



Industria y Comercio
SUPERINTENDENCIA

PCT

SOLICITUD

PATENTE DE INVENCION

03-30679

21. EXPEDIENTE N°

54. TÍTULO

FORMAS DE CRISTAL DE HIDROCLORURO DE 1-[6-CLORO-5-(TRIFLUÓROMETIL)-2-PIRIDINIL]PIPERAZINA

51. CLASIFICACIÓN INTERNACIONAL

A61K31/496, A61P25/60, C07D 213/74

71. SOLICITANTE

AKZO NOBEL N.V.

DOMICILIO

Arnhem, Holanda.

74. APODERADO

EMILIO FERRERO

Código No. 1092

22. BOGOTÁ, D. C.

10-04-2003



33 030679 00

PETITORIO

SUPERINTENDENCIA Y COMERCIO

Radicación: 03038679 00000000

Folios: 66

Fecha (AMB): 2003-04-10 17:19:45

Trámite : 011 PCT-PATENT 3/9 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1	SOLICITUD DE:			
	☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.			
	☐ Capítulo I. ☒ Capítulo II.			
2	SOLICITANTE (71)	Nombre: AKZO NOBEL N.V. sociedad constituida y existente bajo las leyes de Holanda Dirección: Velperweg 76, 6824 BM Amheim. Holanda. Domicilio: Amheim, Holanda.	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: _____	
3	REPRESENTANTE O APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax:: 217 92 11 E-mail: <u>clientes@camvp.com.</u> Domicilio: Bogotá, Colombia.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: <u>438.019</u> T.P. <u>31.829</u>	
4	INVENTOR (ES) (72)	1- Patrick CARLIER 4 Rue des Granges, Le Cohat, F-63310-Saint André Le Coq, Francia. 2- Petrus Jozef Cornelis Maria HOOF VAN c/o N.V. Organon Patent Department, Postbus 20, 5340 BH Oss Holanda 3- Jozef Cornelius Johannes MUYRERS c/o N.V. Organon Patent Department Postbus 20 5340 BH Oss, Holanda.		
5	PCT (86) Solicitud Internacional No. <u>PCT/EP01/11714</u> Publicación Internacional No. <u>WO 02/30902 A1</u>			
6	Título (54) <u>FORMAS DE CRISTAL DE HIDROCLORURO DE 1-(6-CLORO-5-(TRIFLUOROMETIL)-2-PIRIDINIL)PIPERAZINA</u>			
7	Clasificación Internacional (51) <u>C07D 213/74 N61K31/496 A61P 25/00</u>			
8	Prioridad SI ☒ NO ☐	(33) País de Origen <u>NL.</u>	(32) Fecha <u>13 de octubre de 2000</u>	(31) Número de Solicitud <u>00203528.5</u>

9

Comprobante de pago No.: 03 - 23.236 Fecha: 1 de abril de 2003

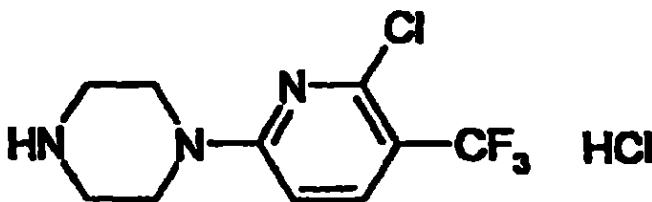
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 400.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11

FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA: 

C.C. 438.019 de Usaquén T.P. 31.929

JBP/mrm-ld-215

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 April 2002 (18.04.2002)

PCT

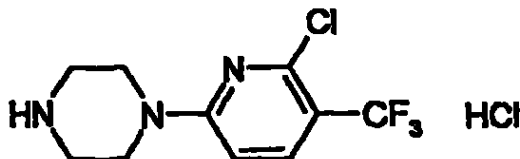
(10) International Publication Number
WO 02/30902 A1

- (51) International Patent Classification: C07D 213/74, A61K 31/496, A61P 25/00 (74) Agents: DE WEERD, P., G., W. et al.; P.O. Box 20, NL-5340 BH Oss (NL).
- (21) International Application Number: PCT/EP01/11714 (81) Designated States (national): AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.
- (22) International Filing Date: 9 October 2001 (09.10.2001)
- (25) Filing Language: English
- (26) Publication Language: English (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (30) Priority Data: 00203528.5 13 October 2000 (13.10.2000) NL
- (71) Applicant (for all designated States except US): AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): CARLIER, P. [FR/FR]; 4, rue des Granges, Le Cohat, F-63310 Saint André le Coq (FR). HOOF VAN, P., J., C., M. [NL/NL]; N.V. Organon, Patent Department, Postbus 20, NL-5340 BH Oss (NL). MUYRERS, J., C., J. [NL/NL]; N.V. Organon, Patent Department, Postbus 20, NL-5340 BH Oss (NL).
- Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/30902 A1

(54) Title: CRYSTAL FORMS OF 1-[6-CHLORO-5-(TRIFLUOROMETHYL)-2-PYRIDINYL]PIPERAZINE HYDROCHLORIDE

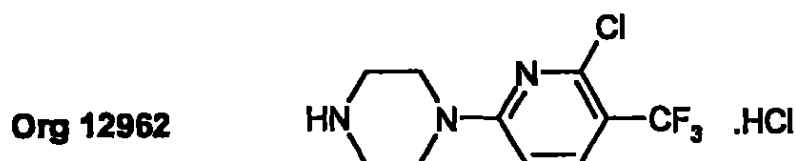


(57) Abstract: The invention relates to crystal forms A and B of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine hydrochloride (Org 12962), to methods for the preparation of those crystal forms and to pharmaceutical compositions comprising crystal form B useful in the treatment of depression, anxiety, obesity, or urinary incontinence.

**CRYSTAL FORMS OF 1-[6-CHLORO-5-(TRIFLUOROMETHYL)-
2-PYRIDINYL]PIPERAZINE.HYDROCHLORIDE.**

The invention relates to new crystal forms A and B of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine.hydrochloride, to methods for the preparation of those forms and to pharmaceutical compositions comprising crystal form B.

1-[6-Chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine.hydrochloride, which will be referred to as Org 12962, is known from European Patent 370 560 (Akzo Nobel N.V.), and is described as useful in the treatment of disorders of the central nervous system, especially depression (Leysen, D.C.M. *Drugs*, 2, 109-120, 1999) and anxiety (Leysen, D. and Kelder, J. *Trends in Drug Research II*, 49-61, 1998 Elsevier Science B.V., Ed. H. van der Groot). Additionally the compound is potentially useful in the treatment of urinary incontinence (WO 9833504: Akzo Nobel N.V.). Org 12962 is described in EP 370 560 (Table I, compound no 3) as a compound lacking a well defined melting point. There is no teaching on the physical form of the compound.



It has now been found that the compound as prepared following the method described in EP 370 560 is polymorphous and consists of a mixture of two crystalline pure forms.

It is generally desirable to prepare therapeutic agents of uniform and defined composition. With regard to polymorphous compounds it may be expected that their biological activity is comparable or identical to that of the crystalline pure forms of which the polymorphous compound consist. Nevertheless, if the polymorphous compound is used as a medicament great drawbacks are associated therewith as compared with its crystalline pure components. The difference in crystal structure can lead to difference in physicochemical parameters such as stability, rate of dissolution, bioavailability, analytical data

CONFIRMATION COPY

and the like, which frequently are strongly influenced by the crystal forms in the polymorphous compound. This is all the more important since in practice it is virtually impossible to make each batch of a polymorphous compound exactly identical in respect of its composition. As a consequence of these differences it is often regarded as undesirable to incorporate polymorphous compounds in medicaments and it is sometimes demanded that only one of the crystalline pure components of the polymorphous compound is used.

It is the aim of the present invention to provide substantially pure crystal forms of the compound Org 12962, which are completely or virtually completely free from the other crystalline forms.

The term "crystalline pure form which is completely or virtually completely free from the other crystalline forms" means a crystal form which contains less than 10% and preferably less than 5 % of another crystalline form.

It is one aspect of the invention that by using specific crystallization methods three crystalline pure forms, which will be denoted as form A, form B and form C, can be obtained from the polymorphous compound Org 12962.

It has further been found that crystal form B of Org 12962 is the thermodynamically most stable form. The crystal form B is moreover more stable than form A when stored in the dark in mixtures with various pharmaceutical auxiliaries, especially in admixtures comprising lactose and/or cornstarch. In another aspect therefore the present invention relates to the provision of pharmaceutical preparations of solid Org 12962, comprising Org 12962 in the crystalline pure form B. A pharmaceutical composition of this type has the advantage that the reproducibility is appreciably increased and that the physical data, within acceptable limits, are always identical.

When Org 12962 is prepared by treating a solution of the free base of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine in ethanol with hydrochloric acid, following the general procedure described in EP 370 560, either an

amorphous or a polymorphous product, wherein the ratio of amounts of form A and form B will vary widely from batch to batch, is obtained.

Pure crystalline forms A and B can be prepared by crystallizing the hydrochloride salt of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine under controlled conditions from ethanol or ethanol-water mixtures.

