CADTH

CADTH COMMON DRUG REVIEW

Common Drug Review Subsequent Entry Non-Biologic Complex Drug Submission

GLATIRAMER ACETATE (GLATECT™)

(Pendopharm, a division of Pharmascience Inc.)

Indication: (GLATECT) (glatiramer acetate injection) is indicated for: Treatment of ambulatory patients with relapsing-remitting multiple sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain MRI:

- to decrease the frequency of clinical exacerbations
- to reduce the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans.

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Table of Contents

Abbreviations

AB	Alberta
ACTH	Adrenocorticotropic Hormone
ADA	Anti-Drug Antibody
AE	Adverse Event
ANS	8-Anilino-lnaphthalenesulfonic acid
ARR	Annualized Relapse Rate
ASR Group	All Subjects Randomized Group
ASSG	All Subjects Screened Group
BC	British Columbia
BMI	Body Mass Index
CBA	Cell-based Assay
CBB	Coomassie Brilliant Blue
CD	Circular Dichroism
CDMS	Clinically Definite Multiple Sclerosis
CDR	Common Drug Review
CI	Confidence Interval
cIEF	Capillary Isoelectric Focusing
CIS	Clinical Isolated Syndrome
CL	Confidence Limits
CNS	Central Nervous System
CPA	Collaborative Prescribing Agreement
CTD	Common Technical Document
DB	Double-blind
DMT	Disease Modifying Therapy
DND	Department of National Defence
EAE	Experimental Autoimmune Encephalomyelitis
EAP	Exceptional Access Program
ECG	Echocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EU	European Union
EX	Exception item for which coverage is determined on a case-by-case basis
FAS	Full Analysis Set
FB	Full Benefit
FDA	Food and Drug Administration
FS	Functional Systems
GATE	Glatiramer Acetate Clinical Trial to Assess Equivalence With COPAXONE®
Gd	Gadolinium
GdE	Gadolinium Enhancing
GPC	Gel Permeation Chromatography
GTR	GLATECT™
HBsAg	Hepatitis B surface Antigen
hCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IL-2	Interleukin-2

LISR	Local Injection Site Reactions
LSMEAN	Least Squares Mean
MALDI-TOF	Matrix-Assisted Laser Desorption Ionization coupled to a Time of Flight mass analyzer
MALS	Multi-Angle Light Scattering
MB	Manitoba
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MWD	Molecular Weight Distribution
NA	Not Applicable
NB	Not a Benefit
NDS	New Drug Submission
NF	Newfoundland
NIHB	Non-Insured Health Benefits Program
NS	Nova Scotia
NT	Northern Territories
ODB	Ontario Drug Benefit
ON	Ontario
PBMC	Peripheral Blood Monocytic Cell
PDI	Polydispersity Index
PE	Prince Edward Island
PK	Pharmacokinetic
PBMC	Peripheral Blood Monocytic Cell
PPS	Per-Protocol Set
QC	Quebec
RES	Restricted benefit with specified criteria
RGC	Retinal Ganglion Cells
RP-HPLC	Reversed Phase High Performance Liquid Chromatography
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SDS-PAGE	Sodium Dodecyl Sulfate - Poly Acrylamide Gel
SENBCD	Subsequent Entry Non Biologic Complex Drug
SK	Saskatchewan
T1-GdE	T1-weighted Gadolinium Enhancing
UR	Under Review
UV	Ultraviolet
VAC	Veteran Affairs Canada
WDAE	Withdrawal Due to Adverse Event
WHO	World Health Organization
YK	Yukon
-	Information not available

Drug	Glatiramer acetate (GLATECT™)
Indication	(GLATECT) (glatiramer acetate injection) is indicated for: Treatment of ambulatory patients with relapsing-remitting multiple sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain MRI: • to decrease the frequency of clinical exacerbations • to reduce the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans.
Reimbursement Request	List with each public plan's current listing criteria for glatiramer acetate, for treatment of COPAXONE-naive and COPAXONE-experienced patients.
Manufacturer	Pendopharm, a division of Pharmascience Inc.

Executive Summary

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Glatect (glatiramer acetate subsequent entry non-biologic product [SEP]) followed the CDR Procedure and Submission Guidelines for Subsequent Entry Biologics (March 2014). Glatect is a non-biologic complex drug where the entire related structures of the molecule are active. As such, the properties cannot be fully characterized by physicochemical analysis. The CDR review team validated the information provided by the manufacturer regarding product information (Section 1), the indication under review (Section 2), the rationale for the reimbursement criteria requested by the manufacturer (Section 3), drug similarity (Section 4), and the comparative cost of the new product (Section 7). CDR reviewers provided a critical appraisal of the clinical evidence (Section 5) and the cost comparison (Section 7).

Product Information

Glatect is a subsequent entry product based on the originator product, glatiramer acetate (Copaxone), and was granted a Notice of Compliance (NOC) by Health Canada to decrease the frequency of clinical exacerbations and to reduce the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans in ambulatory patients with relapsing-remitting multiple sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain MRI.

The manufacturer is requesting that Glatect be reimbursed according to the current public drug plans' reimbursement criteria for glatiramer acetate, for both Copaxone-naive and Copaxone-experienced patients. The exact wording of the manufacturer's reimbursement request can be found in Section 3.1 Requested Reimbursement Criteria.

Clinical Evidence

The manufacturer-submitted information included one equivalence randomized controlled clinical trial that evaluated the efficacy of Glatect versus Copaxone (GATE GTR001 trial) with an open-label extension phase; and one phase I, controlled, randomized, double-blind replicate study to assess injection site reactions and tolerance of Glatect versus Copaxone (GTR002 trial) in healthy volunteers.

The GATE trial enrolled 796 patients to allow for a 12% dropout rate while maintaining a 92% power to show equivalence between Glatect and Copaxone in the primary outcome of the numbers of gadolinium-enhancing (GdE) lesions during months 7 through 9. The equivalence margin was calculated based on a historical pivotal trial of glatiramer acetate versus placebo where at least 50% of the effect over placebo would be maintained. This resulted in an equivalence margin with a lower limit of 0.727 and an upper limit of 1.375. Patients were randomized using an interactive voice/web response system (IXRS) through a computer-generated randomization list, stratified by geographical location and lesion count, with a ratio of 4.3:4.3:1 to receive Glatect, Copaxone, or placebo for a period of nine months. Patients, investigators, MRI personnel, and other study personnel were kept blinded until the end of the double-blind period. Glatect (20 mg in 1 mL), Copaxone (20 mg in 1 mL), and placebo (1 mL) were self-administered. All patients recorded a treatment compliance of 80% to 120%.

Baseline and demographic characteristics in the GATE trial were similar across treatment arms. The primary outcome in this study, total number of GdE lesions, was evaluated between months 7 through 9; the ratio of number of GdE lesions assessed during the evaluation period between Glatect and Copaxone was required to fall within the pre-defined equivalence margin. The design and conduct of the trial was meant to mimic Copaxone pivotal studies as much as possible. The proportion of patients who withdrew before the conclusion of the double-blind period was 7.0%, 9.2%, and 3.6% in the Glatect, Copaxone, and placebo groups, respectively. The most common reason for withdrawal was withdrawal of consent. Withdrawal due to adverse event was recorded as 2.0%, 0.6%, and 2.4% in the Glatect, Copaxone, and placebo groups, respectively.

The mean numbers of GdE lesions identified between months 7 through 9 were similar in the two active groups (0.45 in the Glatect group versus 0.41 in the Copaxone group) with a comparison ratio falling within the pre-defined equivalence margin of 0.727 to 1.375 (Glatect compared with Copaxone ratio = 1.095 [95% confidence interval (CI), 0.883 to 1.360]). Analysis using the per-protocol set produced a similar point estimate and 95% CI (ratio = 1.097 [95% CI, 0.880 to 1.368]), also falling within the pre-defined equivalence margin of 0.727 to 1.375.

The extension phase of the phase III study provides supportive, non-comparative evidence of the longer-term efficacy and tolerability of Glatect up to 15 months. Patients switched from Copaxone or continued on Glatect maintained similar levels of improvement, whereas patients switched to Glatect from placebo experienced an improvement (in GdE lesions) after three months that was then maintained at levels similar to the other two groups in subsequent measurements.

GTR002 (N = 20) was a controlled, randomized, double-blind replicate study to assess injection site reaction and tolerance of Glatect versus Copaxone in healthy volunteers. Participants had similar demographic characteristics and reported similar numbers of injection site reactions between the two treatment groups, with no reported serious adverse events. However, the study provided no power analysis, and thus it is uncertain if the lack of difference is accurate or due to lack of power.

The external validity of the GATE trial is limited by the lack of Canadian sites, lack of ethnic/racial diversity beyond white/Caucasians in the study population, and lack of patients older than 55. The generalizability of the results from GTR002 to the MS patient population is limited given that the study participants were healthy volunteers.

Potential Place in Therapy[a]

Multiple sclerosis is a common neurological disease in Canada, and is second only to trauma as a cause of neurological disability in adults younger than 50. Many lines of evidence support the idea that MS is caused by abnormal immune system activity, which produces relapsing and remitting episodes of neurological dysfunction due to foci of demyelination and axonal injury in the brain and spinal cord. In most patients with relapsing-remitting MS, recovery from an episode is incomplete, and over time, progressive, permanent functional impairment accumulates.

The first disease-modifying drugs for MS were introduced into clinical practice in the early 1990s. In the last decade in particular there has been an increasing number of drugs available, but in current Canadian practice, four drugs are

[a] This section is written by the Clinical Expert consulted on this review.

considered by most experts to be first-line therapy in treatment-naive MS patients: beta-interferon, glatiramer acetate, teriflunomide, and dimethyl fumarate. The efficacy of these agents is broadly similar, and the choice of drug for a given patient is largely determined by the mode of administration and side effects. Beta-interferon and glatiramer acetate (the "injectables") must be given by subcutaneous injection; whereas, teriflunomide and dimethyl fumarate are oral medications. There is at least a decade more experience with the "injectables," and in many clinics they are the treatments most likely to be offered to a new patient. Glatiramer acetate usually requires daily injections, while beta-interferon can be given on alternate days or even once a week. However, many clinicians and patients prefer glatiramer acetate, because patients typically experience considerably fewer flu-like side effects and less monitoring is required than the beta-interferon.

Glatect is being positioned by the manufacturer as equivalent in efficacy and side-effect profile to the established preparation of glatiramer acetate, Copaxone, but with a somewhat lower price. From the perspective of an individual patient with adequate insurance coverage, the potentially lower price of Glatect would have only a minor advantage. However, given the annual cost per patient of any of the first-line MS drugs (several thousand dollars per annum) and the prevalence of MS in Canada, a lower-cost glatiramer acetate preparation may have a positive effect on health care costs in Canada. There is likely to be some resistance from patients and perhaps clinicians to switching from Copaxone in patients who are doing well ("don't rock the boat") but, if less expensive, Glatect could potentially replace Copaxone in many or most treatment-naive MS patients who are currently prescribed Copaxone.

Cost comparison

At $37.82 per 20 mg/mL vial, the cost of subsequent entry glatiramer is 15% less than the Ontario Drug Benefit (ODB) Exceptional Access Program (EAP) list price of the originator product, leading to a savings of $2,436 per patient per year. The actual cost paid by Canadian public drug plans for the originator product may be lower than that listed on publicly available formularies, which would reduce the relative attractiveness of the submitted price of the subsequent entry product. Teva-glatiramer, made by the same manufacturer as the originator product, has received a Health Canada indication for the treatment of RRMS. When available, this will be a comparator of interest and, depending on its price, may further reduce the relative attractiveness of the submitted price of this subsequent entry product.

Conclusion

Overall, the manufacturer provided evidence from one phase III equivalency trial that enrolled treatment-naive MS patients to demonstrate similar efficacy and safety between the subsequent entry non-biologic complex product, Glatect, and the originator drug, Copaxone; the ratio of mean numbers of GdE lesions between months 7 through 9 fell within the pre-defined equivalence margin of 0.727 to 1.375 (Glatect compared with Copaxone ratio 1.095 [95% CI, 0.883 to 1.360]). Available data from the GATE trial extension phase suggest that patients who were switched from Copaxone to Glatect maintained the results achieved in the double-blind period. The evidence from the extension study, however, is limited due to the lack of a comparison group that was maintained on Copaxone.

At $37.82 per vial, the cost of subsequent entry glatiramer is 15% less than the ODB EAP list price of the originator product, leading to a savings of $2,436 per patient per year. Actual costs paid by plans for the originator product, as well as the approval and potential availability of Teva-glatiramer, may reduce the relative attractiveness of the submitted price of this subsequent entry product.

1. Product Information

1.1 Overview of the Subsequent Entry Non-Biologic Complex Drug

Characteristics	Manufacturer-Provided Details	
	GLATECT™ 20 mg/mL	COPAXONE© 20 mg/mL
Brand name:	Brand name	GLATECT™ 20 mg/mL
Non-proprietary name:	Non-proprietary name	Glatiramer acetate
Manufacturer:	Manufacturer	Pharmascience Inc.
Strength(s):	Strength	20 mg/mL
Dosage form:	Dosage form	Pre-filled syringe (1 mL)
Route of administration:	Route of administration	Subcutaneous injection
Drug Identification Number(s):	Drug Identification Number(s)	02460661
Therapeutic classification:	Therapeutic classification	92:20.00 Immunomodulatory Agents L03AX Other immunostimulants
Excipients	Excipients	Mannitol (40 mg) in sterile water for injection
[redacted]	[redacted]	[redacted]

Characteristics	Manufacturer-Provided Details	
	GLATECT™ 20 mg/mL	COPAXONE© 20 mg/mL
		[redacted]

[redacted]

GLATECT™ [b](glatiramer acetate) 20 mg/mL has the same quantitative and qualitative composition as COPAXONE® 20 mg/mL and is available as the same pharmaceutical dosage form. Both drug products are aqueous solutions supplied in a 1 mL single-use pre-filled syringe containing 20 mg/mL glatiramer acetate, to be used with a handheld reusable auto-injector intended to deliver daily subcutaneous doses of glatiramer to adult patients to facilitate self-injection and hence, patient compliance. Manufacturers of both products offer a patient assistance program including training, co-pay assistance (in jurisdictions where it is allowed) and reimbursement navigation.

Glatiramer is not a biologic as it is not derived from living cells. GLATECT™ 20 mg/mL is a Subsequent Entry Non-Biologic Complex Drug (SENBCD). A SENBCD is characterized by the following key attributes: it consists of a multitude of closely related structures; the entire complex is the active pharmaceutical ingredient; the properties cannot be fully characterized by physicochemical analysis; and the well-controlled, robust manufacturing process is fundamental to reproduce the product.[1]

Due to glatiramer's inherent complex nature, full characterization is not possible based on the current technology. Pharmaceutical equivalence is challenging to demonstrate and bioequivalence to COPAXONE® 20 mg/mL cannot be established (see section 4.3).

The regulatory process for subsequent entry glatiramer has varied by jurisdiction. In the European Union (EU), Synthon, who developed the subsequent entry glatiramer acetate and with whom Pharmascience is in partnership for the commercialization of GLATECT™ in Canada, submitted a hybrid application referencing clinical studies and experience with the innovator product. Although the product is not a biological medicinal product as such, Synthon followed a strategy similar to the dossier requirements of biosimilar applications and provided non-clinical and clinical data in addition to quality data, in support of similarity. In the US, Glatopa™, a subsequent entry glatiramer acetate product, was approved in 2015. It had been submitted by Sandoz as a standard generic through an Abbreviated New Drug Approval (ANDA) with the same indication as the innovator (COPAXONE® 20 mg/mL), i.e, for the treatment of patients with Relapsing Remitting Multiple Sclerosis (RRMS). Clinical data (including extrapolation data) were not required.

On March 11, 2015 Health Canada indicated during a Pre-NDS meeting that the data derived from the clinical plan based on the European Medicine Agency (EMA) Scientific Advice would be acceptable for filing a new drug submission (NDS) for GLATECT™ 20 mg/mL in Canada. A phase III therapeutic equivalence trial (GATE trial) was conducted to demonstrate the safety and efficacy of GLATECT™ 20 mg/mL versus COPAXONE® 20 mg/mL. The trial consisted of a 9-month randomised, placebo-controlled, double-blind period that looked at the equivalence of GLATECT™ 20 mg/mL vs. COPAXONE® 20 mg/mL in COPAXONE®-naïve patients with RRMS. This was followed by a 15-month open-label extension period in which patients could either continue on GLATECT™

[b] GLATECT ™ is a trademark of Pharmascience Inc.

