Development of the First FDA-Approved MS Generic Disease-modifying Therapy: Glatopa® (glatiramer acetate injection)

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BACKGROUND

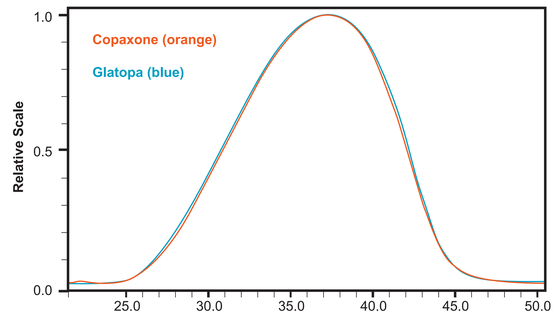
In the United States (US), disease-modifying therapy (DMT) costs for multiple sclerosis (MS) continue to rise despite the availability of numerous treatment options, with first-generation DMTs costing approximately $80,000 annually per patient[1]. Copaxone® (glatiramer acetate injection; Teva Pharmaceutical Industries Ltd.) 20 mg/mL has been approved in the US for nearly two decades; the price (AWP) has more than doubled in the past 5 years[1]. Glatiramer acetate (GA) is a mixture of synthetic polypeptides, made through a chemical synthesis from four amino acids (alanine, glutamic acid, lysine, and tyrosine)[2-4] without using cellular/biological starting materials (and therefore is not a biologic.) In April 2015, the Food and Drug Administration (FDA) approved the first generic disease-modifying therapy for MS: Glatopa® (GA injection; Sandoz, Inc.) 20 mg/mL. Glatopa is fully substitutable for Copaxone 20 mg/mL for relapsing-forms of MS. The exact mechanism of GA is unknown, but GA is believed to exert its biological effects as an antigen-based immunomodulatory agent by targeting multiple pathways on both the innate and adaptive arms of the immune system. This poster reviews the development of Glatopa 20 mg/mL.

METHODS

Glatiramer acetate is a complex mixture of polypeptides (not a biologic) and, consequently, its characterization presented challenges not generally encountered in generic drug development. Utilizing the Abbreviated New Drug Application (ANDA) regulatory pathway – the pathway used for development and FDA approval of generic drugs in the US – equivalence of Glatopa to Copaxone 20 mg/mL was shown based on starting materials and basic chemistry; structural signatures associated with the process used to manufacture GA; structural properties; and biological and immunological properties. Multiple samples of Glatopa and Copaxone 20 mg/mL were used for analyses. Examples of the structural and functional studies are shown below; methods for these have been previously published[5,6].

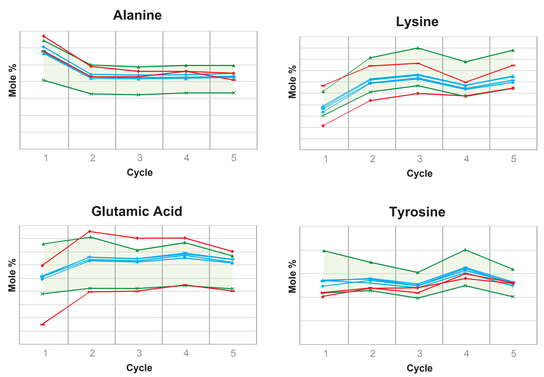
RESULTS

Figure 1. Molar Mass Distributions



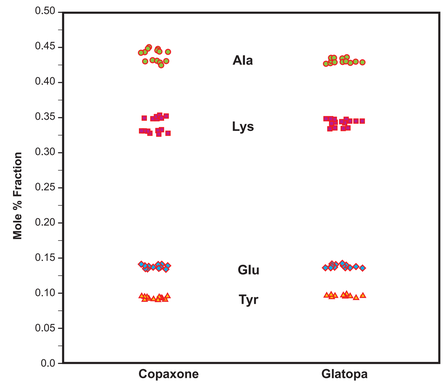
Overlay of the molar mass distributions of Glatopa and Copaxone, as measured by size exclusion chromatography.

Figure 2. Amino Acid Levels for First 5 Cycles of N-Terminal Analysis by Edman Degradation



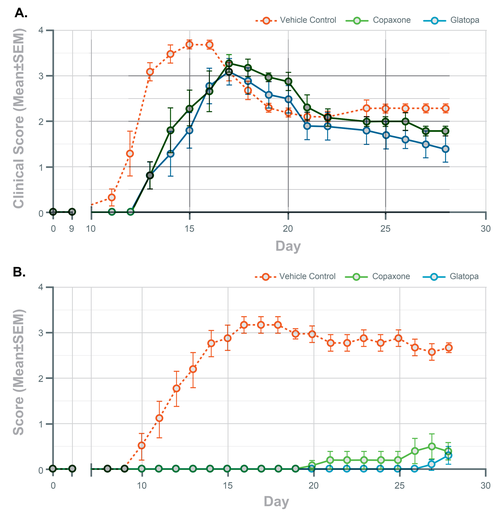
Relative amino acid levels at the N-termini of GA for the first 5 cycles of N-terminal analysis by Edman degradation. The green lines represent the Copaxone-based specifications for each amino acid for each cycle. Within these lines are the results for 4 Glatopa lots (blue). Also shown are 2 negative controls (red): one is a Step-1 reaction negative control where the reaction was run with a different solvent; the other is a Step-2 negative control, in which the depolymerization reaction was altered.

