PCT
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61J 1/05, 1/14

A1

(11) International Publication Number: WO 00/12043

(43) International Publication Date: 9 March 2000 (09.03.00)

(21) International Application Number: PCT/SE99/01440

(22) International Filing Date: 24 August 1999 (24.08.99)

(30) Priority Data:
9802938–2 1 September 1998 (01.09.98) SE

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMPROVED STABILITY FOR INJECTION SOLUTIONS

(57) Abstract

A primary package containing a low molecular weight peptide–based thrombin inhibitors which package is sealed with a rubber stopper or plunger containing bromobutyl rubber.

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IMPROVED STABILITY FOR INJECTION SOLUTIONS

Field of the invention

The present invention relates to solutions of low molecular weight thrombin inhibitors stored in primary packages containing rubber components, such as vials, bottles, cartridges and prefilled syringes. The invention also relates to the medical use of such stored thrombin inhibitor solutions.

Background of the invention

Solutions for parentheral use of pharmaceutically active substances are normally stored in primary packages such as, vials, bottles, cartridges or in prefilled syringes. The primary packages are sealed by a rubber stopper or plunger. A commonly used rubber material contains chlorobutyl. Solutions of low molecular weight thrombin inhibitors stored in vials, bottles, cartridges and prefilled syringes sealed by a stopper or plunger containing chlorobutyl rubber exhibits increased degradation, leading to shortened time of storage.

Disclosure of the invention

It has now surprisingly been found that by using rubber material containing bromobutyl instead of chlorobutyl, the stability of the low molecular weight thrombin inhibitors in solution can be considerably improved.

The present invention provides a primary package, such as a vial, a bottle, a cartridge or a prefilled syringe containing a solution of a low molecular weight thrombin inhibitor for parentheral injection, sealed by a rubber stopper or plunger containing bromobutyl rubber instead of chlorobutyl rubber.

The present invention further provides a medical use of such thrombin inhibitor, or salts of such thrombin inhibitor, solutions kept in a primary package as mentioned above sealed by bromobutyl stoppers or plungers.

The present invention further provides an aqueous solution for parenteral administration comprising a low molecular weight peptide-based thrombin inhibitor or a salt thereof, having a pH in the range 3 to 8, preferably a pH about 5 and stored in a primary package, such as a vial, a bottle, a cartridge or a prefilled syringe, sealed by a rubber stopper or plunger containing bromobutyl.

Thrombin inhibitors referred to in this application are low molecular weight peptide-based thrombin inhibitors. The term "low molecular weight peptide-based thrombin inhibitors" will be well understood by one skilled in the art to include thrombin inhibitors with one to four peptide linkages, and/or with a molecular weight below 1000, and includes those described generically and, more preferably, specifically in the review paper by Claesson in Blood Coagul. Fibrin. (1994) 5, 411, as well as those disclosed in US Patent No. 4,346,078; International Patent Applications WO 97/23499, WO 97/02284, WO97/46577, WO 98/01422, WO 93/05069, WO93/11152, WO 95/23609, WO95/35309, WO 96/25426, WO 94/29336, WO WO 93/18060 and WO 95/01168; and European Patent Applications 623 596, 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317 and 601 459.

Preferred low molecular weight peptide-based thrombin inhibitors include those known collectively as the "gatrans". Particular gatrans which may be mentioned include HOOC-CH_2(R)Cha-Pic-Nag-H (known as inogatran; see International Patent Application WO 93/11152 and the list of abbreviations therein) and HOOC-CH_2-(R)Cgl-Aze-Pab-H (known as melagatran; see International Patent Application WO 94/29336 and the list of abbreviations therein).

The preferred low molecular weight peptide-based thrombin inhibitor to be kept in glass vials or syringes is selected from the group consisting of inogatran, *(Glycine, N-[2-[2-[[[3-[(aminoimino-methyl)amino]propyl]amino]carbonyl]-1-piperidinyl]-1-(cyclohexylmethyl)-2-oxoethyl]-, [2R-[2S]]-)*, melagatran, *(Glycine, N-[2-[2-[[[[4 (aminoiminomethyl)phenyl]-methyl]amino]carbonyl]-1-azetidinyl]-1-cyclohexyl-2-oxoethyl]-, [2R-[2S]]-)* and
compound A, *(Glycine, N-[1-cyclohexyl-2-[2-[[[[4-[(hydroxyimino)aminomethyl]-phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]-, ethyl ester, [S-(R*, S*)]-).*

In one embodiment of the invention the thrombin inhibitor (preferably melagatran) solutions for parentheral injection is a water solution and are kept in primary packages such as vials, bottles, cartridges or prefilled syringes having a rubber stopper or plunger containing bromobutyl.

In another embodiment of the invention; the thrombin inhibitor for parentheral injection is in a water solution with an addition of hydroxy-propyl-β-cyclodextrin (HPβCD). The concentration of the thrombin inhibitor is in the range 0.001-100 mg/ml, preferably 2.5-20 mg/ml.

Working Example

Analytical technique

Liquid Chromatography (LC), for all analysis

The following equipment and parameters were used at the analysis of melagatran in solution.

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