20 mg/mL, or switch from placebo or COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL. The data were filed under the NDS category and included this Phase III clinical trial data in addition to quality and comprehensive non-clinical data.

Synthon has performed an extensive physicochemical and nonclinical characterization of its active substance to demonstrate that glatiramer acetate contained in GLATECT™ 20 mg/mL is of the same quality as the active substance contained in Canadian-, United States (US)- and European Union (EU)-sourced COPAXONE® 20 mg/mL.

The impurities that may be present in GLATECT™ 20 mg/mL include product-related impurities only (see Table 1). [redacted]

[redacted]

Table 1: Potential Impurities in Glatect™ 20 mg/mL

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] [redacted]

GLATECT™ 20 mg/mL is a sterile aqueous solution of glatiramer acetate polymer (20 mg/mL), contained in a single-use pre-filled syringe with the tonicity agent mannitol in water for injection. [redacted]

[redacted]

1.2 Overview of the Reference Product

A phase I study and a phase III trial were conducted with [redacted] COPAXONE® 20 mg/mL, respectively, along with the physicochemical, biological, and toxicology comparisons with the [redacted] reference products.

Due to the particular nature of GLATECT™ 20 mg/mL, to the lack of product specific guidance for SENBCD and to its similarity to a biosimilar product, the guidance related to subsequent entry biologics was used as basis to develop the application strategy in Canada. It should be noted that, as per the Health Canada's Guidance Document, *Information and Submission Requirements for Subsequent Entry Biologics*,[2] a non-Canadian reference biologic drug may be used if it can be confirmed that both the non-Canadian reference biologic drug and the Canadian reference biologic drug are marketed by the same innovator company or corporate entity.

As publicly documented, COPAXONE® 20 mg/mL, which is currently marketed by different divisions of TEVA, is available in 57 countries with an identical formulation.[3] Therefore, it would be unwarranted to conduct additional phase III studies with COPAXONE® 20 mg/mL sourced from each country. It should be noted also that several characterization studies were performed and have demonstrated that the active substance in COPAXONE® 20 mg/mL [redacted] is the same with respect to primary and higher order structures, physicochemical properties and biological activity. Finally, multiple characterizations studies were performed to compare GLATECT™ 20 mg/mL to the [redacted] COPAXONE® 20 mg/mL.

As GLATECT™ 20 mg/mL was being developed as therapeutically similar to COPAXONE® 20 mg/mL, COPAXONE® 20 mg/mL was selected as the active comparator for the phase III GATE trial (GTR001), and GLATECT™ 20 mg/mL was administered using the approved dosing regimen of COPAXONE® 20 mg/mL, i.e., 20 mg daily by subcutaneous (SC) injection for the duration of the trial.

COPAXONE® 20 mg/mL was approved in Canada in 1997 for the treatment of ambulatory patients with RRMS:

- To decrease the frequency of clinical exacerbations; and
- To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.

In 2009, it was also approved for the treatment of patients who have experienced a single demyelinating event, accompanied by abnormal MRI scans and are considered to be at risk of developing Clinically Definite MS (CDMS), after alternative diagnoses are excluded:

- To delay the onset of definite Multiple Sclerosis (MS);
- To decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans).

In August 2016, the COPAXONE® 20 mg/mL indication was modified and it is now indicated for the treatment of ambulatory patients with RRMS, including patients who have experienced a single demyelinating event and have lesions typical of MS on brain MRI:

- To decrease the frequency of clinical exacerbations
- To reduce the number and volume of active brain lesions identified on MRI scans.[4]

For the sake of completion, it is noted that, in August 2016, COPAXONE® 40 mg/mL, a new dose and strength, was authorized by Health Canada for three times-a-week treatment of ambulatory patients with RRMS to decrease the frequency of clinical exacerbations and to reduce the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans. [5]

2. Indications

2.1 Health Canada-Approved Indications

Indication(s)	Extrapolation
Treatment of ambulatory patients with relapsing remitting multiple sclerosis (RRMS), including patients who have experienced a single demyelinising event and have lesions typical of multiple sclerosis on brain MRI: • To decrease the frequency of clinical exacerbations • To reduce the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans	No

2.2 Proposed Indications under Review by Health Canada

Proposed Indication(s)	Extrapolation
NA	NA

3. Manufacturer's Requested Reimbursement Criteria

3.1 Requested Reimbursement Criteria

The requested reimbursement criteria is listed in the table below.

Requested Reimbursement Criteria for Indications to be Reviewed by the CADTH Common Drug Review
List with each public plan's current listing criteria for glatiramer, for treatment of COPAXONE®-naïve and COPAXONE®-experienced patients.

3.2 Rationale for Requested Reimbursement Criteria

In the first part of the phase III GATE trial, the 9-month double-blind period compared GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, to placebo, in COPAXONE®-naïve patients with RRMS. If the pooled GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL groups were better than placebo, then the GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL groups were compared. The trial was conducted in a representative RRMS population with clinically and radiographically active disease. The treatment groups were comparable for demographic and other baseline and disease characteristics. The results of this 9-month period demonstrated that GLATECT™ 20 mg/mL is effective and similar to COPAXONE® 20 mg/mL in reducing T1-GdE lesions in RRMS. This supports the listing criteria for GLATECT™ 20 mg/mL for the treatment of COPAXONE®-naïve patients.[6]

During the 15-month open-label part of the trial, patients who received GLATECT™ 20 mg/mL during the first 9-month study could continue on GLATECT™ 20 mg/mL and patients who had received either COPAXONE® 20 mg/mL or placebo during the double-blind phase had the opportunity to switch to GLATECT™ 20 mg/mL. In those patients switched from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL, the effect established on MRI parameters during the 9-month double-blind phase of the study was maintained.[8] This supports the listing criteria for GLATECT™ 20 mg/mL for the treatment of patients previously treated with on COPAXONE® 20 mg/mL.[7]

This supports a listing for GLATECT™ 20 mg/mL with each drug plan's current listing criteria for glatiramer for COPAXONE®- naïve and COPAXONE®-experienced patients.

4. Drug Similarity

To establish similarity of the active ingredient, an extensive physicochemical and biological characterization program was developed. The characterization program comparing the active substance present in GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL included the following experiments and assays:

- [redacted]

[redacted]

[redacted]

Table 2: Comparison of the Physicochemical Properties and Biological Activity of Glatect™ 20 Mg/Ml and Copaxone® 20 Mg/Ml

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Even though it has been demonstrated that both GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL are similar with regard to primary and higher order structures as well as biological activity, it must be noted that the mechanism of action of glatiramer remains unknown and that the exact amino acid sequences that are responsible for clinical efficacy are unknown. It is currently not possible for any manufacturer to identify and quantify all of the molecules present in glatiramer acetate due to the heterogeneity and to the complex nature of polypeptide mixture.

4.2 Pivotal Clinical Studies

The following clinical trials were included in the development program for GLATECT™ 20 mg/mL:

- GTR002 trial: although not a pivotal clinical trial this phase I study is included as part of the GLATECT™ 20 mg/mL clinical program. The study compared the safety and tolerability of GLATECT™ 20 mg/mL to COPAXONE® 20 mg/mL (US sourced) in healthy volunteers;
- The Glatiramer Acetate Clinical Trial to Assess Equivalence With COPAXONE® (GATE; GTR001): a phase III, randomized, double-blind, placebo-controlled, parallel group, 9-month, equivalence trial comparing the efficacy, safety and tolerability of GLATECT™ 20 mg/mL to EU-sourced COPAXONE® 20 mg/mL in COPAXONE®-naïve patients with RRMS. This was followed by a 15-month open-label period in which patients could either continue on GLATECT™ 20 mg/mL treatment or switch from placebo or COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL. This extension period evaluated the efficacy, safety and tolerability of switching to GLATECT™ 20 mg/mL treatment in COPAXONE®-experienced and evaluated the long-term (2 years) treatment effects of GLATECT™ 20 mg/mL.

Table 3 provides an overview of the clinical trials.

Table 3: Clinical Trials in the Development Program for Glatect™ 20 Mg/Ml

Study Name	Design	Objectives	Population
GTR002 trial	Phase I safety and tolerability trial	To compare the occurrence of local injection site reactions (LISRs) of a single-dose of subcutaneously administered GLATECT™ 20 mg/mL versus COPAXONE® 20 mg/mL (Teva Pharmaceuticals, US)	Healthy volunteers (n=20)
GATE (GTR001) trial	Phase III, randomized, double-blind, placebo-controlled, parallel group, 9-month, equivalence trial, followed by an open-label 15-month extension phase in which patients could either continue on GLATECT™ 20 mg/mL treatment or switch from placebo or COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL	Double-blind 9-month phase: To compare the efficacy and safety and tolerability of GLATECT™ 20 mg/mL to EU-sourced COPAXONE® 20 mg/mL in COPAXONE® -naïve patients with RRMS Open label 15-month extension phase: To evaluate efficacy, safety and tolerability of switching COPAXONE® -experienced patients.to GLATECT™ 20 mg/mL treatment Total study: To evaluate efficacy, safety and tolerability of long-term (2 years) treatment with GLATECT™ 20 mg/mL	Double-blind 9-month phase: Patients (n=796) with a diagnosis of RRMS (2010 McDonald criteria), age of 18 to 55 years, a score of 0 to 5.5 on the EDSS, at least one clinically documented relapse in the previous 12 months and at least one T1-GdE lesion on the screening MRI. Open label 15-month extension phase: All patients completing the double-blind phase of the study on the assigned treatment were eligible to continue in the 15-month extension study (n=728)

4.2.1 GTR002 trial

a) Study Characteristics

GTR002 trial was a phase I safety and tolerability trial in healthy volunteers to compare the occurrence of local injection site reactions (LISRs) of a single-dose of subcutaneously administered GLATECT™ 20mg/mL versus COPAXONE® 20mg/mL, the reference product (Teva Pharmaceuticals, US). Table 4 summarizes the study characteristics.

Table 4: Study Characteristics of GTR002 Trial for Glatect™

Characteristics		Details for GTR002
Study Design	**Objective**	To compare the occurrence of local injection site reactions (LISR) for GLATECT™ 20 mg/mL administered subcutaneously (SC) to COPAXONE® 20 mg/mL administered SC, during short-term exposure in healthy [redacted] male and female volunteers.
	Blinding	Randomized, double-blinded
	Study period	[redacted]
	Study centres	One centre (Toronto, Ontario)
	Design	Single-dose, four-period, two-sequence, two-treatment, replicate study. Each subject received a total of 2 treatments by the end of the study and each treatment was given twice.
Study Population	**Randomized (N)**	20
	Inclusion criteria	[redacted]
	Exclusion criteria	[redacted]
Drugs	**Intervention**	A. GLATECT™ 20 mg/mL administered subcutaneously; [redacted] Subjects received study drugs according to one of the two injection sequences A-B-A-B or B-A-B-A.
	Comparator(s)	B. COPAXONE® 20 mg/mL administered subcutaneously; [redacted] Subjects received study drugs according to one of the two injection sequences A-B-A-B or B-A-B-A.
Duration	**Run-in**	The study consisted of 4 study periods. Each study period consisted of a single-dose injection of either the test or the reference product. There was a washout period of 4 days between each injection.
	Treatment	Subjects were confined to the clinic from at least 4 hours prior to injection until at least 8 hours after injection, for a total of at least 12 hours for each study period.
	Follow-up	Subjects were required to return to the clinic for the 24-hour assessment after each injection.

Characteristics		Details for GTR002
Outcomes	**Primary End Point(s)**	LISR assessment was conducted by the subject and by a nurse. A. **Subject**: Self-assessment for five categories of LISR (pain, itching, redness, swelling and lumps), using a diary, of (a) absence or presence of LISR; and (b) severity of LISR, at all indicated time points [The time points for subject self-assessment were immediately (within the first 30 seconds) after each injection and 5 min (+1 minute), 1 hour (±2 minutes), 8 hours (±2 minutes) and 24 hours (±2 minutes) after each injection.] B. **Nurse:** assessment of the injection site was restricted to redness, swelling and lumps, and was categorized as not present, mild, moderate and severe. Time points were immediately after injection (within 30 seconds) and 5 min (+1 minute), 1 hour (±2 minutes), 8 hour (±2 minutes) and 24 hours (±2 minutes) after injection.
	Other End Points	Safety: evaluated by adverse events reported by subjects who received a drug treatment and by vital signs measurements: blood pressure and heart rate, obtained pre-dose (at check-in, within 4 hours prior to injection) and at 1.0 and 8.0 hours after injection in each study period. Clinical laboratory tests (including hematology, serum chemistry, urine analysis, and serum human Chorionic Gonadotrophin (hCG) [females only] tests), physical examinations and electrocardiograms were performed to assure subject safety at entry and upon completion of the trial.
Notes	**Publications**	• Oberyé J, van den Tweel E, Mulder M, Voortman G, Hooftman L. Randomized, double-blind, cross-over trial of GTR (generic glatiramer acetate) in healthy volunteers shows similar tolerability and safety to Copaxone®; presented at European Neurological Society 2012. • Study 1308

Intervention and Comparators

The study consisted of four study periods. Each study period consisted of a single-dose injection of either GLATECT™ 20 mg/mL or COPAXONE® 20 mg/mL. There was a washout period of 4 days between each injection. Participants were confined to the clinic from at least 4 hours prior to injection until at least 8 hours after injection, for a total of at least 12 hours for each study period. Participants were required to return to the clinic for the 24-hour assessment after each injection.

Outcomes

LISRs were self-assessed by the participants for five categories of LISR (pain, itching, redness, swelling and lumps), using a diary.

The participants' self-assessment consisted of two parts:

- Presence or absence of LISRs: The participant had to indicate the presence or absence of any of the five categories of LISRs at all indicated time points.
- Severity of the LISRs during the prior period was to be qualitatively scored as none, mild, moderate or severe for all indicated time points except for the immediately after injection time point. The severity was assessed for the following periods at the time-points indicated below:
  - 5 minutes: from immediately after injection to 5 minutes after injection
  - 1 hour: from 5 minutes after injection to 1 hour after injection
  - 8 hours: from 1 hour after injection to 8 hours after injection
  - 24 hours: from 8 hours after injection to 24 hours after injection

The time points for participant self-assessment were immediately (within the first 30 seconds) after each injection and 5 min (+1 minute), 1 hour (±2 minutes), 8 hours (±2 minutes) and 24 hours (±2 minutes) after each injection.

The LISR assessment of the nurse was performed immediately after injection (within 30 seconds) and 5 min (+ 1 minute), 1 hour (± 2 minutes), 8 hour (± 2 minutes) and 24 hours (± 2 minutes) after injection. The nurse assessment of the injection site was restricted to redness, swelling and lumps, and was categorized as not present, mild, moderate and severe.

Statistical Analyses

ANOVA analysis was performed to compare the total number of LISRs per subject as reported by the subjects and as reported by the nurse for subcutaneously administered GLATECT™ 20 mg/mL to subcutaneously administered COPAXONE® 20 mg/mL combined for all time points and at any time point (immediately after injection and at 5 min, 1 hour, 8 hours and 24 hours) after injection of study medication.

b) Results

Baseline Characteristics

The following table provides the baseline characteristics for the 20 subjects included in the data set. There were 12 males and 8 females.

Table 5: Demographics For Subjects Included In Data Set Of Gtr002 Trial For Glatect™

	Age	Height (cm)	Weight (kg)	BMI	Race/Ethnicity	
Mean	40	168.0	72.7	25.6	White	5
+/- SD	11	8.3	12.3	2.8	Black	9
Median	42	166.0	71.7	25.9	Native	1
Range	21-55	150.6-185.6	50.4-102.5	20.6-29.8	Hispanic/ Latino	5

Patient Disposition

20 subjects enrolled in the study

- 17 subjects completed all 4 periods
- 3 subjects completed the first 2 periods
  - [redacted]

[redacted]

Results

For all time points combined after injection of GLATECT™ 20 mg/mL, the study drug, a total of 92 LISRs (9.9%) were reported to be present out of the 925 possible LISR reports. 78 LISRs (8.4%) were reported to be present out of a total of 925 possible reports after injection of COPAXONE® 20 mg/mL, the reference product.

Both the results from the subjects' self-assessment and the results from the nurse assessment showed that a statistically significant difference could not be demonstrated between the occurrence of LISRs after administration of GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, the reference product, for all time points combined, immediately after injection and at 5 minutes, 1 hour, 8 hours and 24 hours after injection, respectively (see Tables 7 and 8).

