

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
12 September 2019 (12.09.2019)



(10) International Publication Number
WO 2019/171093 A2

(51) International Patent Classification:

C07C 59/72 (2006.01) C07C 51/41 (2006.01)
C07C 59/58 (2006.01) C07C 213/08 (2006.01)
C07C 59/90 (2006.01) C12P 15/00 (2006.01)

(21) International Application Number:

PCT/HU2019/050007

(22) International Filing Date:

07 March 2019 (07.03.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

P1800089 09 March 2018 (09.03.2018) HU

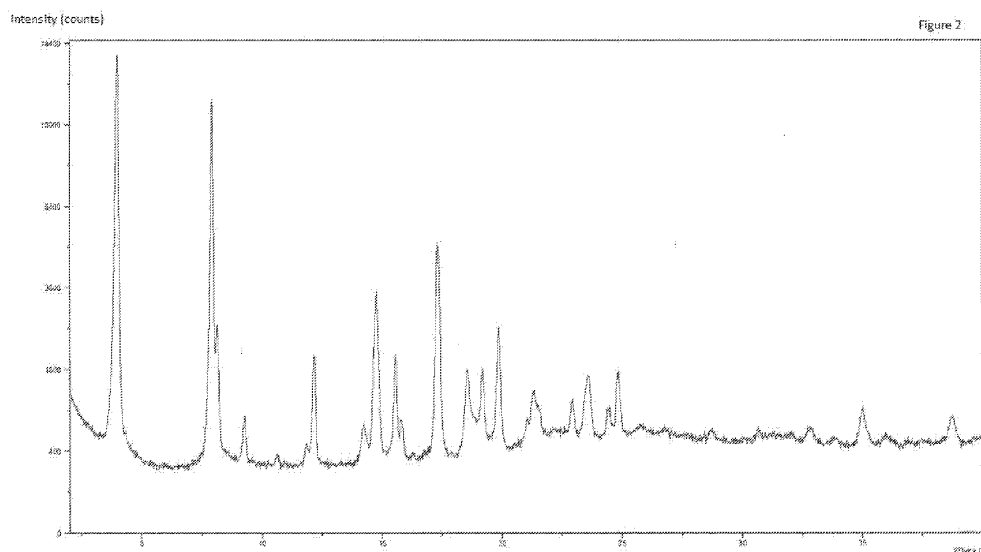
(71) Applicant: **CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA ZRT.** [HU/HU]; Tó u. 1-5., 1045 Budapest (HU).

(72) Inventors: **HORTOBÁGYI, Irén**; c/o Chinoín Gyógyszer és Vegyészeti Termékek Gyára Zrt., Tó u. 1-5., 1045 Budapest (HU). **LÁSZLÓFI, István**; c/o Chinoín Gyógyszer és Vegyészeti Termékek Gyára Zrt., Tó u. 1-5., 1045 Budapest (HU). **VARGA, Zoltán**; c/o Chinoín Gyógyszer és Vegyészeti Termékek Gyára Zrt., Tó u. 1-5., 1045 Budapest (HU). **JUHÁSZ, Imre**; c/o Chinoín Gyógyszer és Vegyészeti Termékek Gyára Zrt., Tó u. 1-5., 1045 Budapest (HU). **RITZ, Imola**; c/o Chinoín Gyógyszer és Vegyészeti Termékek Gyára Zrt., Tó u. 1-5., 1045 Budapest (HU). **KARDOS, Zsuzsanna**; c/o Chinoín Gyógyszer és Vegyészeti Termékek Gyára Zrt., Tó u. 1-5., 1045 Budapest (HU).

(74) Agent: **TEPFENHÁRT, Dóra**; DANUBIA Patent & Law Office LLC, Bajcsy-Zsilinszky út 16., 1051 Budapest (HU).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

(54) Title: PROCESS FOR THE PREPARATION OF POLYMORPH FORM B OF TREPROSTINIL DIETHANOLAMINE SALT



(57) Abstract: The invention relates to a robust and reproducible process for the preparation of polymorph form B of treprostinil diethanolamine salt, comprising the following steps: a. treprostinil is dissolved in methanol, b. to the solution of step a) diethanolamine or its methanol solution is added, c. the reaction mixture of step b) is agitated till dissolution, d. when salt formation is completed in step c), first portion of an aprotic solvent is added to the solution, e. the solution of step d) is filtered to remove insoluble impurities, f. the filtrate of step e) is seeded with polymorph form B of treprostinil diethanolamine salt, g. to the crystal suspension obtained in step f) a second portion of the aprotic solvent is added, h. the suspension of step g) is agitated until crystallisation is completed, i. the crystals are separated, washed and dried.

[Continued on next page]

WO 2019/171093 A2

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*