Pure form A can be prepared by rapidly cooling a concentrated solution of the hydrochloride salt in an ethanol/water mixture from reflux temperature to below 0°C and initiate nucleation at subzero temperatures (cooling crystallization procedure). Rapid cooling can be effected for instance by keeping the crystallisation flask in ice-acetone (about -10 °C).

Pure form B can be prepared by treating the free base 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine in ethanol (or ethanol-water) solution at reflux temperature with an excess (up to 5 equivalents) of hydrochloric acid whereby the nucleation is initiated at the reflux temperature followed by slowly cooling of the crystallizing salt to ambient temperature (reaction crystallization).

The thermodynamically most stable form B can also be prepared by stirring a suspension of a polymorphous batch of Org 12962 in an ethanol/water mixture until the conversion to form B is complete. This process will take several days when carried out at room temperature [for example: 96 hours for complete conversion of a 20 gram batch in ethanol-water=3:1 at 20 °C]. In a preferred embodiment the suspension is stirred at reflux temperature so that the conversion to form B is complete in several hours [for example: 3 hours for complete conversion of a 1 gram batch in ethanol-water=3:1 at reflux temperature].

A third crystalline form of Org 12962 can be obtained by crystallization of the compound from 2-methyl-butan-2-ol. This form C is a metastable crystal form, which spontaneously converts to form B, even at -20°C.

The melting points of crystal forms A and B do not differ appreciably. Both pure forms melt between 282 – 284 °C.

The crystal forms of the present invention can be characterized, and thus distinguished from each other, by their X-ray powder diffraction patterns, as well as by their RAMAN spectra.

Figure 1 depicts XRPD spectra for crystal forms A and B of Org 12962. Each of the spectra is characterized by intensity peaks at certain specific values of the diffraction angle 2 theta (θ). Form A has characteristic peaks at 2 theta = 17.50 °, 17.80 °, 23.85 °, 24.50 °, 25.55 °, 27.75 ° and 29.40 °.

Form B is characterized by peaks at 2 theta = 20.40 °, 21.05 °, 24.80 °, 25.80 ° and 28.10 °.

From X-ray analysis of a single crystal of form B it was established that the space group of the crystals is $P2_1/c$, monoclinic, with cell dimensions of $a=12.848 \text{ \AA}$, $b=7.151 \text{ \AA}$, $c=14.164 \text{ \AA}$, $\beta=104.85^\circ$, and $V=1257.9 \text{ \AA}^3$.

Similar analysis of form A revealed the crystals to be orthorhombic with space group $Pca2_1$ and cell dimensions: $a=13.823 \text{ \AA}$, $b=7.226 \text{ \AA}$, $c=25.256 \text{ \AA}$ and $V=2522.70 \text{ \AA}^3$.

FT Raman spectra of crystal forms A and B are shown in Figure 2. Each crystal form has characteristic absorption peaks, denoted in Table I. These peaks can be used for the quantitative determination of the amount of crystal form A in pure form B, and the other way around.

Table I: Characteristic absorption peaks in Raman spectra of crystal forms of Org 12962

Form A (cm^{-1})	Form B (cm^{-1})	Form C (cm^{-1})
82.2	104.6	187.1
106.6	147.7	209.3
194.7	192.8	247.3
211.2	209.5	345.4
356.5	360.6	459.3
1037.6	1035.9	680.1
1268.2	1265.3	1058.8
2997.0	2997.1	1151.1
3006.5	3001.8	2853.4
3122.4	3117.2	2998.1
		3105.4

The pharmaceutical preparations of solid Org 12962 according to the invention comprise Org 12962 in the crystalline pure form B in association with one or more pharmaceutically acceptable additives or excipients.

Such pharmaceutical preparations generally take the form of a dosage unit such as a tablet, a capsule or a suppository, but other solid or dry pharmaceutical preparations are included. A preferred pharmaceutical preparation is in the form of a tablet. A tablet may contain in addition to the active principle Org 12962 in the pure crystalline form B, certain excipients, such as diluents, binders, glidants and lubricants, which serve to impart satisfactory processing and compression characteristics to the tablet, as well as disintegrants and flavoring agents, which gives additional desirable physical characteristics to the finished tablet.

Methods for making such dosage units are well known, for example in accordance with standard techniques such as those described in the standard reference, Gennaro *et al.*, Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, especially Part 8: Pharmaceutical Preparations and Their Manufacture).

A dosage unit of Org 12962, suitable for the treatment of depression, anxiety, obesity, or urinary incontinence, may contain from about 5 to 500 mg of the active ingredient, more usually from about 10-100 mg. A preferred dosage unit may contain 20-40 mg of Org 12962 in the crystalline form B, which is to be taken twice a day.

The invention is illustrated by the following examples.

EXAMPLES

General procedures:

X-ray powder diffraction (XRPD) spectra were obtained on a Siemens D5000 transmission diffractometer with primary germanium monochromator, Cu-K α 1 radiation, settings 35 kV and 40 mA. The slits used: anti-scatter slit 2 mm, detector slit 0.2 mm. Measuring conditions: step size 0.02°, time per step 10 seconds. The samples were measured in between Scotch tape and were rotated during the measurements with a speed of 15 rpm. The XRPD spectra of crystalline pure forms A and B are depicted in Figure 1.

FT-Raman spectra were recorded using a Bruker RFS 100 Raman Spectrometer which was equipped with a 1064 nm Nd-YAG laser (Adlas model DPY 421N). Spectra were measured with a resolution of 2 cm^{-1} using a laser power of 200 mW. Typically, 256 interferograms were collected for each spectrum. The laser spot had a diameter of approximately $30\text{ }\mu$ at the sample position. Raman spectra of crystal forms A and B are depicted in Figure 2.

Example 1.

Preparation of Org 12962.

A: preparation of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine

Piperazine (10.337 g; 120 moles) was dissolved in 95% aqueous ethanol (36 l). The solution was heated at reflux, after which a solution of 2,6-dichloro-3-(trifluoromethyl)-pyridine (8640 g; 40 moles) in 95% aqueous ethanol (9 l) was added over 2 hours. The reflux was maintained for another 2 hours. The mixture was cooled to ambient and the precipitated piperazine hydrochloride salt was removed by filtration. The ethanol was removed under vacuum. The residue was dissolved in ethyl acetate (30 l). This solution was washed twice with water (15 l), dried over magnesium sulphate, after which the solvent was removed in vacuo. The residue was poured into water (15 l) while stirring. The resulting solid was filtered off and extensively washed with water.

B: 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine, hydrochloride salt [Org 12962]

The wet solid described under A was dissolved in 96% aqueous ethanol (12 l). The solution was once filtered to remove some insoluble material. The filtrate was diluted with 96 % aqueous ethanol (15 l), after which hydrogen chloride gas was passed through the solution. During the salification the temperature rose to reflux. After cooling to 0°C , the precipitate is filtered off to give the crude product (7600 g), which was redissolved while heating in 96% aqueous ethanol (11 l) and water (2.7 l). After cooling at ambient temperature, the hydrochloride salt was filtered off, washed with cold ethanol (4 l), and dried at 110°C in vacuo to give Org 12962 (5500 g; 45.5 %)

Raman spectroscopy revealed this product to consist of a mixture of crystal forms A (77%) and B (23%).

Elemental analysis:

calculated (%) for $C_{10}H_{12}N_3Cl_2F_3$: C: 39,75; H: 4,01; N: 13,91

found (%): C: 39,81; H: 4,07; N: 13,85

^1H -Nmr (300 MHz in DMSOd6): δ in ppm: 3.26 (4H; triplet $J=5.3$ Hz); 3.99 (4H; triplet $J=5.3$ Hz); 7.08 (1H; doublet $J=9.0$ Hz); 8.04 (1 H; doublet $J=9.0$ Hz); 9.76 (2H; broad singlet: *N-H, HCl*)

Example 2.

Preparation of Org 12962 in pure crystal form A

A solution of Org 12962 (35 gram) in 96% aqueous ethanol (1 liter) was rapidly cooled in an ice/acetone bath from reflux temperature to $-10^\circ C$, while stirring with a magnetic stirring bar. Nucleation occurred spontaneously at subzero temperature. After stirring of the mixture for 2 hours at $-10^\circ C$ the crystalline material was filtered off, washed with a small amount of cold ethanol and dried *in vacuo* at room temperature.

Example 3

Preparation of Org 12962 in pure crystal form B

Polymorphous Org 12962 (10 kg), prepared as described in Example 1, was dissolved in a mixture of ethanol (80 l) and water (11 l). The solution was heated to reflux temperature, whereupon solvent was distilled off until the volume of the mixture was reduced to approximately 15 l and crystallization started. The resulting mixture was kept at reflux temperature for 5 hours, after which the solution was slowly cooled to $2 \pm 2^\circ C$ with a cooling ramp of $17^\circ C/hr$. The crystalline mass was filtered off, washed with ethanol (4 l) and dried *in vacuo* at $60^\circ C$ for 24 hours.

Example 4**Stability of crystal forms A and B in admixture with excipients**

Aliquots of Org 12962 (5-10 mg) in crystal form A (a batch prepared as described in Example 2 and which was found to contain 92% form A and 8 % form B) were weighed into roundbottomed tubes. To each aliquot an excipient mentioned in Table II was added, followed by 10 μ l of water, after which the suspensions were thoroughly mixed.