In both groups, the highest number of LISRs was found immediately after injection and 5 minutes and one hour after injection. Thereafter (at 8 hours and 24 hours after injection), incidentally a LISR was observed.

From the LISR subjects' assessments, the estimated mean LISR score *for all time points combined* was [redacted] for GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, the reference product, respectively. Based on the results of the ANOVA analysis performed, it could not be demonstrated that these mean scores were significantly different at alpha= 0.05 [redacted].

- The estimated mean LISR score *immediately after* injection was [redacted] for GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, the reference product, respectively [redacted].
- The estimated mean LISR score *after 5 minutes* was [redacted] for GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, the reference product, respectively [redacted].
- *After 1 hour*, the estimated mean score was [redacted] for GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, the reference product, respectively [redacted].

Table 6: COMPARISON ON LISRS REPORTED BY THE SUBJECTS BETWEEN GLATECT™20 Mg/Ml AND COPAXONE® 20 Mg/Ml

Time Point	Treatment	N	[redacted]	[redacted]	[redacted]
LISRs Combined All Time Points	GLATECT™ 20 mg/mL	185	[redacted]	[redacted]	[redacted]
LISRs Combined All Time Points	COPAXONE® 20 mg/mL	185	[redacted]		
LISRs Immediate after Injection	GLATECT™ 20 mg/mL	37	[redacted]	[redacted]	[redacted]
LISRs Immediate after Injection	COPAXONE® 20 mg/mL	37	[redacted]		
LISRs 5 Minutes after Injection	GLATECT™ 20 mg/mL	37	[redacted]	[redacted]	[redacted]
LISRs 5 Minutes after Injection	COPAXONE® 20 mg/mL	37	[redacted]		
LISRs 1 Hour After Injection	GLATECT™ 20 mg/mL	37	[redacted]	[redacted]	[redacted]
LISRs 1 Hour after Injection	COPAXONE® 20 mg/mL	37	[redacted]		
LISRs 8 Hours after Injection	GLATECT™ 20 mg/mL	37	[redacted]	[redacted]	[redacted]
LISRs 8 Hours after Injection	COPAXONE® 20 mg/mL	37	[redacted]		
LISRs 24 Hours after Injection	GLATECT™ 20 mg/mL	37	[redacted]	[redacted]	[redacted]
LISRs 24 Hours after Injection	COPAXONE® 20 mg/mL	37	[redacted]		

*Significant at alpha=0.05 (P-value <=0.05)

CI: Confidence limits; LISR: local injection site reactions; LSMEAN: Least Squares mean

Considering subjects' severity scoring over all periods and all LISR categories, pain was reported with the highest severity grading. Of the 148 pain reports per treatment group, moderate and severe pain were scored [redacted] times after GLATECT™ 20 mg/mL and [redacted] times after COPAXONE® 20 mg/mL administration, respectively. Of the other LISR categories only moderate redness and moderate itching was reported [redacted] at 5 minutes after receiving GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, respectively.

Table 7: Comparison On Lisrs Reported By The Nurse Between Glatect™ 20 Mg/Ml And Copaxone® 20 Mg/Ml

Time Point	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
LISRs Combined All Time Points	GLATECT™ 20 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]
LISRs Combined All Time Points	COPAXONE® 20 mg/mL	[redacted]	[redacted]		
LISRs Immediate after Injection	GLATECT™ 20 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]
LISRs Immediate after Injection	COPAXONE® 20 mg/mL	[redacted]	[redacted]		
LISRs 5 Minutes after Injection	GLATECT™ 20 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]
LISRs 5 Minutes after Injection	COPAXONE® 20 mg/mL	[redacted]	[redacted]		
LISRs 1 Hour After Injection	GLATECT™ 20 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]
LISRs 1 Hour After Injection	COPAXONE® 20 mg/mL	[redacted]	[redacted]		
LISRs 8 Hours After Injection	GLATECT™ 20 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]
LISRs 8 Hours After Injection	COPAXONE® 20 mg/mL	[redacted]	[redacted]		
LISRs 24 Hours after Injection	GLATECT™ 20 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]
LISRs 24 Hours after Injection	COPAXONE® 20 mg/mL	[redacted]	[redacted]		

*Significant at alpha=0.05 (P-value <=0.05)

[redacted]

CI: Confidence limits; LISR: local injection site reactions; LSMEAN: Least Squares mean

No serious adverse events (AEs) were reported during the conduct of this study.

Most reported AEs (105 events; 96.2%) were mild in nature. Four (4) events (2 for each treatment) were of moderate intensity. These were injection site pain (3 instances) and vomiting (1 instance).

After both treatments, the most frequently reported events were local reactions related to the injection (54 out of 56 reported events after GLATECT™20 mg/mL and 45 out of 53 reported events after COPAXONE® 20 mg/mL, the reference product). Of the injection site related events, injection site pain was reported most frequently: [redacted] after GLATECT™20 mg/mL and COPAXONE®
20 mg/mL, the reference product, respectively.

Besides the injection site related AEs, which were all considered probably related to GLATECT™
20 mg/mL by the investigator, the following AEs were considered by the investigator as possibly or probably related to GLATECT™ 20 mg/mL:

- somnolence, reported once after both GLATECT™20 mg/mL and COPAXONE® 20 mg/mL treatment; and
- nausea, vomiting, dermatitis, blood pressure decreased and feeling cold, reported once each after COPAXONE® 20 mg/mL treatment.

Apart from two abnormal vital sign measurements that were reported as AE (blood pressure decreased possibly related; blood pressure Increased-not related), no clinically significant changes in vital signs were observed during the clinical trial.

4.2.2 GATE Trial (GTR001)

The GATE trial was designed to include a patient population that closely resembles the population selection criteria for the clinical trials that supported the initial regulatory approval of COPAXONE®
20 mg/mL. The most relevant difference between the GATE trial and the historical clinical trial with COPAXONE® 20 mg/mL was the application of the most recent update (2010) to the McDonald criteria in the GATE trial to be compliant with current practices and standards. The inclusion criteria required eligible subjects to have at least one relapse during the preceding year and to present with at least one T1-GdE lesion on screening MRI.

Please see Table 1.1 in Appendix 1 for complete details about the 2010 McDonald criteria used in the GATE trial. Key highlights of this study can be found in the Clinical Overview section (p. 9-18) of the Health Canada submission.

a) Study Characteristics

The GATE study was a randomized, multicentre, double-blind, active and placebo-controlled phase III, 9- month equivalence clinical trial comparing the efficacy and safety and tolerability of GLATECT™ 20 mg/mL to COPAXONE® 20 mg/mL in patients not previously exposed to COPAXONE®. All patients who completed the double-blind part could receive GLATECT™ 20 mg/mL for up to 15 months during the open-label part. The open-label, 15-month extension phase evaluated the efficacy, safety and tolerability of switching from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL in patients previously treated with COPAXONE® 20 mg/mL and evaluated the long-term (2 years total) treatment effects of GLATECT™ 20 mg/mL. This phase III trial was designed to demonstrate that GLATECT™ 20 mg/mL is clinically similar to the originator brand glatiramer acetate (COPAXONE® 20 mg/mL) product, as measured by imaging and clinical end points, safety, and tolerability in patients with RRMS. Table 9 provides a summary of the study characteristics.

Table 8: Study Characteristics Of The Gate Trial (Gtr001) For Glatect™ 20 Mg/Ml

Characteristics		Details for the GATE Trial (GTR001)
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	During the 9-month double-blind part [multi-national, multi-centre, randomized, active- and placebo-controlled, parallel]
	Study period	Double-blind part: 2011-10-26 to 2013-12-02 Open-label part: 2012-08-14 to 2015-01-22
	Study centres	A total of [redacted] investigational sites were initiated to participate in the trial. Patients were screened at [redacted] investigational sites in the following countries: [redacted].
	Design	Equivalence study
Study Population	**Randomized (N)**	796 [A total of 1549 subjects were screened, 796 subjects were randomized and 753 subjects were screen failures.]
	Inclusion criteria	Experienced at least one relapse in the year before first screening assessment; At least one T1-weighted Gadolinium Enhancing (T1-GdE) lesion on routine brain MRI taken within 3 months of starting screening or on screening brain MRI (as confirmed by central imaging laboratory).
	Exclusion criteria	Any life-threatening, medically unstable or otherwise clinically significant condition or findings other than MS, in particular neoplastic disease, seizure disorders, or psychiatric disease; positive laboratory test results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) at screening; having been treated with or having received: • ***at any time***: glatiramer acetate, cladribine, rituximab, cyclophosphamide, alemtuzumab or

Characteristics		Details for the GATE Trial (GTR001)
		other immunosuppressive treatments with effects potentially lasting for more than 6 months; total lymphoid irradiation or bone marrow transplantation; • ***within 1 year before screening***: mitoxantrone, but patient could not be enrolled when mitoxantrone was taken at a cumulative lifetime dosing above 100 mg/m^2; • ***within 6 months before screening***: fingolimod, immunoglobulins and/or monoclonal antibodies (including natalizumab), leflunomide, or putative MS treatments; chronic oral or injected corticosteroids or injected adrenocorticotropic hormone (ACTH) (more than 30 consecutive days); • ***within 3 months before screening***: azathioprine, methotrexate; plasma exchange; any other experimental intervention, in particular experimental drugs; • ***within 1 month before screening***: interferon-β 1a or 1b; short-term oral or injectable corticosteroids for treatment of a relapse; short-term ACTH.
Drugs	**Intervention**	GLATECT™ 20 mg/mL administered daily by SC injection
	Comparator(s)	COPAXONE® 20 mg/mL administered daily by SC injection; or placebo (1 mL solution for injection containing the excipient mannitol and water for injection)
Duration	**Run-in**	None
	Treatment	9-month (double bind part) + 15-month (open-label part) [total: 2 yrs]
	Follow-up	None
Outcomes	**Primary End Point(s)**	Total number of T1-GdE lesions (i.e., the cumulative number of new and persisting gadolinium-enhancing lesions) during months 7 through 9
	Other End Points	**Double-blind 9-month phase:** Annualized relapse rate; Expanded Disability Status Scale (EDSS) score change from baseline to 9 months; cumulative combined unique active lesions from 7 through to 9 months; change in T2-weighted hyperintense lesion number and volume from baseline to 9 months; change in nonenhancing T1-weighted hypointense lesion volume from baseline to 9 months; percentage change in normalized brain volume from baseline to 9 months; and proportion of participants who were free of disease activity at 9 months. **Open label 15-month extension phase:** Number of T1-GdE lesions at 12, 18 and 24 months; change in T2 lesion number and volume from open-label baseline to 12, 18 and 24 months; change in T1 hypointense lesions volume from open-label baseline to 12, 18 and 24 months; change in brain volume from open-label baseline to 18 months; Annualized Relapse Rate (ARR); and EDSS change from open-label baseline to 12, 18 and 24 months. **Total study (2 years):** Number of T1-GdE lesions at 7, 8, 9, 12, 18 and 24 months; change in T2 lesion number and volume from baseline to 7, 9, 12, 18 and 24 months; change in T1 hypointense lesions volume from baseline to 9, 12, 18 and 24 months; change in brain volume from baseline to 9 and 18 months; ARR; and EDSS change from baseline to 9, 12, 18 and 24 months.
Notes	**Publications**	**Double-blind 9-month study:** • has been published: Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberyé J, et al; Glatiramer Acetate Clinical Trial to Assess Equivalence With COPAXONE® 20 mg/mL (GATE) Study Group. Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial. JAMA Neurol. 2015;72(12):1433-41.

Characteristics	Details for the GATE Trial (GTR001)
	• Identifier: NCT01489254 **The 15-month extension study:** • has been accepted for publication: Selmaj K, Barkhof F, Belova AN, Wolf C, van den Tweel ER, Oberyé JJ, Mulder R, Egging DF, Koper NP, Cohen JA; GATE study group. Mult Scler. 2017 Jan 1:1352458516688956. doi: 10.1177/ 1352458516688956. [Epub ahead of print] • Two posters (Poster 522, Poster 1050) were presented at the European Committee for Treatment and Research in Multiple Sclerosis in Spain in 2015.

Intervention and Comparators

Trial treatments were glatiramer acetate (GLATECT™ or COPAXONE®) 20 mg/mL or placebo administered daily by SC injection. Each product was provided in pre-filled, single-dose syringes with identical appearance. Patients were trained in self-injection techniques. Use of a device for self-injection was allowed after appropriate training.

On the first day of the double-blind part and on the first day of the open-label part, a healthcare professional supervised the self-injection of the product and observed the patient for at least
30 minutes afterwards. Patients were advised to select different injection sites each day, in order to reduce the chances of any irritation or pain at the site of the injection. Areas for self-injection included the abdomen, arms, hips and thighs. The patients were instructed to adhere strictly to the once-daily dosing scheme and not to take any extra injections to catch up for missed injections. An instructional brochure for self-injection was given to each patient. During the double-blind part and the open-label extension part, paper diaries were given to each patient to record the daily injections and local tolerability reporting.

A European-sourced COPAXONE® 20 mg/mL was used in the trial (please see justification in section 1.2). The summary information for each product used in the trial is provided in Table 10.

Table 9: Overview Of The Products Used In The Gate Trial (Gtr0001)

Test Product:	GLATECT™ (glatiramer acetate, 20 mg/mL solution for injection, pre-filled syringe)		
Formulation:	Prefilled syringe with 1 mL solution for injection containing 20 mg glatiramer acetate, the excipient mannitol and water for injection		
Manufactured by:	[redacted]		
Manufactured for:	[redacted]		
Batch number (expiry date)	[redacted]	[redacted]	[redacted]
Reference Product:	COPAXONE® 20 mg/mL (glatiramer acetate)		
Formulation:	Prefilled syringe with 1 mL solution for injection containing 20 mg glatiramer acetate, the excipient mannitol and water for injection		
Manufactured by:	TEVA Pharmaceuticals		
Country of origin:	[redacted]		
Batch number (expiry date)	[redacted]	[redacted]	[redacted]

Reference Product:	Placebo		
Formulation:	Prefilled syringe with 1 mL solution for injection containing the excipient mannitol and water for injection, but not the active ingredient		
Manufactured by:	[redacted]		
Manufactured for:	[redacted]		
Batch number (expiry date)	[redacted]	[redacted]	[redacted]

During the trial, concomitant medication was to be administered only when medically indicated. Symptomatic medication prescribed to a patient prior to the trial could continue to be administered during the trial provided the dose was optimized and stable before the study treatment began. Any concomitant medication (including herbal medication and vitamins) was to be recorded in full detail (drug, dose, start and stop dates, reason for concomitant medication) in the electronic case report form. The use of concomitant medication was to be related to the documented medical history, an adverse event experienced by the patient, or as prophylactic treatment.

With the exception of short-term injectable corticosteroids to treat relapse(s), medications or treatments described in the exclusion criteria were prohibited from the screening visit until the conclusion of the patient's participation in the trial. These included:

- At any time, glatiramer acetate, cladribine, rituximab, cyclophosphamide, alemtuzumab or other immunosuppressive treatments with effects potentially lasting for more than 6 months;
- within 1 year before screening, mitoxantrone (but patient could not be enrolled when mitoxantrone was taken at a cumulative lifetime dosing above 100 mg/m^2);
- within 6 months before screening: fingolimod, immunoglobulins
- within 3 months before screening: azathioprine, methotrexate;
- within 1 month before screening: interferon-β 1a or 1b; short-term ACTH.

Outcomes

Efficacy outcomes

Please see Table 11 for the definition and measurements of the efficacy outcomes.

The primary objective of GATE trial was to demonstrate that the efficacy of GLATECT™ 20 mg/mL is equivalent to Copaxone® in patients with RRMS, as measured by the number of gadolinium-enhancing (GdE) lesions on T1-weighted MRIs during months 7 to 9. The primary endpoint was GdE lesions, as this endpoint has been shown to be treatment-sensitive in RRMS trials and to predict effects on clinical outcomes. Recent meta-analyses further demonstrate that the effects of MS treatments, as measured by MRI endpoints, predict effects on clinical outcomes such as relapse rate[8,9,10] in the typical 2-year trials for regulatory approval. Using a highly sensitive endpoint is important in shortening the length of the double-blind treatment period and minimizing the risk to patients assigned to receive placebo. The use of MRI markers as primary endpoints in clinical trials of treatments for MS can be considered in specific situations, such as in trials testing generics or biosimilars and have accordingly been adopted by the EMA in the guideline on similar biological medicinal products containing interferon beta.[11]

Pivotal clinical trials of novel therapeutic agents in patients with RRMS routinely have relapse rate and/or changes in Expanded Disability Status Scale (EDSS) as primary outcome measures and MRI parameters as secondary outcomes. In clinical trials with COPAXONE® 20 mg/mL, changes in EDSS were small and the relapse rates were low (generally less than 1 relapse per patient-

year).[12,13,14] In contrast, the number of T1-GdE lesions observed in the GATE trial was 1.5 per month, making it a more sensitive endpoint.[6]

a) Magnetic resonance imaging (MRI): During the double-blind part, MRIs were obtained on Day 1 prior to the first injection of study drug and during trial visits at 7, 8 and 9 months. The Day 1 MRI assessment could be done up to 2 days before the other Day 1 assessments provided it was within the overall visit window. Other MRI scans could be obtained 2 days before or after the other assessments of the respective visit provided they were within the overall visit window. The MRI at 9 months was to be taken prior to the first injection of GLATECT™ 20 mg/mL for the open-label part and was used as the baseline for the open-label part. During the open-label part, MRIs were obtained within 3 days before or after scheduled visits at 12, 18 and 24 months to allow the results of the estimated glomerular filtration rate as assessed by the central laboratory to be available (if applicable).

