20000020 54 - 5. For Reference

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/28 — A1

(11) International Publication Number: WO 99/21578

(43) International Publication Date: 6 May 1999 (06.05.99)

(21) International Application Number: PCT/US98/22434

(22) International Filing Date: 22 October 1998 (22.10.98)

(30) Priority Data:

60/063,104	24 October 1997 (24.10.97)	US
60/088,930	11 June 1998 (11.06.98)	US

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: BRADER, Mark, Laurence [NZ/US]; 6465 North Park Avenue, Indianapolis, IN 46220 (US).

(74) Agents: KELLEY, James, J. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: INSOLUBLE INSULIN COMPOSITIONS

(57) Abstract

The present invention relates to insoluble compositions containing acylated proteins selected from the group consisting of acylated insulin, acylated insulin analog, and acylated proinsulin, and formulations thereof. The formulations are suitable for parenteral delivery or other means of delivery, to a patient for extended control of blood glucose levels. More particularly, the present invention relates to compositions comprised of an acylated protein complexed with zinc, protamine, and a phenolic compound such that the resulting microcrystal is analogous to the neutral protamine Hagedorn (NPH) insulin crystal form. Surprisingly, it has been discovered that compositions of such acylated proteins have therapeutically superior subcutaneous release pharmacokinetics, and more extended and flatter glucodynamics, than presently available commercial preparations of NPH insulin. Yet, the present crystals retain certain advantageous properties of NPH crystals, being readily able to be resuspended and also mixable with soluble insulins.