Aliquots of Org 12962 (5-10 mg) in crystal form B (100% form B) were weighed into roundbottomed tubes. To each aliquot an excipient mentioned in Table II was added, followed by 100 μ l of water. Glass beads (250-300 mg) were added to each tube, after which the samples were thoroughly mixed for 1 minute. The residual water was evaporated *in vacuo* at room temperature. The tubes were stored in the dark for 14 days at either 20 °C or at 60 °C. The samples were dissolved in 20.0 ml of a 70:30 mixture of 25 mM phosphate pH 2.6 buffer and acetonitrile. Dissolution was effected by keeping the tubes in a sonifier for 20 minutes.

Quantitative analysis of the amount of Org 12962 per tube was done by high performance liquid chromatography (hplc) using either of the following validated methods : (1) using a Symmetry Shield Reverse Phase RP 18 column (150x4.6 mm), which was operated at 40 °C, using a flow rate of 1.0 ml/min, and as eluent a 69:31 (v/v) mixture of 25 mM phosphate buffer pH 2.6 buffer, also containing 15 mM octanesulphonic acid, and acetonitrile, or (2) using a Lichrospher 60 RP Select B column (125x4.0 mm), which was operated at ambient temperature, using a flow rate of 1.5 ml/min, and as eluent a 55:45 (v/v) mixture of methanol and water, also containing 5 mM octanesulphonic acid. The content of Org 12962 remaining in the samples after storage is given in Table II as the percentage (%) of the initial amount.

Table II Stability of Org 12962 in admixture with excipients

	Storage conditions			
	14 days		14 days	
	20 °C/dark		60 °C/dark	
EXCIPIENT	I %	II %	I %	II %
Lactose (80 mg)*	94.5	99.6	91.2	97.4
HPC (2 mg)	98.0	100.0	n.d.	96.5
Cornstarch (10 mg)	100.0	100.1	82.6	97.9
Mg-stearate (0.5 mg)	97.9	99.9	93.8	97.9
Primojel® (4 mg)	95.0	100.0	94.6	96.0
Talc (0.3 mg)	99.2	99.9	94.5	100.1
Titanium dioxide (0.2 mg)	96.0	99.8	97.5	92.9
HPMC (1.3 mg)	95.0	100.0	91.8	97.8
PEG 400 (0.3 mg)	96.5	99.8	92.5	96.3

I: crystalline Org 12962 : 92% form A and 8 % form B;

II: crystalline Org 12962 : 100% form B;

*: the amount (in mg) of excipient added to 5.0 mg of Org 12962

is quoted in parenthesis

HPC: hydroxypropylcellulose

HPMC: hydroxypropylmethylcellulose

PEG: polyethylene glycol

The data in Table II indicates that Org 12962 in admixture with pharmaceutical excipients is more stable when in the pure crystal form B as compared with pure crystal form A. When storage was at the stress condition of 60 °C, the improved stability of the pure crystal form B was especially notable when in admixture with lactose and with cornstarch, 2 major components of pharmaceutical formulations of Org 12962.

6. A method of preparation of the compound according to claim 3, characterized in that a suspension of polymorphous 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine.hydrochloride in an ethanol/water mixture is kept until conversion to form B is complete.
7. The method according to claim 6 wherein the suspension is kept at the reflux temperature.
8. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and Org 12962, characterized in that Org 12962 is in the substantially pure crystal form B having an X-ray powder diffraction pattern obtained with CuK α 1 radiation with peaks at values of 2-theta (2θ) 20.40 °, 21.05 °, 24.80 °, 25.80 ° and 28.10 ° and a Raman absorption spectrum with absorption peaks at 104.6 cm⁻¹, 147.7 cm⁻¹, 192.8 cm⁻¹, 209.5 cm⁻¹, 360.6 cm⁻¹, 1035.9 cm⁻¹, 1265.3 cm⁻¹, 2997.1 cm⁻¹, 3001.8 cm⁻¹ and 3117.2 cm⁻¹.
9. A method of treating depression, anxiety, obesity, or urinary incontinence in a mammal comprising administering a therapeutically effective amount of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine. hydrochloride in the pure crystal form B of claim 3.

Example 5.

Pharmaceutical formulations comprising pure crystal form B of
Org 12962.

No 5694

Tablets of Org 12962, having the following compositions were prepared:

Ingredients	Mg	Mg
Org 12962 form B	10.0	100.0
Hydroxypropylcellulose (HPC)	4.0	8.0
Corn starch	20.0	40.0
Colloidal silicon dioxide	3.0	6.00
Magnesium stearate	1.0	2.0
Lactose 200M to a total tablet weight of	200	400

Org 12962 is homogeneously mixed with the filling agent lactose and the disintegrant corn starch, giving a blend which is granulated in a low shear operation with a mucilage of the binder hydroxypropylcellulose. The moist mass is screened, dried in a fluidized bed, screened again and finally admixed with the colloidal silicon dioxide and the lubricant magnesium stearate. The resulting granulate is compressed to tablet cores.

Claims.

1. The compound 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine hydrochloride (Org 12962), characterized in that the compound is in a pure crystal form, which is completely or virtually completely free from other crystalline forms.
2. The compound according to claim 1, having the pure crystal form A which is characterized by an X-ray powder diffraction pattern obtained with CuK α 1 radiation with peaks at values of 2-theta (2θ) of 17.50°, 17.80°, 23.85°, 24.50°, 25.55°, 27.75° and 29.40° and by a Raman absorption spectrum with peaks at 82.2 cm⁻¹, 106.6 cm⁻¹, 194.7 cm⁻¹, 211.2 cm⁻¹, 356.5 cm⁻¹, 1037.6 cm⁻¹, 1268.2 cm⁻¹, 2997.0 cm⁻¹, 3006.5 cm⁻¹ and 3122.4 cm⁻¹.
3. The compound according to claim 1, having the pure crystal form B which is characterized by an X-ray powder diffraction pattern obtained with CuK α 1 radiation with peaks at values of 2-theta (2θ) 20.40°, 21.05°, 24.80°, 25.80° and 28.10° and by a Raman absorption spectrum with peaks at 104.6 cm⁻¹, 147.7 cm⁻¹, 192.8 cm⁻¹, 209.5 cm⁻¹, 360.6 cm⁻¹, 1035.9 cm⁻¹, 1265.3 cm⁻¹, 2997.1 cm⁻¹, 3001.8 cm⁻¹ and 3117.2 cm⁻¹.
4. A method of preparation of the compound according to claim 2, characterized in that a concentrated solution of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine hydrochloride salt in an ethanol/water mixture is rapidly cooled to below 0 °C after which spontaneous nucleation is initiated.
5. A method of preparation of the compound according to claim 3, characterized in that a concentrated solution of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine in an ethanol-water solution is treated at reflux temperature with an excess of hydrochloric acid whereby the nucleation is initiated at reflux temperature, after which the solution is slowly cooled to ambient temperature.

Figure 1: X-ray powder diffractograms of forms A (upper) and B (lower) of Org 12962.