Gadolinium (Gd) was the contrast agent for MRI. It was administered as an intravenous infusion of mmoL/kg.

Identification of T1-GdE lesions was done by means of a double read by 2 independent, qualified, expert imaging readers.

b) Neurological Examination and Expanded Disability Status Scale (EDSS): A complete neurological examination was performed by a trained examining neurologist at screening and the time points indicated in the schedules of visits. The neurological examination involved the following functional systems: visual, brainstem, pyramidal, cerebellar, sensory, bowel, bladder and cerebral plus gait. Results of this examination were documented in the patient's medical and/or trial chart.

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.[15] Based on the standard neurological examination, the functional systems (plus the category "other") are rated. These ratings are then used in conjunction with observations and information concerning gait and use of assistive devices to rate the EDSS.

The EDSS score was measured at screening, baseline, and 6 and 9 months.

c) Relapse Assessment: An MS relapse was defined as the appearance of one or more new neurological symptoms or the reappearance of one or more previously experienced neurological symptoms. The neurological deterioration had to last at least 24 hours, occur in the absence of fever and start at least 30 days after the onset of any previous confirmed relapse. Fever was defined as a body temperature measured either axillary, orally or intraauriculary of > 37.5°C or > 99.5°F. An event was counted as a relapse only when the subject's symptoms were accompanied by objective changes in the neurological examination corresponding to an increase of at least 0.5 points on the EDSS or 1 grade in the score of 2 or more Functional Systems (FS) or 2 grades in one FS. A change in bowel/bladder or cognitive function could not be solely responsible for the changes in the EDSS or the FS.

Table 10: Definitions And Measurements

- **Relapse** was defined as new or recurring neurological symptoms, without fever or infection, lasting at least 24 hours and accompanied by new objective neurological findings on the examining neurologist's evaluation.
- **Sustained EDSS score change** was defined as at least a 1.0-point increase from a baseline score of 1.0 or higher or at least a 1.5-point increase from a baseline score of 0, confirmed at 3 months.
- The **combined unique active lesions** were new gadolinium-enhancing lesions or new or enlarged T2-weighted hyperintense lesions without double counting.
- **Disease activity free** was defined as an absence of the following: relapse, sustained EDSS score change, or new or enlarged T2-weighted hyperintense or gadolinium-enhancing lesions.

Safety outcomes

Safety assessments included monitoring of adverse events, local injection site reactions, vital signs, and laboratory test results. Neurological symptoms related to confirmed relapses and local injection site reactions recorded in the tolerability diaries were not additionally reported as adverse events.

Safety assessments were performed at screening, baseline, and 1, 3, 6, and 9 months.

Safety variables included:

- the number of patients with any adverse event (AE), and any AE that was of severe intensity, related to the study drug, led to discontinuation of the study drug, led to withdrawal from the trial, resulted in death or was any other serious adverse event (SAE);
- the duration (number of days) and extent (in mg) of exposure to the study drug;
- the type, frequency, severity and causality of treatment-emergent AEs;
- absolute values and changes from baseline in clinical laboratory tests;
- the number and percent of patients with clinically notable laboratory abnormalities;
- the number and percent of patients with clinically notable abnormalities in vital signs;
- changes from baseline in physical examinations using shift tables;
- the number and percent of patients using concomitant medications;
- LISR scores recorded at 5 minutes and 24 hours after injection of the study drug.

Local tolerability scoring was conducted during four periods of 14 injections each, starting at the time points indicated in the flow chart (i.e. Day 1, Month 3, Month 9 [starting with the first injection of the open-label part] and Month 12). Results were reported in the dosing and local tolerability diaries.

Tolerability of the injection was assessed by scoring:

- Presence or absence of LISRs: patients scored the presence or absence of pain, redness, swelling, itchiness and lumps at the injection site at 5 minutes and at 24 hours after injection (i.e. just prior to the next injection).
- Severity of LISRs: patients scored the severity (i.e. intensity of pain, redness, swelling, itchiness and lumps) of all LISRs over the preceding period from the moment of injection up to 5 minutes afterwards, and from 5 minutes after injection up to 24 hours after injection) as “None”, ”Mild”, “Moderate” or “Severe”. When “None” was scored, this meant that no reaction occurred during the entire preceding interval.

Routine laboratory tests were conducted at screening and at the various time point visits during the double-blind part as well as the open-label part of the trial. Values the investigator considered to be clinically significant were reported as adverse events. Clinical laboratory tests included: hematology, blood chemistry, urinalysis, and urine pregnancy test.

Vital signs included blood pressure, heart rate and body temperature (axillary, orally or intraauriculary). At baseline (Day 1), vital signs were recorded before injection of the study drug (GLATECT™ 20 mg/mL, COPAXONE® 20 mg/mL, or placebo). At other time point visits throughout the trial, vital signs were recorded independently of the injection timing.

Other assessments:

a) Anti-glatiramer Antibodies: Blood samples to test for anti-glatiramer antibodies were collected at various time points during the study.

b) Biomarkers: Blood samples to test for biomarkers to explore the effects of therapy on different cytokine levels and to evaluate whether treatment failure or success correlates to these cytokine levels were collected at the first day and at the 9-month point of the double-blind part and at the 24-month point of the open-label part of the trial.

Statistical Analyses

Summary statistics for continuous variables consisted of the number of patients with a non-missing value of the variable (n), mean, standard deviation, median, minimum and maximum unless otherwise stated. Summary statistics for categorical variables were count and percentage based on the number of patients in a treatment group and the selected analysis population.

Unless otherwise stated, all statistical tests were performed using 2-sided tests at the 5% significance level. P-values below 0.001 were displayed as <0.001.

Based on the European/Canadian Glatiramer Acetate trial,9 it was estimated that the mean number of Gadolinium Enhancing (GdE) lesions during months 7 through 9 would be 1.75 times higher with placebo treatment compared with COPAXONE® 20 mg/mL treatment. The upper limit of the equivalence margin was set at 1.375, representing 50% of the treatment effect versus placebo observed in the European/Canadian Glatiramer Acetate trial. The lower limit of the equivalence margin was set at 0.727 to create a symmetrical margin in the log scale. To conclude equivalence between GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL, efficacy in the combined active treatment groups needed to be superior to placebo (confirming study sensitivity), and the 2-sided 95% CI for the estimated ratio of GLATECT™ 20 mg/mL to COPAXONE® 20 mg/mL needed to be fully enclosed in the prespecified equivalence margin. Given the sample size as calculated and the estimated width of the 95%CI for the ratio of GLATECT™ 20 mg/mL to COPAXONE® 20 mg/mL, the maximal allowable difference between the point estimates to show equivalence would be approximately 10%. In other words, GLATECT™ 20 mg/mL was considered to be similar to COPAXONE® 20 mg/mL when the 95% CI for the ratio of GLATECT™ 20 mg/mL versus COPAXONE® 20 mg/mL on the primary endpoint was between 0.727 and 1.375.

Analysis populations included:

- The All Subjects Screened Group (ASSG) consisted of all patients who received a patient number.
- The All Subjects Randomized Group (ASR) consisted of all patients who were randomized.
- The Safety Set consisted of all patients who signed informed consent and received at least one dose of trial medication. Patients were analyzed in treatment groups based on the treatment received.
- The Full Analysis Set (FAS) included all patients who were randomized and received at least one dose of trial medication. Patients were analyzed in treatment groups based on the treatment to which they were randomized.
- The Per-Protocol Set (PPS) included patients from the FAS who received 80% to 120%, inclusive, of the planned number of study drug doses during the first 7 months of the double-blind part and for whom at least one of the Month 7, Month 8 or Month 9 efficacy assessments was available and who did not have any major protocol violations.

Complete details can be located in section 9.7 (p. 58-70) of the GTR001 Clinical Trial report.

b) Results

Baseline Characteristics

The treatment groups were very similar at randomization for demographic and other baseline characteristics as well as for MS disease characteristics. The trial population was consistent with the intended trial population based on the inclusion and exclusion criteria. There were no important differences between the Full Analysis Set (FAS) and the Per Protocol Set (PPS). Table 12 summarizes demographic and physical characteristics.

In terms of concomitant medications, [redacted] of patients had received at least one prior MS disease modifying medication, with the most frequent prior medication being interferons [redacted] The percentage of patients treated previously with interferons was higher in the GLATECT™ 20 mg/mL [redacted] and COPAXONE® 20 mg/mL (14.8%) groups than in the placebo group [redacted].

Table 11: Summary Of Patient Characteristics For The Gate Trial (Double-Blind Part)6

Disposition	GATE Trial (GTR001)		
	GLATECT™ 20 mg/mL	COPAXONE® 20 mg/mL	Placebo
Age, years (Mean, SD)	32.6 (8.6)	33.8 (9.0)	32.6 (8.7)
Gender **Male (n, %)** **Female (n, %)**	 120 (34%) 233 (65%)	 119 (33%) 238 (67%)	 27 (32%) 57 (68%)
Disease duration, years (Mean, SD)	5.5 (5.3)	6.4 (6.0)	5.7 (6.0)
Number of relapses in prior 2 year (Mean, SD)	1.9 (0.9)	1.8 (0.9)	1.9 (0.9)
EDSS score (mean, SD)	2.6 (1.2)	2.7 (1.2)	2.7 (1.2)
Number of T1-GdE lesions, baseline MRI **(Mean, SD)** **Median (min – max)**	 2.5 (3.5) 1.0 (0-27)	 2.5 (3.9) 1.0 (0-40)	 2.8 (4.1) 1.0 (0-28)

EDSS: Expanded Disability Status Scale; SD: standard deviation; T1-GdE: Gadolinium Enhancing.

Patient Disposition

A total of 1,549 patients were screened, 796 patients were randomized and 753 patients were screen failures. The percentage of randomized patients who completed the double-blind part was 93.0%, 90.8% and 96.4% in the GLATECT™ 20 mg/mL, COPAXONE® 20 mg/mL, and placebo groups, respectively.

Overall, 735 participants (92.3%) completed the 9-month follow-up receiving randomized study drug, with similar proportions in the 3 treatment groups. Table 13 summarizes the patient disposition for the GATE trial.

Table 12: Summary Of Patient Disposition For Gate Trial During Double-Blind Phase6

Disposition	GATE Trial (GTR001)		
	GLATECT™ 20 mg/mL	COPAXONE® 20 mg/mL	Placebo
Screened, N	1549		
Randomized, N	355	357	84
Discontinued, N (%)	25 (7.0%)	33 (9.2%)	3 (3.6%)
***WDAEs,* N (%)**	7 (2.0%)	2 (0.6%)	2 (2.4%)
***Withdrawn consent,* N (%)**	12 (3.4%)	20 (5.6%)	1 (1.2%)
***Lost to follow-up,* N (%)**	1 (0.3%)	2 (0.6%)	0 (0.0%)
Intention to treat, N	353	357	84
Per-protocol, N	[redacted]	[redacted]	[redacted]
Safety, N	353	357	84

WDAE = withdrawal due to adverse event.

Of the 796 randomized to the double-blind part, 728 (91.5%) entered the open-label part, and 670 out of 728 (92.0%) completed the open-label part. Of the patients who entered the open-label part, 93.8%, 92.9% and 81.5% of subjects in the GLATECT™ 20 mg/mL-GLATECT™ 20 mg/mL, COPAXONE® 20 mg/mL- GLATECT™ 20 mg/mL and placebo- GLATECT™ 20 mg/mL groups, respectively, completed the open-label part. Table 14 summarizes the number of patients attending the trial visits during the open-label part.

Table 13: Number Of Patients Attending Trial Visits During The Open-Label Part Of The Gate Trial6

Trial Visit	GLATECT™ 20 mg/mL- GLATECT™ 20 mg/mL N = 324 n (%)	COPAXONE® 20 mg/mL – GLATECT™ 20 mg/mL N = 323 n (%)	Placebo – GLATECT™ 20 mg/mL N = 81 n (%)	TOTAL N = 728 n (%)
Baseline Open-Label Part[a]	324 (100%)	323 (100%)	81 (100%)	728 (100%)
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 21	[redacted]	[redacted]	[redacted]	[redacted]
Month 24[b]	304 (93.8%)	300 (92.9%)	66 (81.5%)	670 (92.0%)

[a] Last observation prior to first open-label GLATECT™ 20 mg/mL administration.

[b] Last visit of the open-label part.

Efficacy Results

The efficacy results of the GATE trial are summarized in Table 15. The estimated mean numbers of GdE lesions during months 7 through 9 for the combined GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL groups and each separately were significantly lower than for the placebo group ($P < 0.001$ for all). GLATECT™ 20 mg/mL was equivalent to COPAXONE® 20 mg/mL in reducing T1-GdE lesions as the 95% confidence interval of the treatment ratio of the number of T1-GdE lesions during months 7 to 9 was within the predefined equivalence margins.

Other MRI endpoints (including change in T2-weighted hyperintense lesion number and volume from baseline to month 9, change in nonenhancing T1-weighted hypointense lesion volume from baseline to month 9, percentage change in normalized brain volume from baseline to month 9, and proportion of participants who were free of disease activity at month 9) supported the primary efficacy outcome and the clinical endpoints (percentage of patients free from disease activity, relapse rate and disability progression) were consistent with the expected profile of glatiramer acetate.

- The percentages of participants disease activity free were 9.3% (33 of 353) in the GLATECT™ 20 mg/mL group, 9.2% (33 of 357) in the COPAXONE® 20 mg/mL group, and 7.1% (6 of 84) in the placebo group.
- The percentages of participants confirmed relapse free were 79.3% (280 of 353), 73.9% (264 of 357), and 73.8% (62 of 84) in the GLATECT™ 20 mg/mL, COPAXONE® 20 mg/mL, and placebo groups, respectively.
- The estimated annualized relapse rates were 0.31 (95%CI, 0.20-0.48) for GLATECT™ 20 mg/mL, 0.40 (95%CI,0.26-0.62) for COPAXONE® 20 mg/mL, and 0.38 (95% CI, 0.22-0.66) for placebo.
- The mean EDSS score was stable in the 3 treatment groups.

The open-label, 15-month extension of the trial aimed to show that GLATECT™ 20 mg/mL is continuously safe and effective over 2 years and that efficacy and safety is maintained when switching from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL. This part of the trial provides information as to whether patients can safely be switched from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL without increased occurrence of disease worsening, or increased incidence of the most frequently occurring adverse events. The results demonstrated that when switching from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL, the effect established on MRI parameters is maintained and when switching from placebo to GLATECT™ 20 mg/mL, the effect on MRI parameters is induced as expected. Altogether the 2-year MRI data collected in this study support that GLATECT™ 20 mg/mL is clinically equivalent to COPAXONE® 20 mg/mL and can be effectively used for the treatment of patients with RRMS.