Figure 3: Total Amino Acid Composition



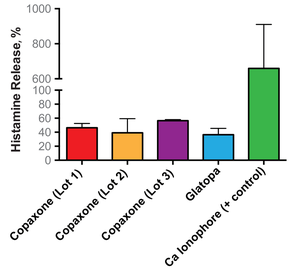
Amino acid compositions as mole fractions of final GA for several lots of Glatopa and Copaxone. Ala = alanine; Glu = glutamate; Lys = lysine; Tyr = tyrosine.

Figure 4: Experimental Autoimmune Encephalomyelitis (EAE) Prophylaxis Model Results



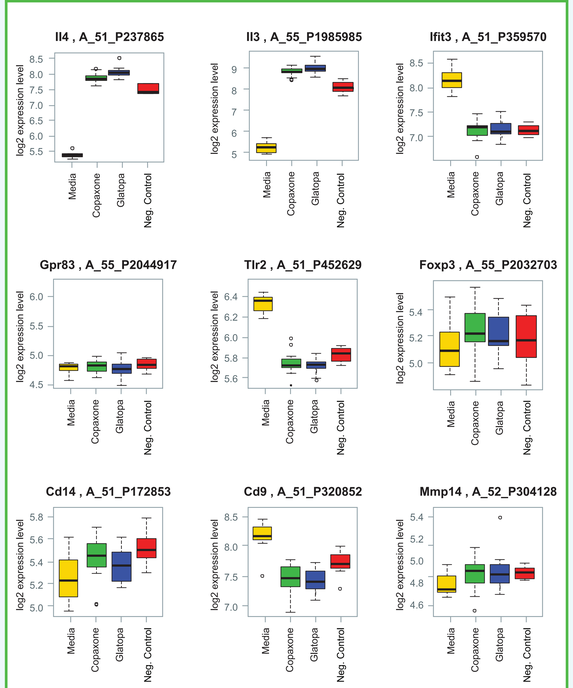
In both proteolipid peptide139–151 (A) and myelin oligodendrocyte glycoprotein35–55 (B) versions of the EAE model, Glatopa and Copaxone delayed symptom onset and reduced the magnitude of disease intensity. There were no statistically significant differences ($p<0.05$) between Glatopa and Copaxone.

Figure 5: Histamine Release from RBL-2H3 Cells



Percentage of histamine release from rat basophilic leukemia 2H3 cells after 1 hr of incubation with 3 lots of Copaxone, Glatopa, or calcium ionophore (positive control). Media only was used as a background control (data not shown). Each bar represents the mean triplicate test runs of histamine released as a % over background control. There were no significant differences ($p<0.05$) in histamine release between Glatopa and Copaxone.

Figure 6: Gene Expression Results



Box plots for gene expression changes for key Th2 cytokines IL-4 and IL-3 and additional genes related to immune cell function. No statistically significant differences ($p<0.05$) between Glatopa and Copaxone were observed for any of these genes.

DISCUSSION

- The results presented in this poster represent a small portion of the comprehensive set of structural and biological/functional assays that were conducted. Structural properties were equivalent across more than 45 tests and biological properties were equivalent across more than 15 assays including gene expression studies and a well-established animal model of MS.
- The development approach taken for Glatopa was further confirmed by FDA's publication of a draft Product-Specific Guidance (published after Glatopa's approval) which provides recommendations for the development of generic GA injection based on the demonstration of active pharmaceutical ingredient (API) sameness
- Glatopa has been available and manufactured in the US for over a year. The content of the Glatopa 20 mg package insert (PI) is the same as the Copaxone 20 mg PI, and the adverse events received from launch until June 30, 2016 for Glatopa are consistent with what is described in the Glatopa PI.
- The estimated savings from January 1, 2016 to present for Glatopa versus the 20 mg/mL dose of Copaxone is ~$17,000 annually per patient based on US wholesale acquisition costs[1].
- A comprehensive patient support program has been established for Glatopa, similar to that offered to users of Copaxone.

CONCLUSIONS

- No significant differences were observed in the structure and function of Glatopa and Copaxone 20 mg/mL following a comprehensive, high resolution scientific evaluation. Glatopa is the first FDA-approved MS generic DMT and remains the sole FDA-approved generic GA to date.
- This experience, along with the prior FDA approval of the complex generic drug enoxaparin, proves that a rigorous scientific approach and thorough characterization can successfully establish equivalence for complex drugs.

REFERENCES

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