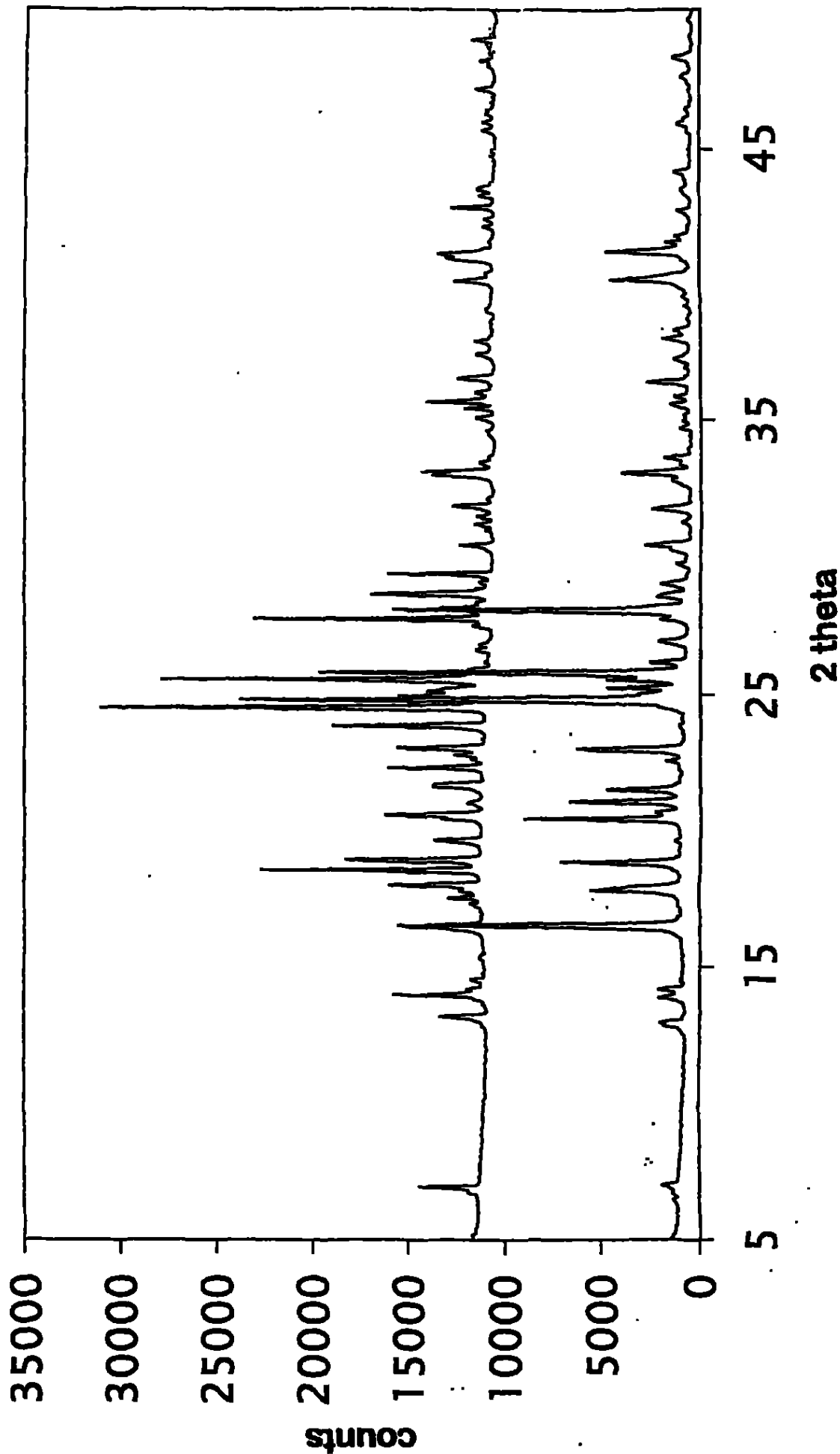
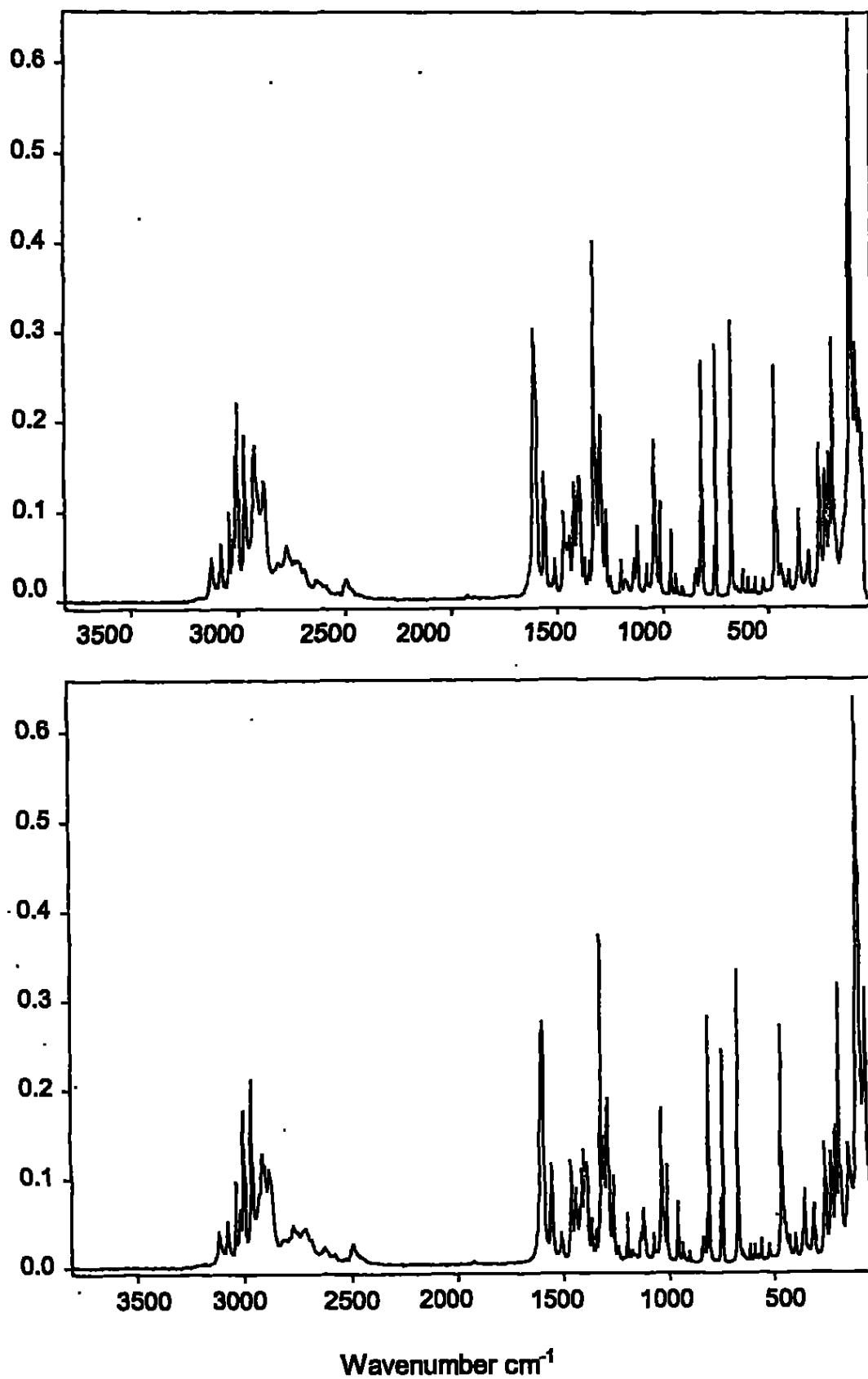


Figure 2: Raman spectrum of crystal forms A (upper) and B (lower).



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/11714

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/74 A61K31/496 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 370 560 A (AKZO NV) 30 May 1990 (1990-05-30) cited in the application Table I, compound 3	1-9
A	LEYSEN D C M: "SELECTIVE 5-HT 2C AGONISTS AS POTENTIAL ANTIDEPRESSANTS" IDRUGS, CURRENT DRUGS LTD, GB, vol. 2, no. 2, 1999, pages 109-120, XP000922503 ISSN: 1369-7056 cited in the application figure 4	1,9
-/-		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claims) or which is cited to establish the publication date of another citation or other special reason (see specified)
- "O" document relating to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "A" document member of the same patent family

Date of the actual completion of the international search

12 February 2002

Date of mailing of the international search report

26/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentian 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/EP 01/11714

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0370560	A	30-05-1990	AT 100087 T	15-01-1994
			AU 621419 B2	12-03-1992
			AU 4538789 A	31-05-1990
			CA 2003665 A1	24-05-1990
			DE 68912282 D1	24-02-1994
			DE 68912282 T2	28-04-1994
			DK 587989 A	25-05-1990
			EP 0370560 A1	30-05-1990
			ES 2061953 T3	16-12-1994
			IE 62792 B	08-03-1995
			JP 2184672 A	19-07-1990
			JP 2873025 B2	24-03-1999
			KR 155543 B1	16-11-1998
			NZ 231487 A	29-01-1991
			US 4971969 A	20-11-1990
			ZA 8908728 A	29-08-1990
WO 9833504	A	06-08-1998	WO 9833504 A1	06-08-1998
			AU 6619398 A	25-08-1998

PATENT COOPERATION TREATY

03 JULI 2002

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

van Wezenbeek, ~~H.M.G.F.~~
P.O. Box 20
NL-5940 BH Oss
PAYS-BAS

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 02/07/2002

Applicant's or agent's file reference
2000.587 WO

IMPORTANT NOTIFICATION

International application No.

PCT/EP 01/ 11714

International filing date (day/month/year)

09/10/2001

Priority date (day/month/year)

13/10/2000

Applicant

AKZO NOBEL N.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**
The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

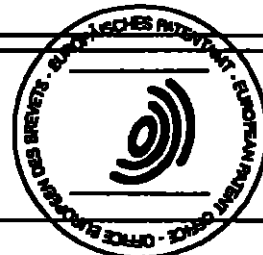
Name and mailing address of the IPEA/



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

CARDENAS C E
Tel. (+49-89) 2399 2828



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2000.587 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 01/11714	International filing date (day/month/year) 09/10/2001	Priority date (day/month/year) 13/10/2000
International Patent Classification (IPC) or national classification and IPC C07D213/74		
Applicant AKZO NOBEL N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 08/05/2002	Date of completion of this report 27/06/2002
Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer VERHULST W Tel. (+49-89) 2399 2828



18

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

Diese Unterlagen stellen die Bestätigung einer durch Telekopie (Telefax) eingereichten Anmeldung dar.

These documents represent confirmation of an application filed by facsimile.

Ces pièces constituent la confirmation d'une demande déposée par la télécopie (téléfax).

Datum der Übermittlung der Telekopie (Telefax):

Date of facsimile: 9-10-2001

Date de l'envoi de la télécopie (téléfax):

Name der Behörde, bei der die Telekopie (Telefax) eingereicht worden ist: EPO Rijnijk

Name of authority with which facsimile was filed:

Nom de l'autorité auprès de laquelle la télécopie (téléfax) a été déposée:

(if desired) (12 characters maximum) **2000.587 WO**

Box No. I TITLE OF INVENTION

"CRYSTAL FORMS OF 1-[6-CHLORO-5-(TRIFLUOROMETHYL)-2-PYRIDINYL]PIPERAZINE.HYDROCHLORIDE."