Table 14: Summary Of Important Efficacy Outcomes For The Gate Trial

Treatment groups (duration)	#	T1 GdE lesions Mean (SD)	Annualized Relapse Rate [95% CI]	EDSS change Mean (SD) [a]
Double-blind part (9 months)	**Assessment at 9 months:**			
GLATECT™ 20 mg/mL COPAXONE® 20 mg/mL Placebo	353 357 84	[redacted]	0.31 [0.20; 0.48] 0.40 [0.26; 0.62] 0.38 [0.22; 0.66]	[redacted]
Ratio of Glatect to Copaxone (95%CI) = 1.095 (0.883 to 1.360) Predefined equivalence margin: 0.727 to 1.375				
Open-label part (15 months)	**Assessment at 24 months:**			
GLATECT™-GLATECT™ COPAXONE® 20 mg/mL - GLATECT™ 20 mg/mL Placebo-GLATECT™ 20 mg/mL	324 323 81	[redacted] [redacted]	0.21 [0.13; 0.34] 0.24 [0.15; 0.39] 0.23 [0.12; 0.42]	[redacted] [redacted]
Total study				
GLATECT™ 20 mg/mL-GLATECT™ 20 mg/mL			[redacted]	[redacted]

Abbreviations: CI: confidence interval; EDSS: Expanded Disability Status; Scale SD: standard deviation; T1 GdE : T1 weighted gadolinium enhancing

[a] Change from baseline for the assessment at 9 months; change from 9 months for the assessment at 24 months

Safety Results

Similar proportions of participants (range, 51.0%-56.0%) in the 3 treatment groups reported adverse events (see Table 16).

No deaths occurred during the total study or within 30 days after a patient's last trial visit. Adverse events (AEs) led to discontinuation from the trial in [redacted] of patients in the GLATECT™ 20 mg/mL-GLATECT™ 20 mg/mL, COPAXONE® 20 mg/mL-GLATECT™ 20 mg/mL and placebo-GLATECT™ 20 mg/mL groups, respectively.

The mean and median values for changes from baseline in clinical laboratory tests and vital signs were low and comparable across treatment groups at all visits, as were the percent of patients with clinically notable values.

Table 15: Adverse Events From The Gate Trial (Safety Population) Double Blind Phase6

Event	Number (%)		
	GLATECT™ 20 mg/mL (N=353)	COPAXONE® 20 mg/mL (N=357)	Placebo (N=84)
Any event	180 (51.0)	194 (54.3)	47 (56.0)
Any severe event	14 (4.0)	10 (2.8)	0
Any event leading to discontinuation of study drug or trial participation	12 (3.4)	4 (1.1)	2 (2.4)
Any serious adverse event	12 (3.4)	17 (4.8)	2 (2.4)
Death	0	0	0
Most frequently reported adverse events [a]			
Injection site reaction	58 (16.4)	62 (17.4)	6 (7.1)

Event	Number (%)		
	GLATECT™ 20 mg/mL (N=353)	COPAXONE® 20 mg/mL (N=357)	Placebo (N=84)
Immediate postinjection reaction	24 (6.8)	18 (5.0)	0
Headache	16 (4.5)	12 (3.4)	7 (8.3)
Injection site swelling	14 (4.0)	12 (3.4)	3 (3.6)
Nasopharyngitis	13 (3.7)	23 (6.4)	6 (7.1)
Injection site pain	11 (3.1)	13 (3.6)	1 (1.2)

[a] The listed adverse events are those that were reported in at least 3% of patients in the GLATECT™20 mg/mL or COPAXONE® 20 mg/mL groups or at least 5 patients in the placebo group. The order is based on the incidence in the GLATECT™ 20 mg/mL group.

4.2.3 Summary of Safety

a) Safety Evaluation Plan

All safety evaluations were performed using the Safety Set, which included all patients who signed an informed consent form and received at least one dose. Patients in the Safety Set were assigned to the treatment actually received.

Safety was assessed by the reporting of serious adverse events (SAEs), adverse events (AE), assessment of routine laboratory parameters (hematology, biochemistry, urinalysis), vital signs and local tolerance. Safety results were all evaluated descriptively, no statistical analysis was performed.

Only adverse events reported to start during the in-treatment period were considered in the analysis. The in-treatment period is defined as the period starting from the first injection of the study drug (GLATECT™20 mg/mL, COPAXONE® 20 mg/mL, or placebo) onwards up to and including the last assessment injection (or 30 days after the last injection if treatment was discontinued prematurely).

Each patient was carefully questioned and/or examined by the investigator to obtain information regarding AEs, including SAEs, at each visit until the last protocol specified visit or contact. The investigator was responsible for following AEs that caused the patient to discontinue before completing the trial until they resolved or stabilized.

The severity of each AE was assessed (mild, moderate or severe) and the causality of each AE was assessed (unlikely, possible, and probable). Definitions for severity of AEs and causality assessment can be found in module 2.7.4 of the Common Technical Document (CTD) (p. 4-5).

b) Safety Populations Evaluated

A total of 777 patients were exposed to at least one dose of GLATECT™ 20 mg/mL: 20 healthy volunteers in the phase I GTR002 trial and 757 RRMS patients in the phase III GATE trial (GTR001) (see Table 17).

Table 16: Number Of Individuals Exposed In Glatect™ 20 Mg/Ml Clinical Studies (Gate And Gtr002)

Trial	Number of Individuals Exposed		
	GLATECT™20 mg/mL	COPAXONE® 20 mg/mL	Placebo
GTR002 (Completed)	20	20	N/A
GATE (Double-blind part)	353	357	84
GATE (Open-label part)[a]	404[b]	N/A	N/A
Total	777	377	84

[a] Excluding 324 patients who were already exposed to GLATECT™ 20 mg/mL in the double-blind part and continued into the open-label part

[b] Consisting of 323 patients who were exposed to COPAXONE® 20 mg/mL and 81 patients who were exposed to placebo during the double-blind part.

Throughout all studies, a dose of GLATECT™ 20 mg daily was administered. Exposure to GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL in the double-blind part of the GATE trial was similar: in both groups patients were treated with the study drug on average for 9 months. Patients continuing in the open-label part were exposed on average to another 1.1 year of GLATECT™ 20 mg/mL treatment. Thus, upon completion of GTR001, patients randomized to GLATECT™ 20 mg/mL received GLATECT™ 20 mg/mL treatment for a total treatment duration of 2 years, which is similar to other reported COPAXONE® 20 mg/mL trials. In the GATE trial, the characteristics of the RRMS population were comparable between the GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL treatment groups. In line with the applied inclusion criteria, the patients enrolled were a representative RRMS population with clinically and radiographically active disease. For details on the overall extent of exposure to study drug, refer to Section 2.7.4.1.2 of the Clinical Safety module of the Common Technical Document; for details on the characteristics of the patient population, refer to Section 2.7.4.1.3.

c) Overview of Safety

Glatiramer acetate has a long history of safe use worldwide and has been proven to be safe and efficacious in the treatment of RRMS. It has been marketed in the European Union since 2003 and has been available in Canada and the U.S. for over 15 years under the same trade name, COPAXONE®. In a recent review, clinical data with COPAXONE® 20 mg/mL have been summarized and data from long-term studies indicate the excellent safety profile of this drug.[16] After decades of continuous use and an overall experience of more than 1 million patient-years, no cumulative toxicities or late-emerging adverse events have been reported, no drug interactions, and due to the absence of immune-suppressive effects, no increase of opportunistic infections or malignancies have been associated with its use . Furthermore, similar efficacy and safety profiles were observed in RRMS patients receiving higher doses of glatiramer (40 mg/dose).

In the GTR002 trial, all 20 participants reported at least one study drug-related AE. No AEs of severe intensity were reported, no SAEs were reported and no participants discontinued the trial due to an AE.

The percentage of patients reporting AEs in the double-blind part of the GATE trial is 51.0% in the GLATECT™ 20 mg/mL group. Study drug-related AEs were reported by 35.4% of patients. The reported AE and study drug-related AE incidences were similar to those reported in the COPAXONE® 20 mg/mL group. The incidence of SAEs and AEs that led to discontinuation of study drug and/or discontinuation of the double-blind part of the trial was low (3.4% each in the GLATECT™ 20 mg/mL group; 4.8% and 1.1% in the COPAXONE® 20 mg/mL group; and 2.4% each in the placebo group). The incidences were again comparable to the COPAXONE® 20 mg/mL group. [For additional details, please see 2.7.4.2.1 - Analysis of Adverse Events].

In the open-label part, the percentage of patients reporting AEs and study drug-related AEs decreased to [redacted] respectively. The incidence of patients reporting SAEs in the open-label part of the trial was 3.0% and the percentage of patients discontinuing study drug and/or the trial due to AEs was 1.4%. Similar incidences were reported for the patients who switched from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL during the trial as compared to patients who were treated with GLATECT™ 20 mg/mL for the entire trial. [For additional details, please see 2.7.4.2.1 - Analysis of Adverse Events]

There were no deaths reported in the trial.

4.3 Pharmacokinetics

Upon subcutaneous injection, glatiramer degrades into smaller peptide fractions and free amino acids, resulting in low or undetectable serum concentrations of the drug and its metabolites. Limited pharmacokinetic (PK) studies in healthy volunteers indicate that a substantial fraction of the glatiramer acetate dose is hydrolyzed locally.[6] It is not presently feasible using current techniques to determine the exact epitopes responsible for the drug's efficacy. In addition, no validated biomarkers exist to assess the clinical relevance of response of glatiramer acetate in MS patients. As a result, no dedicated pharmacokinetic or pharmacodynamic studies have been performed with COPAXONE® 20 mg/mL nor GLATECT™20 mg/mL.

The biological activity of GLATECT™ 20 mg/mL was studied in Experimental Autoimmune Encephalomyelitis (EAE) studies in SJL mice and brown Norway rat. The data indicate that the drug substance and product has biological activity and significantly inhibit the PLP139-151-induced EAE in mice. GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL increased survival of retinal ganglion cells

in rat to a similar extent. The *in vivo* biological activity of GLATECT™ 20 mg/mL is similar to COPAXONE® 20 mg/mL, the comparator.

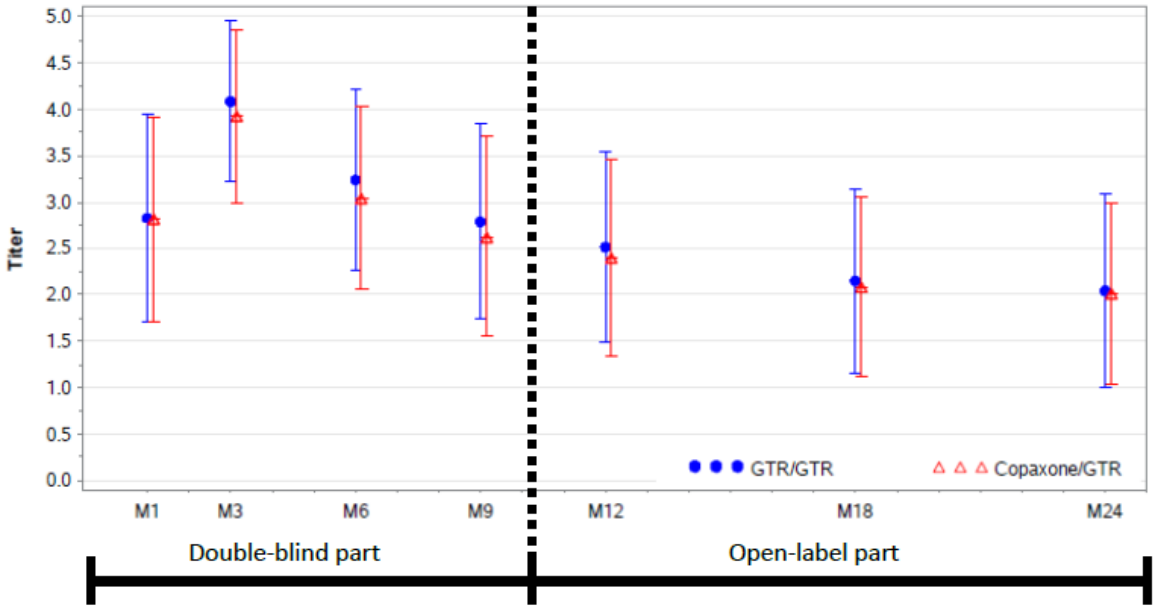
Regulatory guidelines are lacking in Canada regarding development approaches and similarity comparisons of complex synthetic polymers and peptides such as glatiramer acetate. Therefore, an approach in line with the World Health Organization (WHO) recommendation in their *Guidelines on Evaluation of Similar Biotherapeutic Products*[17] was followed to demonstrate similarity of GLATECT™ 20mg/mL to COPAXONE® 20 mg/mL. Synthon has performed an extensive physicochemical and nonclinical characterization of its active substance to demonstrate that glatiramer acetate contained in GLATECT™ 20 mg/mL is of the same quality as the active substance contained in Canadian-, US- and EU-sourced COPAXONE® 20 mg/mL.

4.4 Immunogenicity

With respect to immunogenicity, the COPAXONE® 20 mg/mL label states that glatiramer acetate reactive antibodies were detected in patients' sera during daily chronic treatment with COPAXONE®
20 mg/mL. Maximal levels were attained after average treatment duration of 3 to 4 months and, thereafter, declined and stabilized at a level slightly higher than baseline. There is no evidence to suggest that these glatiramer acetate-reactive antibodies are neutralizing or that their presence affects the clinical efficacy of COPAXONE® 20 mg/mL.

The presence of anti-glatiramer anti-drug antibodies (ADA) and glatiramer ADA titers were measured in the GATE (GTR001) trial. Figure 1 summarizes the titer values of all post-baseline samples in the GLATECT™ 20 mg/mL and COPAXONE® 20 mg/mL groups which were reported as confirmed positive for glatiramer ADA.

Figure 1: Mean Titer Value in Glatect™ 20 Mg/Ml and Copaxone® 20 Mg/Ml Groups (Safety Set)



Note: Error bars represent standard deviation (SD). In the legend the treatments are indicated as GTR/GTR (GLATECT™ 20 mg/mL-GLATECT™ 20 mg/mL), COPAXONE® 20 mg/mL /GTR (COPAXONE® 20 mg/mL -GLATECT™ 20 mg/mL) and Placebo/GTR (Placebo-GLATECT™)which refers to GLATECT™ 20 mg/mL, COPAXONE® 20 mg/mL and Placebo treatment, respectively, in the double-blind part and GLATECT™ 20 mg/mL treatment for all groups in the open-label part of the trial.

Altogether, the immunogenicity and safety data obtained in almost 800 patients in the 2-year GATE study (GTR001) revealed that the formation of glatiramer ADA was comparable following GLATECT™ 20 mg/mL or COPAXONE® 20 mg/mL treatment, as reflected by similar number of patients with positive samples in the confirmatory assay and comparable serum glatiramer ADA titer levels in both groups during the double-blind part. In addition, switching from COPAXONE® 20 mg/mL to GLATECT™ 20 mg/mL treatment had no impact on glatiramer ADA incidence and titer levels. [For additional details, see module 2.7.2.4 Special Studies]

There is no evidence to suggest that these glatiramer ADA are neutralizing or that their formation is likely to have any clinical relevance in terms of reduced efficacy or safety concerns. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded. Noteworthy, anaphylaxis can be associated with the administration of almost any foreign substance and therefore this risk cannot be excluded.

5. Critical Appraisal of Clinical Studies

5.1 Internal Validity

The manufacturer-submitted information included the results from one pivotal phase III study and one phase I study that was not considered pivotal: 1) GATE Trial (GTR001) was an equivalence randomized controlled clinical trial that evaluated the efficacy of Glatect (glatiramer acetate SEP) versus Copaxone (reference product) with an open-label extension phase; and 2) Study GTR002 was a double-blind, randomized controlled replicate study to assess injection site reaction and tolerance of Glatect (glatiramer acetate SEP) versus Copaxone in healthy volunteers. The information presented below is based on an appraisal of the manufacturer's submission.

GATE Trial (GTR001)

The first phase of the GATE trial was a multi-centre, parallel, double-blind, equivalence, randomized, active and placebo-controlled clinical trial. The GATE trial evaluated the efficacy of Glatect (glatiramer acetate SEP) versus Copaxone (reference product) for patients suffering from RRMS. The first phase continued for nine months.[21,22]

Overall, the clinical trial was well-designed with a sufficient number of enrolled patients (N = 796) to allow for a 12% dropout rate while maintaining a 92% power to demonstrate equivalence in the primary outcome of total number of gadolinium-enhancing lesions during months 7 through 9 on T1-weighted images.[22] The power analysis was based on two previously published studies assessing the effects of MS treatment on T1-GdE lesion count.[23,24] The equivalence margin was calculated based on a historical pivotal trial of glatiramer acetate versus placebo where at least 50% of the effect over placebo would be maintained; this resulted in an equivalence margin with a lower limit of 0.727 and an upper limit of 1.375. The equivalence margin aimed to preserve 50% of glatiramer acetate versus placebo effect, for which the manufacturer has indicated translates to a 10% difference in the point estimate between Glatect and Copaxone. It is not clear if this margin exceeds any clinically meaningful differences that might affect the decision-making process of clinicians; however, based on a meta-analysis assessing the correlation between MRI lesions and relapse rate,[25] the manufacturer indicated that a 10% difference in the point estimate between active treatments would translate into a relapse rate of no more than 7%. The clinical expert consulted in this review indicated that, overall, the equivalence margin seems clinically appropriate.

