Contains Nonbinding Recommendations

Draft Guidance on Glatiramer Acetate

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Active Ingredient: Glatiramer acetate

Dosage Form; Route: Injection; subcutaneous

Overview:

This draft guidance provides recommendations for the development of generic products for glatiramer acetate injection. FDA provides recommendations for demonstrating active pharmaceutical ingredient (API) sameness. Since the Reference Listed Drug (RLD) product is a parenteral solution, if the proposed generic (Test) product meets the following criteria for demonstrating API sameness and is qualitatively (Q1) and quantitatively (Q2) the same in terms of active and inactive ingredients as the RLD product, the generic sponsor may request to waive the requirement of in vivo bioequivalence (BE) study based on 21 CFR 320.22(b)(1).

Recommendations for Demonstrating API Sameness:[1]

Glatiramer acetate is a mixture of peptide copolymers containing four specific amino acids in a defined ratio. The amino acids present in glatiramer acetate are L-glutamic acid, L-lysine, L-alanine and L-tyrosine with an average molar ratio of 0.141, 0.338, 0.427 and 0.095 respectively.[2] API sameness can be established by showing equivalence between the Test product and the RLD product as to the four criteria described in detail below. Generic drug sponsors are advised to perform side-by-side comparative studies using the Test API and the API obtained from the RLD product. It is recommended that at least three batches of the Test API and three batches of API from the RLD should be characterized to assess API sameness and robustness in the manufacturing process. The following four criteria should be used to demonstrate API sameness:

1. Equivalence of fundamental reaction scheme;
2. Equivalence of physicochemical properties including compositions;
3. Equivalence of structural signatures for polymerization and depolymerization; and
4. Equivalence of biological assay results.

A. Equivalence of fundamental reaction scheme

[1] For more detailed discussion, see the FDA response to Citizen Petition, Docket No. FDA-2015-P-1050, which is available to the public at: http://www.regulations.gov.
[2] See the labeling information of Copaxone (NDA 020622).

A fundamental reaction scheme for the manufacture of glatiramer acetate has been published which features the polymerization reaction of activated amino acids and initiator, followed by a partial depolymerization of the intermediate copolymers.[3,4] An ANDA applicant may satisfy this first criterion of active ingredient sameness by using the same (or equivalent): (1) NCA-amino acids and polymerization initiator to yield the intermediate copolymer; and (2) chemical reagent(s) for acid-catalyzed cleavage conditions. The elements of a fundamental reaction scheme to manufacture glatiramer acetate can be determined and confirmed using publicly available information on the synthesis process[5] in conjunction with diagnostic analysis of the RLD by orthogonal analytical measurements.

B. Equivalence of physicochemical properties, including composition

Physicochemical properties, such as amino acid composition, molecular weight distribution, spectroscopic fingerprints can provide broad and important characterizations in confirming API sameness and equivalence in underlying reaction schemes. Generic sponsors should perform side-by-side comparative physicochemical characterizations of Test API and the API from the RLD. Methods and results of the characterizations should be reported to the Agency. The following physicochemical characterizations should be performed to demonstrate the API sameness:

1. Amino acid content and optical purity of the four amino acids;
2. Molecular weight distribution, including the molar mass moments (Mn, Mw and Mz) and polydispersity (Ip);
3. Spectroscopic fingerprints, including but not limited to, Fourier Transformation Infrared spectroscopy (FT-IR), nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) and circular dichroism (CD).

C. Equivalence of structural signatures for polymerization and depolymerization

The composition and sequence diversity of peptide copolymers in glatiramer acetate are governed by the polymerization and depolymerization reaction kinetics used in the synthesis. Structural signatures refer to certain characteristics in the API resulting from the underlying reactions, such as initiation chemistry of the peptide chains, coupling between the various amino acids pairs during propagation and any cleavage preference of depolymerization. An important feature of the polymerization step is that the molar fractions of each of the four amino acids in the intermediate copolymer chain vary across the synthesized chain, which is referred to as propagational shift. A generic sponsor should identify and analyze structural signatures that are chemical attributes of glatiramer acetate and correlate to both the polymerization step (including initiation kinetics and propagational shift) and the cleavage step of partial depolymerization. Information should be provided to the Agency to support the validity of the proposed structural signatures and the corresponding methods, which can be supported, for example, by (a) a mechanistic understanding of the synthetic process, (b) published literature, (c) pharmaceutical development studies that link changes in the ANDA manufacturing process to the corresponding

[3] Teitelbaum D., Meshorer A., Hirshfeld T., Arnon R., Sela M., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide". Eur. J. Immunol. 1971, 1 (4), pp. 242-248.
[4] US Patent 7,199,908 describes the synthesis of copolymer-1 (glatiramer acetate).
[5] See notes 2 and 3, for example.

structural signature, (d) negative control studies that introduce variations in the process and corresponding variations to the resulting product and structural signatures and (e) the proposed equivalence range/acceptance criteria should be based on the batch-to-batch variations of the RLD product.

1. Structural signatures for polymerization initiation

Two characteristics should be captured: 1) the distribution of the four amino acid-initiator adducts; and 2) the initiator content in the copolymer.

2. Structural signatures for propagational shift during polymerization

A generic sponsor should identify relevant amino acid sequence properties and corresponding analytical procedures, which can quantitatively measure the propagational shift in the generic and RLD products, and demonstrate that the propagational shift resulting from its process is the same (or equivalent) as the propagational shift present in the RLD.

3. Structural signatures for cleavage reactions in partial depolymerization

A generic sponsor should characterize any preference at the site of cleavage and average number of cleavages for an intermediate copolymer chain. For example, detailed analysis of N-termini and C-termini of the copolymers and the ratio of "uncapped" C-termini formed by the cleavage reaction versus "capped" C-termini produced by initiation reaction in the Test API and API from the RLD should be performed. The results and rationale should be provided to the Agency.

D. Equivalence of biological assay results

A biological assay can serve as a confirmatory test of equivalence and provide complementary confirmation of API sameness. FDA recommends generic sponsors to conduct at least the following two experimental autoimmune encephalomyelitis (EAE) assays[6,7]: 1) prophylactic dosing in the active C57BL/6 mouse model induced by immunization with myelin oligodendrocyte glycoprotein peptide 35-55 in adjuvant, and 2) Therapeutic dosing in the passive SJL mouse model induced by adoptive transfer of encephalitogenic T cells activated in vitro with proteolipid lipoprotein peptide 139 – 151[8,9] .

[6] Robinson A. P., Harp C.T., Noronha A., Miller S.D. "The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment". Handb. Clin. Neurol. 2014, 122, pp. 173-189.

[7] Stern J. N. H., Illés Z., Reddy J., Keskin D. B., Sheu E., Fridkis-Hareli M., Nishimura H., Brosnan C. F., Santambrogio L., Kuchroo V. K., Strominger J. L., "Amelioration of Proteolipid Protein139-151-Induced Encephalomyelitis in SJL Mice by Modified Amino Acid Copolymers and Their Mechanisms". Proc. Natl. Acad. Sci. USA 2004, 101 (32), pp. 11743-11748.

[8] McCarthy D. P., Richards M.H., Miller S.D. "Mouse models of multiple sclerosis: "Experimental autoimmune encephalomyelitis and Theiler's virus-induced demyelinating disease." Methods Mol. Biol. 2012, 900, 99. 381-401.

[9] Miller S.D., Karpus WJ, Davidson TS. "Experimental autoimmune encephalomyelitis in the mouse."Curr. Protoc. Immunol. 2007, Unit–15.1.