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Akzo Nobel N.V.
Imperweg 76
6824 BM ARNHEM
The Netherlands

☐ This person is also inventor

Telephone No.
0412-666219

Facsimile No.
0412-650592

Teleprinter No.

State (i.e. country) of nationality: **The Netherlands**

State (i.e. country) of residence: **The Netherlands**

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Carlier, P.
4, Rue des Granges
Le Cohat
310-Saint André le Coq
France

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: **FR**

State (i.e. country) of residence: **FR**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Weerd de, P.G.W.
P.O. Box 20
5340 BH Oss
The Netherlands

Telephone No.
0412-666307

Facsimile No.
0412-650592

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Hoof van, P.J.C.M.
 c/o: N.V. Organon
 Patent Department
 Postbus 20
 5340 BH Oss
 The Netherlands

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL

This person is applicant for the purposes of

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Muyrers, J.C.J.
 c/o: N.V. Organon
 Patent Department
 Postbus 20
 5340 BH Oss
 The Netherlands

This person is:

- ☒ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL

This person is applicant for the purposes of

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

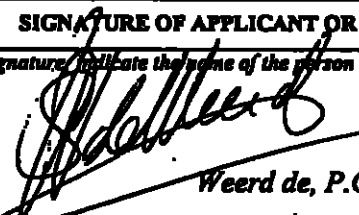
- | | | |
|---|---|--|
| ☒ AE United Arab Emirates | ☐ GH Ghana | ☒ MX Mexico |
| ☒ AG Antigua and Barbuda | ☐ GM Gambia | ☒ MZ Mozambique |
| ☒ AL Albania | ☒ HR Croatia | ☒ NO Norway |
| ☐ AM Armenia | ☒ HU Hungary | ☒ NZ New Zealand |
| ☐ AT Austria | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AU Australia | ☒ IL Israel | ☐ PT Portugal |
| ☐ AZ Azerbaijan | ☒ IN India | ☒ RO Romania |
| ☒ BA Bosnia and Herzegovina | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☐ KE Kenya | ☐ SD Sudan |
| ☒ BR Brazil | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☐ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ CA Canada | ☐ KZ Kazakhstan | ☒ SK Slovakia |
| ☐ CH & LI Switzerland and Liechtenstein | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LK Sri Lanka | ☐ TJ Tajikistan |
| ☒ CO Colombia | ☒ LR Liberia | ☐ TM Turkmenistan |
| ☒ CR Costa Rica | ☐ LS Lesotho | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☐ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☐ DE Germany | ☒ LV Latvia | ☒ UA Ukraine |
| ☐ DK Denmark | ☒ MA Morocco | ☐ UG Uganda |
| ☒ DM Dominica | ☐ MD Republic of Moldova | ☒ US United States of America |
| ☒ DZ Algeria | | |
| ☒ EC Ecuador | ☒ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☐ ES Spain | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☐ FI Finland | ☐ MW Malawi | ☒ ZA South Africa |
| ☐ GB United Kingdom | | ☐ ZW Zimbabwe |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ **PH** Philippines
- ☐
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

21
22

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box ☐	
The priority of the following earlier application(s) is hereby claimed:			
Country <i>(in which, or for which, the application was filed)</i>	Filing Date <i>(day/month/year)</i>	Application No.	Office of filing <i>(only for regional or international application)</i>
item (1) NL	13-10-2000	00203528.5	EPO
item (2)			
item (3)			
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):			
☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): 1			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA /EPO			
Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request			
Country (or regional Office):		Date (day/month/year)	Number:
Box No. VIII CHECK LIST			
This international application contains the following number of sheets:		This international application is accompanied by the item(s) marked below:	
1. request	4 sheets	1. ☐ separate signed power of attorney	5. ☒ fee calculation sheet
2. description:	10 sheets	2. ☒ copy of general power of attorney	6. ☐ separate indications concerning deposited microorganisms
3. claims:	2 sheets	3. ☐ statement explaining lack of signature	7. ☐ nucleotide and/or amino acid sequence listing (diskette)
4. abstract:	1 sheets	4. ☐ priority document(s) identified in Box No VI as item(s):	8. ☐ other (specify):
5. drawings	2 sheets		
6 Sequence listing	_____ sheets		
Total :	19 sheets		
Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
Next to each signature indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)			
 Weerd de, P.G.W.			
For receiving Office use only			
1. Date of actual receipt of the purported international application:		2. Drawings: ☐ received ☐ not received:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:			
4. Date of timely receipt of the required corrections under PCT Article 11(2):			
5. International Searching Authority specified by the applicant: ISA/		6. ☐ Transmittal of search copy delayed until search fee is paid	
For International Bureau use only			
Date of receipt of the record copy by the International Bureau:			

PCT

FEE CALCULATION SHEET

For receiving Office use only

Annex to the Request

International application No.

Applicant's or agent's

file reference 2000.587 WO

Date stamp of the receiving Office

Applicant

Akzo Nobel N.V.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

EUR 102,=

T

2. SEARCH FEE

EUR 945,=

S

International search to be carried out by EPO

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 19 sheets.

EUR 409,=

b₁

X

EUR 9,=

remaining sheets

additional amount

b₂

Add amounts entered at b₁ and b₂ and enter total at B

EUR 409,=

B

Designation Fees

The international application contains 63 designations

number of designation fees payable (maximum 6)

amount of designation fee

EUR 528,=

D

Add amounts entered at B and D and enter total at I

EUR 937,=

I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT

EUR 30,=

P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

EUR 2014,=

TOTAL

COPY

☐

The designation fee is not paid at this time.

MODE OF PAYMENT

☒

authorization to charge deposit account (see below)

☐

bank draft

☐

coupons

☐

cheque

☐

cash

☐

other (specify):

☐

postal money order

☐

revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ EPO

☒

is hereby authorized to charge the total fees indicated above to my deposit account.

☒

is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐

is hereby authorized to charge the fee for preparation and transmission of the international application to the International Bureau of WIPO to my deposit account.

2809 0012

9 Oktober 2001

Deposit Account Number

Date (day/month/year)

Signature Weerd de, P.G.W.

Bitte übermitteln die 3 Blätter 1004.1-3 dem EPA in München, Direktion 5.1.1, und beachten Sie Blatt 1004.4, insbesondere Nr.3 b.
Please forward the 3 sheets 1004.1-3 to the EPO at Munich, Directorate 5.1.1 and pay attention to sheet 1004.4, especially point 3 b.
Prière de faire parvenir les 3 feuilles 1004.1-3 à l'OEB à Munich, Direction 5.1.1 et de tenir compte de la feuille 1004.5, notamment du point 3

**ALLGEMEINE VOLLMACHT
GENERAL AUTHORISATION
POUVOIR GENERAL**

Nur für amtlichen Gebrauch / For official use only
Cadre réservé à l'administration
Nr. der allgemeinen Vollmacht / General Authorisation No.
N° du pouvoir général

59 (rev.)

Ich (Wir) / I (We) / Je (Nous)



Akzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 9300
6800 SB Arnhem
the Netherlands



bevollmächtige(n) hiermit / do hereby authorise / autorise (autorisons) par la présente

Schalkwijk, Pieter Cornelis
Fett, Günter
Van Deursen, Petrus Hubertus
Quelle-Fontijn, Monique
Verbart, Jeannette J.M.
Helmann, Anette
Beetz, Tom
Hessalink, Dinah E.
Aalbers, Ami Reiner
De Vries, Adriaan Jacobus
Zonneveld, Hendrik Jan
Alferink, Petrus Johannes Theodorus

Address of place of business:
Akzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 9300
6800 SB Arnhem
the Netherlands

mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unseren) Patentangelegenheiten zu vertreten, alle Handlungen für mich (uns) vorzunehmen und Zahlungen für mich (uns) in Empfang zu nehmen.

to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions and to receive payments on my (our) behalf.

à me (nous) représenter pour ce qui concerne toutes mes (nos) affaires de brevet dans toute procédure instituée par la Convention sur le brevet européen et, à ce titre, à agir en mon (notre) nom et à recevoir des paiements pour mon (notre) compte.



Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die Internationale Zusammenarbeit auf dem Gebiet des Patentrechts.
This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.
Ce pouvoir s'applique également à toute procédure instituée par le Traité de coopération en matière de brevets.



Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet.
Les autres mandataires sont mentionnés sur une feuille supplémentaire.



Untervollmacht kann erteilt werden. / Sub-authorisation may be given. / Le pouvoir pourra être délégué.



Bitte die gelbe Kopie, ergänzt um die Nr. der allgemeinen Vollmacht, an den Vollmachtgeber zurücksenden.
Please return the yellow copy, supplemented by the General Authorisation No., to the authoriser.
Prière de renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Arnhem, the Netherlands

Datum / Date November 2, 2000

Unterschrift(en) / Signature(s)

P.C. Schalkwijk
(Holder of Proxy)

P.H. van Deursen
(Holder of Proxy)

Das Formular muß vom (von den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterschrieben sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterschriftsetzenden mit Schreibmaschine wiedergeben (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben).