Further, as part of Health Canada's review of Glatect for marketing authorization, the Health Canada reviewer requested the manufacturer to provide analysis of the results based on 60%, 75%, and 90% preservation of Copaxone effect over placebo. It is reported the equivalence was achieved at 60% but not at 75% or 90%. The manufacturer reported, however, that at those levels of effect preservation, the high statistical power needed to show equivalence would have rendered the study unachievable due to the challenges in recruiting such a large number of participants.[26]

The reported procedures for randomization and allocation concealment appear reasonable. Patients were randomized using an interactive voice/web response system (IXRS) through a computer-generated randomization list, stratified by geographical location and lesion count, with a ratio of 4.3:4.3:1 to receive Glatect, Copaxone, or placebo for a period of nine months. The physical appearance of the study product was identical for all three interventions; patients, investigators, MRI personnel, and other study personnel were kept blinded until the end of the double-blind period.

Glatect, Copaxone, and placebo were self-administered subcutaneously at a volume of 1 mL, and a dose of Glatect and Copaxone of 20 mg, daily. Treatment compliance was tracked through a patient dosing and tolerability diary. Concomitant medication was only allowed for symptomatic management of symptoms. All patients recorded a treatment compliance of 80% to 120%.

Demographic characteristics, body mass index, number of gadolinium-enhancing lesions on T1-weighted images, time since the onset of symptoms, number of relapses within two years, and the Expanded Disability Status Scale score were all well balanced between treatment groups at baseline. Small variations were noted in the number of patients with previous history

of treatment and the number of hyperintense lesions on T2-weighted images. However, these small differences were not identified as concerning according to the clinical expert consulted for this review.

The primary outcome in this study, total number of gadolinium-enhancing lesions, was evaluated during months 7 through 9. The choice of the outcome and analysis point was the same as what was used in the pivotal studies for Copaxone. The measure is validated and is also used in clinical practice.[25,27,28] The equivalence margin was applied to the ratio of total number of gadolinium-enhancing lesions, measured from months 7 through 9, between Glatect and Copaxone. Identification of the T1-GdE lesions for the primary outcomes was done by two independent, qualified imaging readers. Radiographic outcomes beyond the primary outcome were assessed by a blinded single qualified imaging reader instead of two independent readers, increasing the potential of measurement bias in either direction of effect.

For all outcomes, the full analysis set (FAS), which included any patient who was randomized and received at least one injection, was used as the basis of calculation for all efficacy and safety outcomes. In addition to the FAS, the per-protocol (PP) analyses set was used for the primary outcome. The PP set included patients that received 80% to 120% of the total number of intended injections. Although the results from the PP set were similar to those of the FAS, the use of FAS as the primary efficacy analysis population in an equivalence trial is not recommended, as it may introduce biases in favour of the intervention.[29] The manufacturer indicated that since superiority over placebo was the first requirement, it was decided to select the FAS population as the primary population for analysis of efficacy. Missing MRI outcome data were not imputed and such observations were excluded from the analysis. However, if the participant had at least one MRI assessment during the months 7 through 9 period, this assessment was included in the analysis. The exact number of non-imputed missing data is not clear. However, a sensitivity analysis of complete and non-imputed data showed similar results to base case.

The proportion of patients who withdrew before the conclusion of the double-blind period were 7%, 9.2%, and 3.6% in the Glatect, Copaxone, and placebo arms, respectively. The most common reason for withdrawal was withdrawal of consent. Withdrawal due to adverse event was recorded in 2%, 0.6%, and 2.4% in the Glatect, Copazone, and placebo arms, respectively. Overall, only three patients (0.4%) were recorded as lost to follow-up. The rate of discontinuation allowed sufficient sample size to maintain statistical power, but was slightly imbalanced between the active arms. The imbalance was larger in the placebo arm, with less patients dropping out of the study, and consequently, may have a marginal effect on the comparative efficacy result in favour of placebo.

The mean numbers of gadolinium-enhancing lesions during months 7 through 9 were similar in the two active groups (0.45 in the Glatect group versus 0.41 in the Copaxone group) with a comparison ratio falling within the pre-defined equivalence margin (Glatect compared with Copaxone ratio = 1.095 [95% CI, 0.883 to 1.360]). Analysis using the PP set produced similar point estimate and 95% CI results (ratio = 1.097 [95% CI, 0.880 to 1.368]), also falling within the pre-defined equivalence margin of 0.727 to 1.375.

After the initial nine-month double-blind treatment phase, a second phase of the GATE Trial (GTR001) was a 15-month open-label, follow-up, safety and tolerability study that involved switching all patients who completed the double-blind phase to Glatect treatment. This study has recently been published.[30] A total of 729 patients that completed the double-blind phase were all given Glatect 20 mg/mL and assessed at months 12, 15, 18, and 24 for safety, with MRI scans at months 12, 18, and 24. The descriptive results suggest that patients maintained many of the improvements that were gained in the double-blind phase with a similar number of GdE lesions in patients who were maintained on Glatect and in patients that were switched to Glatect at months 12, 18, and 24. At the end of the open-label phase, patients that remained on Glatect had a mean number of 0.7 new and persisting GdE lesions, 0.6 in patients who switched from Copaxone, and 0.9 in patients who were on placebo. No major signs of poor tolerability or safety issues were detected in the extension study. The design of the study, however, lacks a comparative group, and this restricts the results to being descriptive in nature.

GTR002 Trial

GTR002 (N = 20) trial was a non-pivotal, controlled, randomized, double-blind, replicate study to assess injection site reaction and tolerance of Glatect versus Copaxone, in healthy volunteers. The GTR002 was included by the manufacturer in this submission; however, it was not considered pivotal by Health Canada and is not a phase III trial. Participants were

assigned to one of the two possible randomization sequence (e.g., periods ABAB or BABA, receiving in each period an single-dose injection of A (Glatect) or B (Copaxone) and then 4 days rest and then the next period.), thus essentially forming two parallel studies. Participants had similar demographic characteristics and reported a similar number of injection site reactions between the two treatments, with no reported serious adverse events. The study provides evidence of similar number of injection site reactions after injections from both treatments. However, the study provided no power analysis or predefined equivalence margin, and thus it is uncertain of the lack of difference is accurate or due to lack of power. Aside from the lack of power analysis, the study was appropriately randomized using a computer-generated randomization procedure, investigators and patients were blinded, and the two treatments had identical appearance. Assessment of injection site reaction was conducted by both the participant and the nurse. Injections were self-administered under the supervision of a nurse, providing a higher quality of data collection. There were three dropouts (15%) due to protocol violations or absence, with unclear consequence on the internal validity of the study. The study showed no statistically significant difference (i.e., fails to reject the null hypothesis) in the number of injection site reactions between the treatments. However, with the lack of power analysis and a pre-defined equivalence margin, it is difficult to assert whether this result is due to lack of statistical power to detect differences, or whether it is truly reflective of lack of any meaningful differences between the two drugs.

5.2 External Validity

GATE Trial (GTR001)

The trial recruited patients with relapsing-remitting multiple sclerosis from 118 centres and practices across 17 countries in Europe and North America (Mexico and US). Participants were 18 to 55 years old, had established RRMS, had experienced at least one documented relapse in the previous year, and had 1 to 15 gadolinium-enhancing lesions on T1-weighted MRI images. The clinical expert identified the study population as reflective of the overall patient population seen at practice. The primary outcome measure is commonly used in research, has been validated, and is considered the most appropriate surrogate marker to measure progression of MS.[25,27,28] A large percentage of screened patients were not randomized (48.5%); over half of these patients did not meet the inclusion criteria (56.4%), about one quarter of patients withdrew consent, and another quarter of patients were screen failures for various unspecified reasons. The clinical expert consulted on this review had no issues with the remaining population as reflective of the general patients seen in the practice.

However, the generalizability of the results to the Canadian population has the following limitations:

- No Canadian sites were included in the trial; it is unclear how this may affect outcomes.
- All but one of the randomized patients (99.9%) were Caucasian; generalizability of the results to other racial groups is unclear.
- Since patients over 55 years of age were excluded, generalizability of the results to those over age 55 is unclear.
- The applicability of the results to populations with more concomitant medications and comorbidities is unknown.
- The extension study lacks a comparison group where patients stayed on the originator/reference drug; thus there is no comparative evidence to inform the efficacy and safety for treatment-experienced patients.
- The period of the double-blind comparative part of the study (nine months) is considered short compared with the lifelong nature of MS; generalizability of the results may be uncertain on long periods of treatment.

GTR002 Trial

This was a Phase I study on healthy volunteers; as such the generalizability of the results is limited.

6. Extrapolation of Indications

6.1 Manufacturer's Rationale for Extrapolation

Not applicable.

6.2 Health Canada's Conclusion on Extrapolation

Not applicable.

6.3 International Regulatory Conclusions on Extrapolation

Not applicable.

6.4 CDR Comments on Extrapolation

Not applicable

7. Cost Comparison

GLATECT™ 20 mg/mL is priced at a 15% discount versus COPAXONE® 20 mg/mL, as presented in Table 18. Please note that COPAXONE® 40 mg/mL is priced at parity with COPAXONE® 20 mg/mL (in terms of annual drug costs), but is not included in the cost comparison as it is not yet reimbursed by any public drug plan in Canada.

Table 17: Cost Comparison of GlatectTM 20 mg/mL and COPAXONE® 20 mg/mL for RRMS

Drug / Comparator	Strength	Dosage Form	Price ($)[1]	Recommended Dose[2]	Average Annual Drug Cost ($)
GLATECT™ 20 mg/mL (glatiramer)	20 mg/mL	Pre-filled syringes for subcutaneous injection	$37.8216	20 mg once daily	$13,804.88
COPAXONE® 20 mg/mL (glatiramer)	20 mg/mL	Pre-filled syringes for subcutaneous injection	$44.4960	20 mg once daily	$16,241.04

COPAXONE® 20 mg/mL unit cost retrieved on November 4, 2016 from the Ontario Drug Benefit (ODB) Exceptional Access Program (EAP) Formulary available at http://health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx

Dose recommended in each drug's product monograph

When compared to its reference product (COPAXONE® 20 mg/mL), GLATECT™ 20 mg/mL offers comparable efficacy and safety at an annual drug cost significantly lower and therefore represents a superior treatment alternative.

Availability of GLATECT™ 20 mg/mL will represents a significant opportunity to improve patient access to glatiramer while addressing the cost-effectiveness demands on healthcare systems in Canada. Its reimbursement could result in significant savings in drug costs. But to maximize these benefits, public payers will need to implement policies to support its reimbursement and market acceptance in COPAXONE®-naïve, as well as COPAXONE®-experienced patients.

CDR Reviewers' Comments Regarding Cost Information

At $37.82 per 20 mg/mL vial, the cost of subsequent entry glatiramer is 15% less than the ODB EAP list price of the originator product, leading to a savings of $2,436 per patient per year.

Issues for consideration

The actual cost paid by Canadian public drug plans for the originator product may be lower than that listed on publicly available formularies, which would reduce the relative attractiveness of the submitted price of the subsequent entry product.

Teva-glatiramer,[31] made by the same manufacturer as the originator product, has received a Health Canada indication for the treatment of RRMS. If it becomes available, this will be a comparator of interest and, depending on its price, may further reduce the relative attractiveness of the submitted price of this subsequent entry product.

8. Discussion

Glatect is a non-biologic complex drug where the entire related structure of the molecule is active. As such, the properties cannot be fully characterized by physicochemical analysis. The CDR approach to reviewing Glatect (glatiramer acetate SEP) followed the CDR *Procedure and Submission Guidelines for Subsequent Entry Biologics* (March 2014). Health Canada required the manufacturer to submit equivalence clinical information in a way similar to a biosimilar submission. Health Canada's approach to reviewing Glatect was similar to that of EMA, where Glatect was treated in a similar way to biosimilars. In contrast, the FDA considered Glatect to be a generic drug to Copaxone.[32,33] In such, the CDR approach is in line with that of Health Canada and EMA.

The manufacturer has provided one equivalence randomized controlled clinical trial that evaluated the efficacy of Glatect versus Copaxone (GATE GTR001 trial) and included an open-label extension phase; and a phase I controlled, randomized, double-blind, replicate study to assess injection site reactions and tolerance of Glatect versus Copaxone (GTR002 trial) in healthy volunteers. The GATE trial demonstrated that Glatect falls within the equivalence margin to the reference product, Copaxone, for the primary outcome of the number of GdE lesions on T1-weighted MRI images. The extension phase of the phase III study provided supportive, non-comparative evidence of longer-term efficacy and tolerability of Glatect as well as safety and efficacy data for treatment-experienced patients. The evidence from the extension study, however, is limited in value due to the lack of a comparative group of patients that were maintained on Copaxone. GTR002 demonstrated a lack of statistically significant difference in injection site reactions between Glatect and Copaxone. However, the lack of significant differences in the GTR002 should not be interpreted as equivalence, due to the lack of a reported power analysis.

The evidence provided in this submission had several limitations regarding generalizability to the Canadian population. These limitations included the lack of Canadian sites, a limited representation of racial and ethnic minorities, and no representation of geriatric population over the age of 55 years. Likewise, based on a review of the product monograph for Copaxone, patients included in the clinical trials were 96% Caucasian with the majority between the ages of 18 to 45 years.[34]

Input from one patient group supplying input to the submission indicated that patients who are already on the originator drug might not be comfortable moving to the SEP, largely because they trust and comfort in staying on a drug that is already working. However, patient group input also indicated that many patients would consider the SEP as a means to save resources and offer the potential for greater access to treatment. The extension phase of the GATE trial involved all patients that were in the Copaxone and placebo arms to switch to Glatect, and data suggested that patients who were on Copaxone maintained the outcomes that were experienced in the double-blind phase of the trial while placebo patients showed improved results, with no major safety or tolerability issues during the 15-month period. However, these results are not compared statistically against a group of patients that remained on the originator product, Copaxone, and as such, any results obtained are considered descriptive in nature.

At $37.82 per vial, the cost of subsequent entry glatiramer is 15% less than the ODB EAP list price of the originator product, leading to a savings of $2,436 per patient per year. Actual costs paid by plans for the originator product, as well as the approval and potential availability of Teva-glatiramer, may reduce the relative attractiveness of the submitted price of this subsequent entry product.

Potential Place in Therapy[c]

Multiple sclerosis is a common neurological disease in Canada, and is second only to trauma as a cause of neurological disability in adults younger than 50. Many lines of evidence support the idea that MS is caused by abnormal immune system activity, which produces relapsing and remitting episodes of neurological dysfunction due to foci of demyelination and axonal

[c] This section is written by the Clinical Expert consulted on this review.

injury in the brain and spinal cord. In most patients with relapsing-remitting MS, recovery from an episode is incomplete, and over time, progressive, permanent functional impairment accumulates.[35]

The first disease-modifying drugs for MS were introduced into clinical practice in the early 1990s. In the last decade in particular there has been an increasing number of agents available, but in current Canadian practice, four agents are considered by most experts to be first-line therapy in treatment-naive MS patients: beta-interferon, glatiramer acetate, teriflunomide, and dimethyl fumarate. The efficacy of these agents is broadly similar, and the choice of agent for a given patient is largely determined by the mode of administration and side effects. Beta-interferon and glatiramer acetate (the "injectables") must be given by SC injection, whereas teriflunomide and dimethyl fumarate are oral medications. There is at least a decade more experience with the "injectables," and in many clinics they are the treatments most likely to be offered to a new patient. Glatiramer acetate usually requires daily injections, while beta-interferon can be given on alternate days or even once a week. However, many clinicians and patients prefer glatiramer acetate, because patients typically experience considerably fewer flu-like side effects and less monitoring is required than the beta-interferons.

Glatect is being positioned by the manufacturer as equivalent in efficacy and side effect profile to the established preparation of glatiramer acetate, Copaxone, but with a somewhat lower price. From the perspective of an individual patient with adequate insurance coverage, the potentially lower price of Glatect would have only a minor advantage. However, given the annual cost per patient of any of the first-line MS drugs (several thousand dollars per annum) and the prevalence of MS in Canada, a lower-cost glatiramer acetate preparation may have a positive effect on health care costs in Canada. There is likely to be some resistance from patients and perhaps clinicians to switching from Copaxone in patients who are doing well ("don't rock the boat"), but, if less expensive, Glatect could potentially replace Copaxone in many or most treatment-naive MS patients who are currently prescribed Copaxone.

