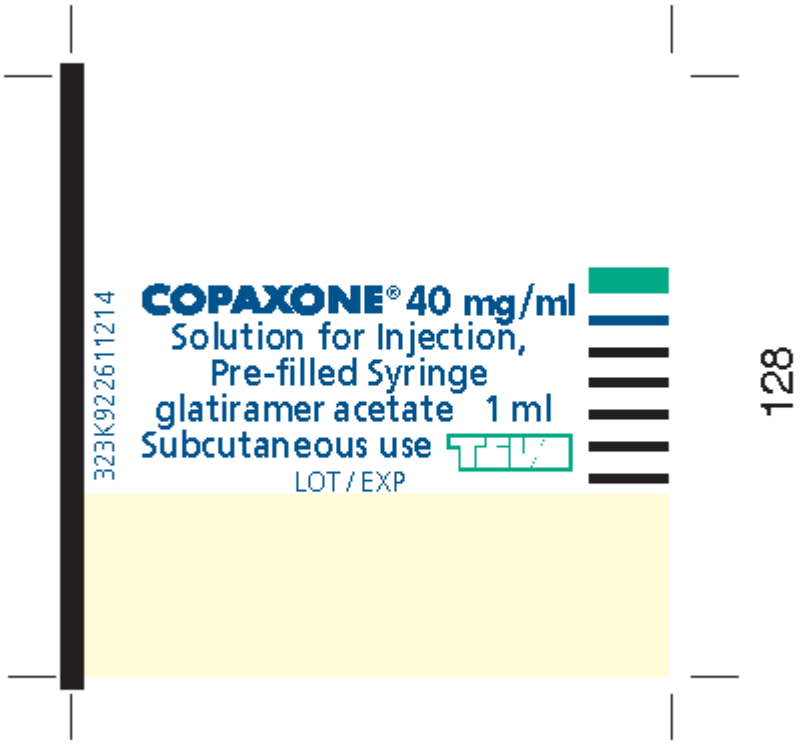
The application is approved. For intermediate amendments see current product information.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory and in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product is available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labels are listed below:

COPAXONE®
40 mg/ml
12 Pre-filled Syringes of 1 ml Solution for Injection
Solution for Injection, Pre-filled Syringe
glatiramer acetate
Subcutaneous use
TEVA
COPAXONE®
40 mg/ml
12 Pre-filled Syringes of 1 ml Solution for Injection
Solution for Injection, Pre-filled Syringe
glatiramer acetate
Subcutaneous use
TEVA
POM
1 ml of solution for injection contains 40 mg glatiramer acetate, equivalent to 36 mg of glatiramer base, in pre-filled syringe.
Excipients: mannitol, water for injections.
Please see the enclosed leaflet for further information.
Use as directed by the doctor.
TEVA Pharmaceuticals Limited,
Ridings Point, Whistler Drive, Castleford,
West Yorkshire, WF10 5HX,
United Kingdom
PL 10921/0026
321K55761
1214
POxxxx
Pharmacode 26
12 Pre-filled Syringes of 1 ml Solution for Injection
COPAXONE®
40 mg/ml
Solution for Injection, Pre-filled Syringe
glatiramer acetate
Subcutaneous use
TEVA
LOT
EXP
Precautions:
• Store in a refrigerator. Do not freeze.
• Keep the pre-filled syringes in the outer carton, in order to protect from light.
• Keep out of the sight and reach of children.
• For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.
• Please read the package leaflet before use.


Solution for Injection, Pre-filled Syringe
glatiramer acetate
Subcutaneous use
COPAXONE®
40 mg/ml
3 Pre-filled Syringes of 1 ml Solution for Injection
1 ml of solution for injection contains 40 mg glatiramer acetate, equivalent to 36 mg of glatiramer base, per pre-filled syringe.
Excipients: mannitol, water for injections.
Please see the enclosed leaflet for further information.
Use as directed by the doctor.
POM
TEVA Pharmaceuticals Limited,
Ridings Point, Whistler Drive, Castleford,
West Yorkshire, WF10 5HX,
United Kingdom
PL 10921/0026
321Kxxxxx
mmyy
PCxxxx
3 Pre-filled Syringes of 1 ml Solution for Injection
Solution for Injection, Pre-filled Syringe
glatiramer acetate
Precautions:
• Store in a refrigerator. Do not freeze.
• Keep the pre-filled syringes in the outer carton, in order to protect from light.
• Keep out of the sight and reach of children.
• For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.
• Please read the package leaflet before use.
Place for barcode
1 2 3 4 5
6 7 8 9 0


323K922611214
COPAXONE® 40 mg/ml
Solution for Injection,
Pre-filled Syringe
glatiramer acetate 1 ml
Subcutaneous use
LOT / EXP
128