The form must bear the personal signature(s) of the authoriser(s). (In the case of legal persons, that of the officer empowered to sign). After the signature, please type the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company.

Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter à la machine, après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

24
25

SUPPLEMENTARY SHEET

This sheet is part of: EPA/EPO/OEB Form 1004 04.92
concerning: General Authorisation No. 59 (rev.)
signed in the name of: Akzo Nobel N.V.
dated: October 4, 2000

Additional representatives:

Hermans, Franciscus G.M.
Mestrom, Joannes Jozef Louis
Ogilvie-Emanuelson, Claudia Maria
Van Gent, Marieke
Hogenbirk, Marijke
Kraak, Hajo
De Weerd, Petrus Gerardus Wilhelmus
Keus, Jacobus A.R.
van Wezenbeek, Petrus M.G.F.

Address of place of business:
Patent Department Pharma
N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands

Schöld, Zald Olof
Jönsson, Christer

Address of place of business:
Eka Nobel Patent Department
Sickla Industriväg
Box 11556
S - 10061 Stockholm
Sweden

Andersson, Rolf Erling

Address of place of business:
Akzo Nobel Surface Chemistry AB
Intellectual Property Department
S-444 85 Stenungsund
Sweden

25
26

Power of Attorney
(Concerning a Given International Application)

PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

POWER OF ATTORNEY

The undersigned applicant(s):

Carlier, P
4, Rue des Granges
Le Cohat
63310 - Saint André Le Coq
France

Hoof van, P.J.C.M.
c/o: N.V. Organon
Patent Department
Postbus 20
5340 BH Oss
The Netherlands

Muyrers, J.C.J.
c/o: N.V. Organon
Patent Department
Postbus 20
5340 BH Oss
The Netherlands

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) [Name, address]:

J.J.L. Mestrom

M. van Gent

J.A.R. Keus

P.G.W. de Weerd

F.G.M. Hermans

M. Hogenbirk

P.M.G.F. van Wezenbeek

H. Kraak

All residing at:

Postbus 20
5340 BH Oss
The Netherlands

☒ as agent

☐ as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2000.587 WO

Title: "Crystal forms of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine hydrochloride."

filed with the [name of the Office]: *Epo*
as receiving Office and to make or receive payments on his (her, their) behalf.

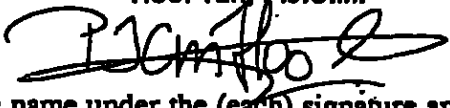
Place.....*Oss*..... Date:*30-10-2001*.....

Signature of the applicant (where there are several applicants, each of them must sign):

Carlier, P.

Hoof van, P.J.C.M.

Muyrers, J.C.J.


[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

26
27

**Power of Attorney
(Concerning a Given International Application)**

**PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE**

POWER OF ATTORNEY

The undersigned applicant(s):

Carlier, P
4, Rue des Granges
Le Cohat
63310 - Saint André Le Coq
France

Hoof, P.C.J.M.
N.V. Organon
c/o: Postbus 20
5340 BH Oss
The Netherlands

Muyrers, J.C.J.
N.V. Organon
c/o: Postbus 20
5340 BH Oss
The Netherlands

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) [Name, address]:

J.J.L. Mestrom

M. van Gent

J.A.R. Keus

P.G.W. de Weerd

F.G.M. Hermans

M. Hogenbirk

P.M.G.F. van Wezenbeek

H. Kraak

All residing at:

Postbus 20
5340 BH Oss
The Netherlands

☒ as agent

☐ as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2000.587 WO

Title: "Crystal forms of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine.hydrochloride."

filed with the [name of the Office]: **Epo**
as receiving Office and to make or receive payments on his (her, their) behalf.

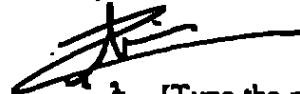
Place: Saint André Le Coq..... Date: 29-10-2001.....

Signature of the applicant (where there are several applicants, each of them must sign):

Carlier, P.

Hoof, P.C.J.M.

Muyrers, J.C.J.



[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

Diese Unterlagen stellen die Bestätigung einer durch Telekopie (Telefax) eingereichten Anmeldung dar.

These documents represent confirmation of an application filed by facsimile.

Ces pièces constituent la confirmation d'une demande déposée par la télécopie (téléfax).

Datum der Übermittlung der Telekopie (Telefax):

Date of facsimile: 8-5-2002

Date de l'envoi de la télécopie (téléfax):

Name der Behörde, bei der die Telekopie (Telefax) eingereicht worden ist:

Name of authority with which facsimile was filed: EPO...MÜNCHEN...

Nom de l'autorité auprès de laquelle la télécopie (téléfax) a été déposée:

For International Preliminary Examining Authority use only

Identification of IPEA

Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference
2000.587 WO

International application No.

PCT/EP01/11714

International filing date (day/month/year)

09-10-2001

(Earliest) Priority date (day/month/year)

13-10-2000

Title of invention

" CRYSTAL FORMS OF 1-[6-CHLORO-5-(TRIFLUOROMETHYL)-2-PYRIDINYLIPIPERAZINE]HYDROCHLORIDE "

Box No. II APPLICANT(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

**Akzo Nobel N.V.
Velperweg 76
6824 BM ARNHEM
The Netherlands**

Telephone No.:
0412-666380

Facsimile No.:
0412-650592

Teleprinter No.:

State (i.e. country) of nationality:

NL

State (i.e. country) of residence:

NL

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

**Carlier, Patrick
; Rue des Granges
Le Cohat
63310-Saint André Le Coq
France**

State (i.e. country) of nationality:

FR

State (i.e. country) of residence:

FR

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

**Hoof van, Petrus, Jozef, Cornelis, Maria
c/o: N.V. Organon
Patent Department
Postbus 20
5340 BH OSS
The Netherlands**

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL



Further applicants are indicated on a continuation sheet.

Continuation of Box No. II APPLICANT(S)	
<i>If none of the following sub-boxes is used, this sheet is not to be included in the demand</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Muyrers, Jozef, Cornelius, Johannes c/o: N.V. Organon Patent Department Postbus 20 5340 BH OSS The Netherlands	
State (i.e. country) of nationality: NL	State (i.e. country) of residence: NL
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (i.e. country) of nationality:	State (i.e. country) of residence:
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (i.e. country) of nationality:	State (i.e. country) of residence:
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (i.e. country) of nationality:	State (i.e. country) of residence:
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (i.e. country) of nationality:	State (i.e. country) of residence:
☐ Further applicants are indicated on another continuation sheet.	

24
30

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

P.M.G.F. van Wazerbeek
 P.O. Box 20
 5340 BH Oss
 The Netherlands

Telephone No.:

0412-666219

Facsimile No.:

0412-650592

Teleprinter No.:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the international Preliminary Examining Authority*

- (i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.
- (ii) ☐ to take into account the amendments under Article 34 of
- ☐ the description (amendments attached).
 - ☐ the claims (amendments attached).
 - ☐ the drawings (amendments attached).
- (iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except.....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. amendments under Article 34 | : | |
| description | : | sheets |
| claims | : | sheets |
| drawings | : | sheets |
| 2. letter accompanying amendments under Article 34 | : | sheets |
| 3. copy of amendments under Article 19 | : | sheets |
| 4. copy of statement under Article 19 | : | sheets |
| 5. other (specify): | : | sheets |

For International Preliminary
Examining Authority use only

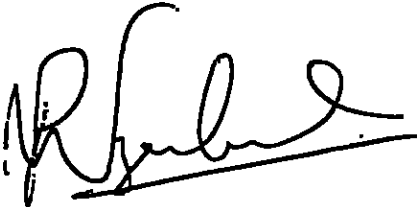
received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☐ separate signed power of attorney | 4. ☒ fee calculation sheet |
| 2. ☐ copy of general power of attorney | 5. ☐ other (specify): |
| 3. ☐ statement explaining lack of signature | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



P.M.G.F. van Wezenbeek

For International Preliminary Examining Authority use

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

COPY

FEE CALCULATION SHEET

Annex to the Demand for International preliminary examination

International application No. PCT/EP01/11714 Applicant's or agent's file reference 2000.587 WO Applicant Akzo Nobel N.V. Calculation of prescribed fees 1. Preliminary examination fee..... Euro 1530,= P - Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)..... Euro 159,= H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box..... Euro 1689,= TOTAL Mode of Payment	For International Preliminary Examining Authority use only Date stamp of the IPEA
Deposit Account Authorization (this mode of payment may not be available at all IPEAs) The IPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account. ☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account. 2809 0012 08 May 2002 P.M.G.F. van Werenbeek Deposit Account Number Date (day/month/year) Signature Form PCT/IPEA/401 (Annex) (January 1996) Substitutes to the fee calculation sheet	

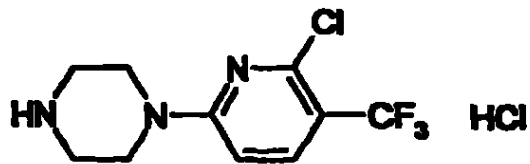
FORMAS DE CRISTAL DE HIDROCLORURO DE 1-[6-CLORO-5-
(TRIFLUOROMETIL)-2-PIRIDINIL]PIPERAZINA

La invención se relaciona con nuevas formas de cristal A y B de hidrocloreuro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina, a métodos para la preparación de estas formas y a composiciones farmacéuticas que comprenden el cristal de forma B.