9. Conclusion

Overall, the manufacturer provided evidence from one phase III equivalency trial that enrolled treatment-naive MS patients to demonstrate similar efficacy and safety, between the subsequent entry non-biologic complex product Glatect and the originator drug Copaxone; the ratio of mean numbers of gadolinium-enhancing lesions between months 7 through 9 fell within the pre-defined equivalence margin of 0.727 to 1.375 (Glatect compared with Copaxone ratio 1.095 [95% CI, 0.883 to 1.360]). Available data from GATE trial extension phase suggest that patients who were switched from Copaxone to Glatect maintained the results achieved in the double-blind period. The evidence from the extension study, however, is limited due to the lack of a comparison group that was maintained on Copaxone.

At $37.82 per vial, the cost of subsequent entry glatiramer is 15% less than the ODB EAP list price of the originator product, leading to a savings of $2,436 per patient per year. Actual costs paid by plans for the originator product, as well as the approval and potential availability of Teva-glatiramer, may reduce the relative attractiveness of the submitted price of this subsequent entry product.

Appendix 1: Additional Data

Categories of the 2010 McDonald Criteria

Table 18: Categories Of The 2010 Mcdonald Criteria For Diagnosis Of Multiple Sclerosis20

Clinical presentation	Additional Data Needed for MS Diagnosis
≥ 2 attacks[a]; objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥ 2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the Central Nervous System (CNS) (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or • await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥ 2 lesions	Dissemination in time, demonstrated by: • simultaneous presence of asymptomatic GdE and Gd nonenhancing lesions at any time; or • a new T2 and/or GdE lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or • await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space: • ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)d; or • await a second clinical attack[a] implicating a different CNS site; and For dissemination in time: • simultaneous presence of asymptomatic GdE and Gd nonenhancing lesions at any time; or • a new T2 and/or GdE lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or • await a second clinical attack[a]

[a] An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b] Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c] No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, cerebrospinal fluid) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d] Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

Appendix 2: Drug Plan Listing Status for Reference Product

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review
–	Information not available

Listing Status for (name of reference product)

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
RRMS	**RES**	**RES**	**RES**	**RES**	**EX**	**RES**	**RES**	**FB**	**RES**	**RES**	**RES**	**-**	**EX**	**-**
CIS	**NB**	**NB**	**NB**	**-**	**EX**	**RES**	**RES**	**FB**	**NB**	**NB**	**NB**	**-**	**EX**	**-**

AB = Alberta, BC = British Columbia, DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC =Veterans Affairs Canada; YK = Yukon.

Restricted Benefit Criteria for COPAXONE® 20 mg/mL for the Treatment of RRMS

Drug Plan	Criteria for Restricted Benefit
BC	**Initial (approval period 1 year):** As first-line monotherapy for the treatment of relapsing-remitting multiple sclerosis (MS) diagnosed according to the current McDonald[i] clinical criteria and magnetic resonance imaging (MRI) evidence, when prescribed by a neurologist from a designated MS clinic, for patients who meet **ALL** of the following criteria: 1. Patient has had at least 2 disabling attacks[ii] of MS in the previous 2 years, **AND** 2. Patient is ambulatory with or without aid (EDSS of 6.5 or less), **AND** 3. Patient is 18 years of age or older. Note: • The McDonald clinical criteria for the diagnosis of MS are current as of October 26, 2010. • An attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least 1 month. **Renewal (approval period 1 year):** As monotherapy, when prescribed by a neurologist from a designated MS clinic, for the treatment of patients with relapsing-remitting MS, **AND** who have demonstrated that the therapeutic benefits outweigh any potential risks, as shown by relapse rate, EDSS, MRI scan, or overall clinical impression.

Drug Plan	Criteria for Restricted Benefit
	Change of Therapy: As monotherapy, when prescribed by a neurologist from a designated MS clinic, for the treatment of patients with relapsing-remitting MS who have experienced failure or intolerance to a previous disease modifying therapy. **Practitioner Exemptions** • A Collaborative Prescribing Agreement (CPA) (PDF, 400KB) is available to neurologists specializing in MS whose primary place of practice is in a designated MS clinic. Neurologists who have signed a CPA are not required to submit a Special Authority request form for coverage. • **Important**: PharmaCare coverage covers glatiramer acetate for patients who meet the Limited Coverage criteria and whose prescription has been written by a neurologist who has entered into a CPA. • PharmaCare coverage and actual reimbursement is subject to the rules of a patient's PharmaCare plan, including any annual deductible requirement and any other applicable PharmaCare pricing policy. • Each CPA must be signed by the neurologist who is requesting coverage and not a delegate. • Practitioners who have not signed a CPA may submit a Special Authority request if the patient meets the criteria above. These prescriptions will not be covered automatically. **Reference:** http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-glatiramer-acetate Information retrieved on June 14, 2016
AB	Relapsing Remitting Multiple Sclerosis (RRMS): Special authorization coverage may be provided for the reduction of the frequency and severity of clinical relapses and reduction of the number and volume of active brain lesions, identified on MRI scans, in ambulatory patients with relapsing remitting multiple sclerosis. **Coverage** For coverage, this drug must be prescribed by a registered MS Neurologist. A current assessment must be completed by a registered MS Neurologist at every request. To register to become an MS Neurologist please complete the Registration for MS Neurologist Status Form (ABC 60002). **Initial Coverage** 1) The registered MS Neurologist must confirm a diagnosis of RRMS; 2) The patient must have active disease which is defined as at least two relapses* of MS during the previous two years or in the two years prior to starting an MS disease modifying therapy (DMT). *A relapse is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 48 hours in the absence of fever, not associated with withdrawal from steroids. Onset of clinical relapses must be separated by a period of at least one month. At least one definite gadolinium-enhancing T1 MRI lesion (not questionable faint enhancement) obtained at least 90 days after initiation of the DMT and at least 90 days before or after a relapse may substitute for one clinical relapse.

Drug Plan	Criteria for Restricted Benefit
	3) The patient must be ambulatory with or without aid (The registered MS Neurologist must provide a current updated Expanded Disability Status Scale (EDSS) score less than or equal to 6.5). Coverage may be approved for up to 12 months. Patients will be limited to receiving a one-month supply of glatiramer acetate per prescription at their pharmacy for the first 12 months of coverage. **Continued Coverage** For continued coverage beyond the initial coverage period, the patient must meet the following criteria: 1) The patient must be assessed by a registered MS Neurologist; 2) The registered MS Neurologist must confirm a diagnosis of RRMS; 3) The registered MS Neurologist must provide a current updated EDSS score. The patient must not have an EDSS score of 7.0 or above sustained for one year or more. Coverage of this drug may be considered in a patient with a sustained EDSS score of 7.0 or above in exceptional circumstances. For MS DMT coverage to be considered, details of the exceptional circumstance must be provided in a letter from the registered MS Neurologist and accompany the Special Authorization Request Form. Continued coverage may be approved for up to 12 months. Patients may receive up to 100 days' supply of glatiramer acetate per prescription at their pharmacy. Restarting After an Interruption in Therapy Greater Than 12 Months In order to be eligible for coverage, after an interruption in therapy greater than 12 months, the patient must meet the following criteria: 1) At least one relapse* per 12 month period; or 2) At least two relapses* during the previous 24 month period. All requests (including renewal requests) for glatiramer acetate must be completed using the Dimethyl Fumarate/Glatiramer Acetate/Interferon Beta-1a/Interferon Beta-1b/Teriflunomide Special Authorization Request Form (ABC 60001). **Reference:** https://idbl.ab.bluecross.ca/idbl/lookupCoverageCriteria.do?productID=0000022977&priceListID=0014 Information retrieved on July 26, 2016
Sask	Approval for coverage will be given to patients who are assessed and meet the following criteria: • have clinical definite relapsing and remitting multiple sclerosis; • have had at least two documented attacks of MS during the previous two years (an attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, preceded by stability for at least one month); • are fully ambulatory for 100 meters without aids (canes, walkers or wheelchairs)

Drug Plan	Criteria for Restricted Benefit
	• Extended Disability Status Scale (EDSS) 5.5 or less; • are age 18 or older (Note: Applications for patients under 18 will be considered.) *Physicians should also forward the following information:* • documentation of attacks, date of onset, date of diagnosis; • neurological findings, Extended Disability Status Scale (EDSS); • MRI reports or other significant information; • list of current medications **Reference:** http://formulary.drugplan.health.gov.sk.ca/PDFs/APPENDIXD.pdf Information retrieved on July 26, 2016
Manitoba	Specialists from the MS Clinic may apply for Part 3 EDS. Please contact the EDS Program at MB Health for specific criteria. **Reference:** http://www.gov.mb.ca/health/mdbif/edsnotice.pdf information retrieved on August 19, 2016
Ontario	**Dosage Form/Strength:** 20 mg/mL pre-filled syringe for subcutaneous injection **For CDMS:** COPAXONE® requests for patients with CDMS will be reviewed by external medical experts when the following information is provided: • Date and details of the most recent neurological examination (within the last 90 days); and • Dates and details (e.g., neurological findings) of at least two clinical attacks, including one clinical attack within the past year; and • EDSS score ≤ 5. **Renewal** requests for COPAXONE® can be submitted through the Telephone Request Service and will be considered for patients who have benefited from therapy and have an EDSS score ≤ 5. The physician must provide the following information: • Description of the patient's clinical course in the last year, including details of all attacks; • Date and details of the most recent neurological examination (within the last 90 days); and • The patient's most recent EDSS score. **Standard approval duration:** First renewal: 2 years Second and subsequent renewals: 5 years **Reference:** http://www.health.gov.on.ca/en/pro/programs/drugs/pdf/frequently_requested_drugs.pdf Information retrieved on July 26, 2016

Drug Plan	Criteria for Restricted Benefit
Quebec	**Indication:** Pour le traitement des personnes souffrant de sclérose en plaque de forme rémittente, diagnostiquée selon les critères de McDonald (2010), ayant présenté 1 poussée dans la dernière année et dont le résultat sur l'échelle EDSS est inférieur à 7 **Initial Coverage:** L'autorisation de la demande initiale est d'une durée maximale d'un an. **Continued Coverage:** Les autorisations des demandes subséquentes sont d'une durée maximale d'un an. Cependant, le médecin doit fournir la preuve d'un effet bénéfique par l'absence de détérioration. Le résultat sur l'échelle EDSS doit demeurer inférieur à 7. Toutefois, le glatiramère demeure couvert pour les personnes assurées ayant utilisé ce médicament au cours des 3 mois précédant le 2 juin 2014 en autant que le médecin fournisse la preuve d'un effet bénéfique par l'absence de détérioration. Le résultat sur l'échelle EDSS doit demeurer inférieur à 7 **Reference:** http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/liste_med_2016_10_03_fr.pdf Information retrieved on October 6, 2016
NB	For the treatment of patients with clinically definite multiple sclerosis (CDMS) including relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis who meet the following criteria: • Two disabling attacks of MS in the previous two years, AND • Ambulatory with or without aid (EDSS of less than or equal to 6.5) **Clinical Note:** • An attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least one month. **Claim Note:** • Prescriptions written by New Brunswick neurologists do not require special authorization. **Reference:** http://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/NewBrunswickDrugPlansFormulary.pdf Information retrieved on July 26, 2016
NS	The province of Nova Scotia through the Dalhousie MS Research Unit provides multiple sclerosis drug funding assistance. This funding provides coverage of select high cost medications for multiple sclerosis to Nova Scotia residents who meet established disease state criteria and who do not have other drug coverage. **Reference:** http://drugcoverage.ca/en-ca/Provincial-Coverage/nova-scotia/reimbursement-overview.aspx Information retrieved on November 10, 2016

Drug Plan	Criteria for Restricted Benefit
Nfld	For the treatment of Multiple Sclerosis (MS) in patients who meet the following criteria: • Written request from a neurologist. • Subjects over 18 years. • Confident diagnosis of relapsing-remitting , relapsing-progressive, or secondary progressive MS. • Two relapses in the previous 24 months (Relapse defined as the appearance of symptoms and signs compatable with MS, lasting greater than 24 hours and not due to a rise in temperature.) • Kurtzke EDSS score of 6.5 or less (assistance needed to walk about 20m without resting). **Reference:** http://www.health.gov.nl.ca/health/prescription/special_auth_drug_products.pdf Information retrieved on July 26, 2016
PEI	For the treatment of patients 18 years of age or older, diagnosed with relapsing-remitting and secondary progressive multiple sclerosis, who have had two attacks within the past two years, and have an EDSS score of 6.5 or less. **Reference:** http://www.gov.pe.ca/photos/original/hpei_formulary.pdf?_ga=1.165429753.798784050.1461245592 Information retrieved on July 26, 2016
Yukon	**Initial (approval period 1 year. Only a one-month supply to be dispensed at a time for the first year):** As first or second-line monotherapy for the treatment of RRMS when prescribed by an MS neurologist. Specialist's consult to be provided. For patients who meet ALL of the following criteria: • Patient has had at least two (2) clinical relapses in the previous two (2) years AND • patient is ambulatory with or without aid (EDSS of 6.5 or less), AND • patient is 18 years or older **Renewal (approval period 1 year):** When prescribed by an MS neurologist for patients who demonstrate continued therapeutic benefit outweighing any potential risks, as shown by relapse rate, EDSS, MRI scan (when possible), and overall clinical impression. Specialist's consult to be provided. A relapse is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least one (1) month.
NIHB	Glatiramer is not listed on the NIHB formulary but it is reimbursed, according to IMS Pharmastat reports. **Reference:** http://www.healthycanadians.gc.ca/publications/health-system-systeme-sante/nihb-drug-list-2016-liste-medicaments-ssna/index-eng.php Information retrieved on November 10, 2016

Drug Plan	Criteria for Restricted Benefit
BC	**Initial (approval period 1 year):** As first-line monotherapy for the treatment of relapsing-remitting multiple sclerosis (MS) diagnosed according to the current McDonald[i] clinical criteria and magnetic resonance imaging (MRI) evidence, when prescribed by a neurologist from a designated MS clinic, for patients who meet **ALL** of the following criteria: 1. Patient has had at least 2 disabling attacks[ii] of MS in the previous 2 years, **AND** 2. Patient is ambulatory with or without aid (EDSS of 6.5 or less), **AND** 3. Patient is 18 years of age or older. Note: • The McDonald clinical criteria for the diagnosis of MS are current as of October 26, 2010. • An attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least 1 month. **Renewal (approval period 1 year):** As monotherapy, when prescribed by a neurologist from a designated MS clinic, for the treatment of patients with relapsing-remitting MS, **AND** who have demonstrated that the therapeutic benefits outweigh any potential risks, as shown by relapse rate, EDSS, MRI scan, or overall clinical impression. **Change of Therapy:** As monotherapy, when prescribed by a neurologist from a designated MS clinic, for the treatment of patients with relapsing-remitting MS who have experienced failure or intolerance to a previous disease modifying therapy. **Practitioner Exemptions** • A Collaborative Prescribing Agreement (CPA) (PDF, 400KB) is available to neurologists specializing in MS whose primary place of practice is in a designated MS clinic. Neurologists who have signed a CPA are not required to submit a Special Authority request form for coverage. • **Important**: PharmaCare coverage covers glatiramer acetate for patients who meet the Limited Coverage criteria and whose prescription has been written by a neurologist who has entered into a CPA. • PharmaCare coverage and actual reimbursement is subject to the rules of a patient's PharmaCare plan, including any annual deductible requirement and any other applicable PharmaCare pricing policy. • Each CPA must be signed by the neurologist who is requesting coverage and not a delegate. • Practitioners who have not signed a CPA may submit a Special Authority request if the patient meets the criteria above. These prescriptions will not be covered automatically. **Reference:** http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-glatiramer-acetate Information retrieved on June 14, 2016
AB	Relapsing Remitting Multiple Sclerosis (RRMS): Special authorization coverage may be provided for the reduction of the frequency and severity of clinical relapses and reduction of the number and volume of active brain lesions, identified on MRI scans, in ambulatory patients with relapsing remitting multiple sclerosis.

