2005022173

07 APR 2005

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2004 (22.04.2004)

PCT

162162

(10) International Publication Number
WO 2004/033428 A1

(51) International Patent Classification[7]: C07D 211/58, 413/14, 409/14, 401/14, 471/04, 405/14, 417/14

(21) International Application Number:
PCT/EP2003/050697

(22) International Filing Date: 7 October 2003 (07.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP02/11328 8 October 2002 (08.10.2002) EP
PCT/EP02/14836 23 December 2002 (23.12.2002) EP

(71) Applicant *(for all designated States except US)*: **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JANSSENS, Frans, Eduard** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **SOMMEN, François, Maria** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **DE BOECK, Benoît, Christian, Albert, Ghislain** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **LEENAERTS, Joseph, Elisabeth** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **VAN ROOSBROECK, Yves, Emiel, Maria** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **DIELS, Gaston, Stanislas, Marcella** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Common Representative: **JANSSEN PHARMACEUTICA N.V.**; Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

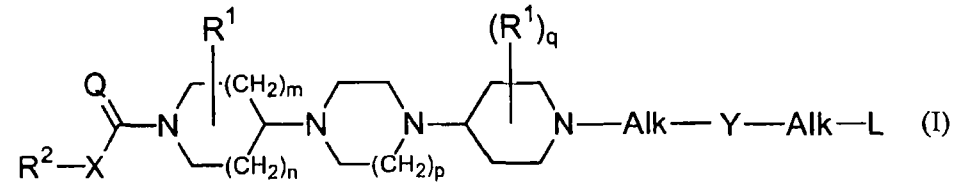
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

[Continued on next page]

(54) Title: SUBSTITUTED 1,4-DI-PIPERIDIN-4-YL-PIPERAZINE DERIVATIVES AND THEIR USE AS NEUROKININ ANTAGONISTS



(I)

(57) Abstract: The invention concerns substituted 1,4-di-piperidin-4-yl-piperazine derivatives having neurokinin antagonistic activity, in particular NK_1 antagonistic activity, their preparation, compositions comprising them and their use as a medicine, in particular for the treatment of emesis, anxiety, depression, pain, pancreatitis and IBS. The compounds according to the invention can be represented by general Formula (I), and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1. In view of their capability to antagonize the actions of neurokinins by blocking the neurokinin receptors, and in particular antagonizing the actions of substance P by blocking the NK_1 receptor, the compounds according to the invention are useful as a medicine, in particular in the prophylactic and therapeutic treatment of neurokinin-mediated conditions, such as, for instance CNS disorders, in particular depression, anxiety disorders, stress-related disorders, sleep disorders, cognitive disorders, personality disorders, schizoaffective disorders, eating disorders, neurodegenerative diseases, addiction disorders, mood disorders, sexual dysfunction, pain and other CNS-related conditions; inflammation; allergic disorders; emesis; gastrointestinal disorders, in particular irritable bowel syndrome (IBS); skin disorders; vasospastic diseases; fibrosing and collagen diseases; disorders related to immune enhancement or suppression and rheumatic diseases and body weight control.

WO 2004/033428 A1

ACTION