El hidrocloreuro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina, que será referido como Org 12962, es conocido a partir de la patente europea 370560 (Akzo Nobel N.V.), y es descrita y útil en el tratamiento de desórdenes del sistema nervioso central, especialmente depresión (Leysen, D.C.M. IDrugs, 2, 1009-120, 1999) y ansiedad (Leysen, D. y Kelder, J. Trenes in Drug Research II, 49-61, 1998 Elsevier Science B.V., Ed. H. van der Groot). Adicionalmente el compuesto es potencialmente útil en el tratamiento de incontinencia urinaria (WO 9833504: Akzo Nobel N.V.). El Org 12962 está descrito en la EP 370560 (tabla 1, compuesto No. 3) como un compuesto que carece de un punto de fusión bien definido. No hay ninguna enseñanza sobre la forma física del compuesto.

~~33~~
34

Org 12962



Se ha encontrado ahora que el compuesto según se prepara siguiendo el método descrito en EP 370 560 es polimorfo y consiste de una mezcla de dos formas cristalinas puras.

Esto es deseable generalmente para preparar agentes terapéuticos de composición uniforme y definida. Con respecto a los compuestos polimorfos puede esperarse que su actividad biológica sea comparable o idéntica a aquella de las formas cristalinas puras de las cuales los compuestos polimorfos consisten. Sin embargo, si el compuesto polimorfo es usado como un medicamento grandes inconvenientes se asocian con este cuando se comparan con

sus componentes cristalinos puros. La diferencia en la estructura de cristal puede llevar a la diferencia en parámetros físico químicos tales como estabilidad, velocidad de disolución, biodisponibilidad, datos analíticos y similares, que frecuentemente y fuertemente están influenciados por las formas cristalinas en el compuesto polimorfo. Esto es más importante ya que en la práctica es virtualmente imposible llevar a cada tanda de compuesto polimorfo idéntico exactamente con respecto a su composición. Como consecuencia de estas diferencias frecuentemente se mira como no deseable incorporar compuestos polimorfos en medicamentos y esto es algunas veces requiero que solamente uno de los componentes cristalinos puros del compuesto polimorfo sean usados.

Es un propósito de la presente invención suministrar formas de cristal sustancialmente puro del compuesto Org 2962 que estén completa o virtualmente completamente libres de otras formas cristalinas.

El término "forma cristalina pura que es completa o virtualmente completamente libre de otras formas cristalinas" significa una forma de cristal que contiene

menos de 10% y preferiblemente menos de 5% de otra forma cristalina.

Es un aspecto de la presente invención que usando métodos de cristalización específicos 3 formas cristalinas puras, que van a ser llamadas como forma A, forma B y forma C pueden ser obtenidas para el compuesto polimorfo Org 12962.

También se ha encontrado adicionalmente que las formas de cristal B del Org 12962 es la forma termodinámicamente más estable. La forma cristal B es más aún mucho más estable que la forma A cuando se almacena en la oscuridad en mezclas con varios auxiliares farmacéuticos, especialmente en mezclas que comprenden lactosa y/o almidón de maíz. En otro aspecto por lo tanto la presente invención se relaciona con la provisión de preparaciones farmacéuticas del sólido Org 12962 que comprende Org 12962 en la forma cristalina pura B. Una composición farmacéutica de este tipo tiene la ventaja de que la reproducibilidad es incrementada apreciablemente y que los datos físicos, dentro de límites aceptables, son siempre idénticos.

~~26~~
37

Cuando el Org 12962 es preparado por medio de tratar una solución de base libre de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina en etanol con ácido clorhídrico, siguiendo el procedimiento general descrito en EP 370 560, sea que un producto amorfo o un producto polimorfo, en donde la proporción de cantidades de la forma A o la forma B varían ampliamente de tanda a tanda se obtiene.

Las formas cristalinas puras A y B pueden ser preparadas por medio de cristalizar la sal de hidrocloreuro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina bajo condiciones controladas a partir de etanol o mezclas de etanol con agua.

La forma pura A puede ser preparada por medio de enfriar rápidamente una solución concentrada de sal de hidrocloreuro en una mezcla de etanol/agua a partir de una temperatura de reflujo hasta cerca de 0° C e iniciar la nucleación en temperaturas sub cero (procedimiento de enfriamiento de cristalización). El enfriamiento rápido puede ser efectuado por ejemplo por medio de mantener el frasco de cristalización en hielo - acetona (cerca de -10° C).

La forma pura B puede ser preparada por medio de tratar la base libre de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina en etanol (o etanol con agua) a una temperatura de reflujo con un exceso de (hasta 5 equivalentes) de ácido clorhídrico mientras que la nucleación es iniciada en la temperatura de reflujo seguido por un enfriamiento lento de la sal de cristalización hasta temperatura ambiente (reacción de cristalización).

La forma termodinámicamente más estable también puede ser preparada agitando una suspensión de una tanda polimorfa de Org 12962 en una mezcla de etanol/agua hasta que la conversión a la forma B es completa. Este proceso tomará varios días cuando se lleva a cabo a temperatura ambiente (por ejemplo: 96 horas para la conversión completa de una tanda de 20 gramos en etanol-agua igual 3:1 a 20° C). En una modalidad preferida la suspensión es agitada a temperatura de reflujo de modo que la conversión a la forma B se completa en varias horas (por ejemplo: 3 horas para la conversión completa de una tanda de un gramo en etanol-agua = 3:1 a temperatura de reflujo).

Una tercera forma cristalina de Org 12962 puede ser obtenida por cristalización del compuesto a partir de 2-metil-butan-2-ol. Esta forma C es una forma de cristal metaestable, que se convierte espontáneamente en la forma B, aún a -20° C.

Los puntos de fusión de las formas de cristal A y B no difieren apreciablemente. Ambas formas puras se funden entre 282 a 284° C.

Las formas de cristal de la presente invención pueden estar caracterizadas, y por lo tanto distinguidas unas de otras por sus patrones de difracción en polvo de rayos X, como se hace por el espectro RAMAN.

La figura 1 ilustra el espectro XRPD para la forma de cristal A y B de Org 12962. Cada uno de los espectros está caracterizado por picos de intensidad en ciertos valores específicos del ángulo de difracción 2θ (θ). La forma A tiene unos picos característicos en $2\theta = 17,50^{\circ}$, $17,80^{\circ}$; $23,85^{\circ}$, $24,50^{\circ}$, $25,55^{\circ}$, $27,75^{\circ}$, y $29,40^{\circ}$.

La forma B está caracterizada por picos en $2\theta = 20,40^\circ$, $21,05^\circ$, $24,80^\circ$, $25,80^\circ$ y $28,10^\circ$.

A partir del análisis por rayos X de un cristal único de forma B se estableció que el grupo de espacio de los cristales es $P2_1/c$, monoclinico, con dimensiones de célula de $A = 12,848 \text{ \AA}$, $B = 7,151 \text{ \AA}$, $C = 14,164 \text{ \AA}$, $\beta = 104,85^\circ$, y $V = 1257,9 \text{ \AA}^3$.

En un análisis similar de la forma A reveló que los cristales son ortorómbicos con grupos de espacio $Pca2_1$ y dimensiones de célula: $A = 13,823 \text{ \AA}$, $B = 7,726 \text{ \AA}$, $C = 25,256 \text{ \AA}$ y $V = 2522,70 \text{ \AA}^3$.

El espectro FT Raman de las formas de cristal A y B se muestran en la figura 2. Cada forma de cristal tiene picos de absorción características, que se dan en la tabla 1. Estos picos pueden ser usados para las determinaciones cuantitativas de la cantidad de forma de cristal A en forma de cristal B puro, y de otra manera al revés.

~~40~~
41Tabla I

Tipos de absorción característicos en el espectro Raman
de las formas de cristal Org 12962

Forma A (Cm ⁻¹)	Forma B (Cm ⁻¹)	Forma C (Cm ⁻¹)
82,2	104,6	187,1
106,6	147,7	209,3
194,7	192,8	247,3
211,2	209,5	345,4
356,5	360,6	459,3
1037,6	1035,9	680,1
1268,2	12,65,3	1058,8
2997,0	2997,1	1151,1
3006,5	3001,8	2853,4
3122,4	3117,2	2998,1
		3105,4

Las preparaciones farmacéuticas del sólido Org 12962
de acuerdo con la invención comprende Org 12962 en la

24
42

forma cristalina pura B en asociación con uno o más aditivos o excipientes farmacéuticamente aceptables.