Drug Plan	Criteria for Restricted Benefit
	Coverage For coverage, this drug must be prescribed by a registered MS Neurologist. A current assessment must be completed by a registered MS Neurologist at every request. To register to become an MS Neurologist please complete the Registration for MS Neurologist Status Form (ABC 60002). **Initial Coverage** 1) The registered MS Neurologist must confirm a diagnosis of RRMS; 2) The patient must have active disease which is defined as at least two relapses* of MS during the previous two years or in the two years prior to starting an MS disease modifying therapy (DMT). *A relapse is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 48 hours in the absence of fever, not associated with withdrawal from steroids. Onset of clinical relapses must be separated by a period of at least one month. At least one definite gadolinium-enhancing T1 MRI lesion (not questionable faint enhancement) obtained at least 90 days after initiation of the DMT and at least 90 days before or after a relapse may substitute for one clinical relapse. 3) The patient must be ambulatory with or without aid (The registered MS Neurologist must provide a current updated Expanded Disability Status Scale (EDSS) score less than or equal to 6.5). Coverage may be approved for up to 12 months. Patients will be limited to receiving a one-month supply of glatiramer acetate per prescription at their pharmacy for the first 12 months of coverage. **Continued Coverage** For continued coverage beyond the initial coverage period, the patient must meet the following criteria: 1) The patient must be assessed by a registered MS Neurologist; 2) The registered MS Neurologist must confirm a diagnosis of RRMS; 3) The registered MS Neurologist must provide a current updated EDSS score. The patient must not have an EDSS score of 7.0 or above sustained for one year or more. Coverage of this drug may be considered in a patient with a sustained EDSS score of 7.0 or above in exceptional circumstances. For MS DMT coverage to be considered, details of the exceptional circumstance must be provided in a letter from the registered MS Neurologist and accompany the Special Authorization Request Form. Continued coverage may be approved for up to 12 months. Patients may receive up to 100 days' supply of glatiramer acetate per prescription at their pharmacy. Restarting After an Interruption in Therapy Greater Than 12 Months In order to be eligible for coverage, after an interruption in therapy greater than 12 months, the patient must meet the following criteria: 1) At least one relapse* per 12 month period; or 2) At least two relapses* during the previous 24 month period.

Drug Plan	Criteria for Restricted Benefit
	All requests (including renewal requests) for glatiramer acetate must be completed using the Dimethyl Fumarate/Glatiramer Acetate/Interferon Beta-1a/Interferon Beta-1b/Teriflunomide Special Authorization Request Form (ABC 60001). **Reference:** https://idbl.ab.bluecross.ca/idbl/lookupCoverageCriteria.do?productID=0000022977&priceListID=0014 Information retrieved on July 26, 2016
Sask	Approval for coverage will be given to patients who are assessed and meet the following criteria: • have clinical definite relapsing and remitting multiple sclerosis; • have had at least two documented attacks of MS during the previous two years (an attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, preceded by stability for at least one month); • are fully ambulatory for 100 meters without aids (canes, walkers or wheelchairs) • Extended Disability Status Scale (EDSS) 5.5 or less; • are age 18 or older (Note: Applications for patients under 18 will be considered.) *Physicians should also forward the following information:* • documentation of attacks, date of onset, date of diagnosis; • neurological findings, Extended Disability Status Scale (EDSS); • MRI reports or other significant information; • list of current medications **Reference:** http://formulary.drugplan.health.gov.sk.ca/PDFs/APPENDIXD.pdf Information retrieved on July 26, 2016
Manitoba	Specialists from the MS Clinic may apply for Part 3 EDS. Please contact the EDS Program at MB Health for specific criteria. **Reference:** http://www.gov.mb.ca/health/mdbif/edsnotice.pdf information retrieved on August 19, 2016
Ontario	**Dosage Form/Strength:**20 mg/mL pre-filled syringe for subcutaneous injection **For CDMS:** COPAXONE® requests for patients with CDMS will be reviewed by external medical experts when the following information is provided: • Date and details of the most recent neurological examination (within the last 90 days); and • Dates and details (e.g., neurological findings) of at least two clinical attacks, including one clinical attack within the past year; and • EDSS score ≤ 5. **Renewal** requests for COPAXONE® can be submitted through the Telephone Request Service and will be considered for patients who have benefited from therapy and have an EDSS score ≤ 5.

Drug Plan	Criteria for Restricted Benefit
	The physician must provide the following information: • Description of the patient's clinical course in the last year, including details of all attacks; • Date and details of the most recent neurological examination (within the last 90 days); and • he patient's most recent EDSS score. **Standard approval duration:** First renewal: 2 years Second and subsequent renewals: 5 years **Reference:** http://www.health.gov.on.ca/en/pro/programs/drugs/pdf/frequently_requested_drugs.pdf Information retrieved on July 26, 2016
Quebec	**Indication:** Pour le traitement des personnes souffrant de sclérose en plaque de forme rémittente, diagnostiquée selon les critères de McDonald (2010), ayant présenté 1 poussée dans la dernière année et dont le résultat sur l'échelle EDSS est inférieur à 7 **Initial Coverage:** L'autorisation de la demande initiale est d'une durée maximale d'un an. **Continued Coverage:** Les autorisations des demandes subséquentes sont d'une durée maximale d'un an. Cependant, le médecin doit fournir la preuve d'un effet bénéfique par l'absence de détérioration. Le résultat sur l'échelle EDSS doit demeurer inférieur à 7. Toutefois, le glatiramère demeure couvert pour les personnes assurées ayant utilisé ce médicament au cours des 3 mois précédant le 2 juin 2014 en autant que le médecin fournisse la preuve d'un effet bénéfique par l'absence de détérioration. Le résultat sur l'échelle EDSS doit demeurer inférieur à 7 **Reference:** http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/liste_med_2016_10_03_fr.pdf Information retrieved on October 6, 2016
NB	For the treatment of patients with clinically definite multiple sclerosis (CDMS) including relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis who meet the following criteria: • Two disabling attacks of MS in the previous two years, AND • Ambulatory with or without aid (EDSS of less than or equal to 6.5) **Clinical Note:** • An attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least one month.

Drug Plan	Criteria for Restricted Benefit
	Claim Note: • Prescriptions written by New Brunswick neurologists do not require special authorization. **Reference:** http://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/NewBrunswickDrugPlansFormulary.pdf Information retrieved on July 26, 2016
NS	The province of Nova Scotia through the Dalhousie MS Research Unit provides multiple sclerosis drug funding assistance. This funding provides coverage of select high cost medications for multiple sclerosis to Nova Scotia residents who meet established disease state criteria and who do not have other drug coverage. **Reference:** http://drugcoverage.ca/en-ca/Provincial-Coverage/nova-scotia/reimbursement-overview.aspx Information retrieved on November 10, 2016
Nfld	For the treatment of Multiple Sclerosis (MS) in patients who meet the following criteria: • Written request from a neurologist. • Subjects over 18 years. • Confident diagnosis of relapsing-remitting , relapsing-progressive, or secondary progressive MS. • Two relapses in the previous 24 months (Relapse defined as the appearance of symptoms and signs compatable with MS, lasting greater than 24 hours and not due to a rise in temperature.) • Kurtzke EDSS score of 6.5 or less (assistance needed to walk about 20m without resting). **Reference:** http://www.health.gov.nl.ca/health/prescription/special_auth_drug_products.pdf Information retrieved on July 26, 2016
PEI	For the treatment of patients 18 years of age or older, diagnosed with relapsing-remitting and secondary progressive multiple sclerosis, who have had two attacks within the past two years, and have an EDSS score of 6.5 or less. **Reference:** http://www.gov.pe.ca/photos/original/hpei_formulary.pdf?_ga=1.165429753.798784050.1461245592 Information retrieved on July 26, 2016
Yukon	**Initial (approval period 1 year. Only a one-month supply to be dispensed at a time for the first year):** As first or second-line monotherapy for the treatment of RRMS when prescribed by an MS neurologist. Specialist's consult to be provided. For patients who meet ALL of the following criteria: • Patient has had at least two (2) clinical relapses in the previous two (2) years AND • patient is ambulatory with or without aid (EDSS of 6.5 or less), AND • patient is 18 years or older

Drug Plan	Criteria for Restricted Benefit
	Renewal (approval period 1 year): When prescribed by an MS neurologist for patients who demonstrate continued therapeutic benefit outweighing any potential risks, as shown by relapse rate, EDSS, MRI scan (when possible), and overall clinical impression. Specialist's consult to be provided. A relapse is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least one (1) month.
NIHB	Glatiramer is not listed on the NIHB formulary but it is reimbursed, according to IMS Pharmastat reports. **Reference:** http://www.healthycanadians.gc.ca/publications/health-system-systeme-sante/nihb-drug-list-2016-liste-medicaments-ssna/index-eng.php Information retrieved on November 10, 2016

Restricted Benefit Criteria for COPAXONE® 20 mg/mL for the Treatment of RRMS

Drug Plan	Criteria for Restricted Benefit
ON	**Dosage Form/Strength:** 20 mg/mL pre-filled syringe for subcutaneous injection **For the treatment of Clinically Isolated Syndrome (CIS):** requests for patients who have experienced a single demyelinating event will be reviewed by external medical experts when the following information is provided: • Date and details of the most recent neurological examination which must have been conducted within the last ninety days of the request; • The patient's EDSS is less than or equal to 6.0 (please provide EDSS score); AND • The patient's clinically isolated syndrome occurred within the last twelve months. **Renewal** requests will be assessed according to the following criteria: • the requesting physician provides the date and details of the patient's most recent neurological examination and EDSS scores; • the patient's neurological examination occurred within that last ninety days; • the patient is stable (i.e. no relapses or attacks during the last year) and • the patient's EDSS is less than or equal to 6.0 **Standard approval duration**: 1 year **Reference:** http://www.health.gov.on.ca/en/pro/programs/drugs/pdf/frequently_requested_drugs.pdf Information retrieved on July 26, 2016

Drug Plan	Criteria for Restricted Benefit
QC	**Indication:** Pour le traitement des personnes ayant présenté une première poussée clinique aigue de démyélinisation documentée **Initial Coverage:** Le médecin doit fournir, au début du traitement, les résultats d'une résonance magnétique démontrant: • la présence d'au moins 1 lésion hyperintense en T2 non symptomatique touchant au moins 2 des 4 régions suivantes: périventriculaires, juxtacorticale, infratentorielle ou moelle épinière; et • le diamètre de ces lésions est de 3mm ou plus. • la durée maximale de l'autorisation initiale est de 1 an. **Continued Coverage:** Lors de demandes subséquentes, le médecin doit fournir la preuve d'un effet bénéfique par l'absence de nouvelle poussée clinique. Toutefois, le glatiramère demeure couvert pour les personnes assurées ayant utilisé ce médicament au cours des 3 mois précédant le 2 juin 2014 en autant que le médecin fournisse la preuve d'un effet bénéfique par l'absence de nouvelle poussée clinique. **Reference:** http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/liste_med_2016_10_03_fr.pdf Information retrieved on October 6, 2016
NB	For the treatment of patients who have experienced a clinically isolated syndrome (CIS) and are considered at risk for developing CDMS. **Clinical Note:** • An attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, and preceded by stability for at least one month. **Claim Note:** • Prescriptions written by New Brunswick neurologists do not require special authorization. **Reference:** http://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/NewBrunswickDrugPlansFormulary.pdf Information retrieved on July 26, 2016

Appendix 3: Summary of Patient Input

This section was summarized by CDR staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

One patient group, Multiple Sclerosis (MS) Society of Canada, provided input for this review.

The MS Society provides services to people with multiple sclerosis, their families and caregivers, and funds research to find the cause and cure for multiple sclerosis.

In the past 12 months, the MS Society received educational grants from the following companies: Bayer, Biogen, EMD Serono, Novartis, Pfizer, Genzyme – A Sanofi Company, Allergan, and Teva Neuroscience. No conflicts of interest were declared for this submission.

Information for this review was gathered from publicly available information about the impact of MS and through a survey posted to the MS Society of Canada website and social media channels from January 23, 2017 to February 5, 2017.

2. Condition Related Information

Multiple sclerosis is an unpredictable, sometimes disabling disease of the central nervous system for which there is no cure. The most common symptoms affecting MS patients include fatigue, difficulty in walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. Other symptoms may include issues with balance, sexual dysfunction, spasticity, tremor, weakness and difficulty speaking and swallowing. Depending on the type and severity of the symptom, an individual's quality of life can be greatly impacted. The episodic nature of MS and its symptoms can have a negative impact on an individual living with MS as well as their family members. MS can interfere with, or introduce a barrier to employment, education, physical activity, family commitments, interpersonal relationships and social and recreational life.

Patients who responded to the survey also provided some context with regard to the impact of MS on their lives:

"I currently cannot work; I had to discontinue attending post-secondary school, change career paths and move back home with my parents. Everyday life is completely different than before I had MS." – patient with MS
"It has ruined my life I can't do the things that I once could; it has taken my vision, balance, and coordination just to name a few [things]." – patient with MS

3. Current Therapy Related Information

Many MS therapies have similar mechanisms of action; however, dosing and administration are not the same and therefore the options available to people are selected based on tolerance, known (expected) side-effects, lifestyle choices, disease course and cost. It is very common for one treatment to work well in one individual, and fail in another.

Over 89% of respondents reported that they are currently, or were previously treated with Copaxone 20mg. Of those, about half reported experiencing fewer relapses while taking Copaxone 20mg (as compared with no treatment). Approximately 27% reported not knowing if treatment with Copaxone 20mg was effective in managing their MS and 18% felt it did not manage their MS. Other respondents reported they had fewer hospitalizations, maintained stable Expanded Disability Status Scale (EDSS) scores, were able to remain in the workforce, had fewer lesions and experienced symptom improvements while taking Copaxone 20mg. Close to 100% of respondents who were taking, or previously took Copaxone 20mg were aware of the patient support program offered by the pharmaceutical company and over half of those had used the program for information related to medication side-effects; 16% contacted the program for financial assistance. Eighty-four per cent of all respondents felt that the patient support program was helpful. Side-effects of Copaxone 20mg include injection site reactions (redness, pain, inflammation, itching, or a lump), immediate post-injection reaction (flushing, chest tightness or pain with heart palpitations, anxiety, and trouble breathing) and lipoatrophy.

Other DMTs used by respondents included Tecfidera, Rebif, Aubagio, Avonex and Tysabri. Sixty per cent of respondents taking medications other than Copaxone 20mg felt that their medication was effective in managing their MS while 28% were unsure. The most common side-effects reported included flu-like symptoms, pain, headache, gastrointestinal symptoms, and injection site reactions. Approximately 24% reported they did not experience any side-effects. More than half of those who experienced side-effects reported that their side-effects were managed effectively with over-the-counter medications. Twenty-three per cent reported that the side-effects resolved on their own within several months of taking the medication. Medication side-effects were reported as the most important factor to consider when selecting a DMT, followed by the safety profile of the drug, advice given by their clinician, route of administration and cost. About 20% of respondents indicated that high cost, access to public drug plans, limited transportation to receive drug administration (i.e., infusion clinic) were issues in accessing their medication.

Approximately 60% of respondents said they would switch medication from Copaxone 20mg to a different DMT. Many commented on the desire to switch from Copaxone 20mg daily to Copaxone 40mg three times weekly. The other reason given for switching from Copaxone 20mg to another therapy was to avoid daily injections.

Patients who responded to the survey also provided some context with regard to current MS therapies and their on their lives:

“Please approve the larger dosage for Copaxone after 5 years I hate injections and try each night to find a reason not to do it. Of course, I do the injection, but would be happier with doing the injection 3 days a week. Injection fatigue is real.” – patient with MS
“Needles every day is part of my life I hate. The ability to take 3 a week would make a huge difference in my life, if it didn’t come with a hefty price. The pain is real, the dents are real, lipoatrophy is real and it sucks.” – patient with MS

4. Expectations about the Drug being Reviewed

Information for this section was gathered from publicly available information about the impact of MS and through a survey posted to the MS Society of Canada website and social media channels from January 23, 2017 to February 5, 2017.

Approximately 63% of respondents reported they would choose the originator drug over a subsequent-entry product based on trust and comfort in taking the originator. This preference was stated to be due to length of time it has been on the market and its known safety and efficacy data. Fear of switching to a subsequent entry product was also reported because it is ‘similar’ rather than ‘equivalent’.

The main reason provided for choosing a subsequent entry product over the originator was related to cost to the individual treated and payers. Some respondents felt they didn’t know enough about subsequent entry products to comment, or make a decision about treatment with a subsequent entry product rather than the originator.

“If the same drug, then I would consider the cost to the province.” – patient with MS

“I think it would be cheaper, and a lot of people with MS are on disability.” – patient with MS

5. Additional Information

Key messages were related to the following themes:

- Individual choice of therapy should be based on lifestyle, perceived benefit versus risk and individual preference of administration.
- The MS Society believes that the decision to use an originator or a subsequent entry product must be made jointly by people living with MS and their health care provider; individuals should be provided with all relevant information to make an informed choice.

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