Tales preparaciones farmacéuticas generalmente toman la forma de una unidad de dosificación tal como una tableta, una cápsula o un supositorio, pero otras preparaciones farmacéuticas sólidas o secas también se incluyen. Una preparación farmacéutica preferida está en la forma de una tableta. Una tableta puede contener en adición al principio activo Org 12962 en la forma pura cristalina B, ciertos excipientes, tales como diluyentes, aglomerantes, deslizantes, y lubricantes, que sirven para impartir procesamiento satisfactorio y característica con presión a las tabletas, lo mismo que desintegrantes y agentes saborizantes, lo que le da características físicas adicionales deseables a la tableta terminada.

Los métodos para hacer tales unidades de dosificación son bien conocidos, por ejemplo de acuerdo con las técnicas estándar tales como aquellas descritas en la referencia estándar Genaro et al., Remington's Pharmaceutical Sciences, (18th Ed., Mack Publishing Company, 1990, Specially Part 8: Pharmaceutical Preparations and Their Manufacture).

Una unidad de dosificación de Org 12962, adecuada para el tratamiento de la depresión, ansiedad, obesidad, o incontinencia urinaria, puede contener entre 5 a 500 mg del ingrediente activo, más usualmente entre cerca de 10 a 100 mg. Una unidad de dosificación preferida puede contener 20 a 40 mg de Org 12962 en la forma cristalina de, lo que es tomado dos veces al día.

La invención se ilustra por los siguientes ejemplos.

Ejemplos

Procedimientos Generales:

Difracción en polvo de rayos X (XRPD) fueron obtenidos sobre un difractómetro de transmisión D500 de Siemens con un monocromador de germanio primario, radiación Cu-K α 1, posiciones 35 kb y 40 MA. Los factores usados: Factor antideslizante 2 mm, detector de ranura 0,2 mm. Condiciones de medida: tamaño de la etapa 0,02°, tiempo por etapa 10 segundos. Las muestras fueron medidas entre cinta Scotch y fueron giradas durante las medidas

V3
44

con una velocidad de 15 rpm. El espectro XRPD de las formas cristalinas puras A y B se ilustra en la figura 1.

FT-Raman fue registrado usando el espectrómetro Broker RFS 100 Raman que está equipado con un láser 1064 nm de Nd-YAG (Adlas model DPY 421N). El espectro fue medido con una resolución de 2 cm^{-1} usando una potencia de láser de 200 mW. Típicamente, 256 interferogramas fueron transfectados por cada espectro. El punto láser tenía un diámetro de aproximadamente $30\text{ }\mu$ en la posición de la muestra. El espectro Raman de las formas de cristal A y B se ilustró en la figura 2.

Ejemplo 1.

Preparación de Org 12962

A: Preparación de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina

Piperazina (10,37 g; 120 moles) fue disuelto en etanol acuoso al 95% (36 l). La solución fue calentada a reflujo, y después de lo cual una solución de 2,6-

24
95

dicloro-2-(trifluorometil)-piridina (8640 g; 40 moles) en etanol acuoso al 95% (9 l) fue agregado durante dos horas. El reflujo fue mantenido durante otras dos horas. La mezcla fue enfriada a temperatura ambiente y la sal de hidrocioruro de piperazina precipitada fue removida por filtración. El etanol fue removido bajo vacío. El residuo fue disuelto en acetato de etilo (30 l). Esta solución fue lavada doble vez con agua (15 l), secada sobre sulfato de magnesio, después de lo cual el disolvente fue removido en vacío. El residuo fue vertido sobre agua (15 l) mientras se agitada. El resultado sólido fue filtrado y lavado extensivamente con agua.

B: Sal de hidrocioruro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina

[Org 12962]

El sólido húmedo descrito bajo A fue disuelto en etanol acuoso al 96% (12 L). La solución fue filtrada una vez para remover algunos materiales insolubles. El filtrado fue diluido con etanol acuoso al 96% (15 l), después de lo cual gas de cloruro de hidrógeno fue pasado por la solución. Durante la salificación la temperatura

~~125~~
06

se elevó hasta reflujo. Después de enfriar a 0° C, el precipitado es filtrado para dar el producto crudo (7600 g), el cual fue redissuelto mientras se calentó en etanol acuoso al 96% (11 l) y agua (2,7 l). Después de enfriar a temperatura ambiente, la sal de hidrocloruro fue filtrada, lavada con etanol frío (4 l), y secada a 110° C en vacío para dar Org 12962 (5500 g; 45,5%)

La espectroscopia Raman reveló que este producto consiste de una mezcla de formas de cristal A (77%) y B (23%).

Análisis Elemental:

Calculado (%) para $C_{10}H_{12}N_3Cl_2F_3$: C: 39,75; H: 4.,01; 13,91

Encontrado (%): C: 39,81; H: 4.,07; N: 13,85

^1H -RMN (300 MHz en DMSOd6): δ en ppm: 3,26 (4H; tripleta J = 5,3 Hz) 3,99 (4H; triple J = 5,3 Hz); 7,08 (1H; doble J = 9,0 Hz); 8,04 (1H; doble J = 9,0 Hz); 9,76 (2H; sencillo amplio: N-H, HCl)

~~26~~
47**Ejemplo 2.****Preparación de Org 12962 en forma de cristal puro A**

Una solución de Org 12962 (35 gramos) en etanol acuoso 96% (1 litro) fue enfriado rápidamente en un baño de hielo/acetona a partir de la temperatura de reflujo hasta -10° C, mientras que se agitó con una barra de agitación magnética. La nucleación ocurrió espontáneamente en la temperatura sub cero. Después de agitación de la mezcla durante 2 horas a -10° C el material cristalino fue filtrado, lavado con pequeña cantidad de etanol frío y secado en vacío a temperatura ambiente.

Ejemplo 3.**Preparación de Org 12962 en forma de cristal puro B**

Org 12962 polimorfo (10 kg), preparado según se describió en el ejemplo 1, fue disuelto en una mezcla de etanol (80 l) y agua (11 l). La solución fue calentada a temperatura de reflujo, después de lo cual el disolvente fue destilado hasta que el volumen de la mezcla se

18

redujo aproximadamente 15 l y la cristalización se inició. La mezcla resultante se mantuvo a temperatura de reflujo durante 5 horas, después de lo cual la solución fue enfriada lentamente a $2 \pm 2^\circ \text{C}$ con una rampa de enfriamiento de 17°C/hora . La masa cristalina fue filtrada y lavada con etanol (4 l) y secada en vacío a 60°C durante 24 horas.

Ejemplo 4.

Estabilidad de las formas cristalinas A y B con en mezcla con excipientes

Alicuotas de Org 12962 (54 a 10 mg) en forma de cristal A (una tanda preparada como se describió en el ejemplo 2 y que se encontró que contenía 92% de forma A y 8% de forma B) fue pesada en tubos de fondo redondeado. A cada alícuota se agregó un excipiente mencionado en la tabla II, seguido por 10 μl de agua, después de lo cual las suspensiones fueron mezcladas muy bien.

Las alícuotas de Org 12962 (5-10 mg) en forma de cristal B (100% forma B) fueron pesadas en tubos de fondo

48
49

redondeado. A cada alícuota se agregó un excipiente mencionado en la tabla 2, seguido por 100 µl de agua. Granitos vidriosos (250-300 mg) fueron agregados a cada tubo, después de lo cual las muestras fueron mezcladas muy bien durante un minuto. El agua residual fue evaporada en vacío a temperatura ambiente. Los tubos fueron almacenados en la oscuridad durante 14 días sea 20° C o 60° C. las muestras fueron disueltas en 20,0 ml de una mezcla de 70:30 de 25 mM de fosfato pH 2,6 como amortiguador y acetonitrilo. La disolución fue efectuada manteniendo los tubos en un zonificador durante 20 minutos.

El análisis cuantitativo de la cantidad de Org 12962 por tubo fue hecho por comportamiento alto de cromatografía líquida (HPLC) usando sea los siguientes métodos validados: (1) usando una columna Symmetry Shield Reverse Phase RP18 (150 x 4,6 mm), que fue operada a 40° C, usando una velocidad de flujo de 1,0 ml/min, y como eluyente una mezcla 69:31 (v/v) del amortiguador de fosfato 25 mM pH 2,6, y también contenía 15 mM de ácido octanosulfónico, y acetonitrilo, o (2) usando Lichrospher 60 RP Select B column (125 x 4,0 mm), que fue operado a

279
50

temperatura ambiente, usando una velocidad de flujo de 1,5 ml/min, y como eluyente una mezcla de 55:45 (v/v) de metanol y agua, que contenía también 5 mm de ácido octanosulfónico. El contenido de Org 12962 permaneció en las muestras después de almacenamiento que se da en la tabla II como el porcentaje (%) de la cantidad inicial.

Tabla II

Estabilidad de Org 126962 en mezclas con excipientes

Condiciones de almacenamiento

14 días	14 días
20° C/oscurο	60° C/oscurο

	I	II	I	II
EXCIPIENTE	%	%	%	%
Lactosa (80 mg)*	94,5	99,6	91,2	97,4
HPC (2 mg)	98,0	100,0	n.d.	96,5
Almidón de maíz (10 mg)	100,0	100,1	82,6	97,9
Estearato-Mg (0,5 mg)	97,9	99,9	93,8	97,9
Primojel® (4 mg)	95,0	100,0	94,6	96,0
Talco (0,3 mg)	99,2	99,9	94,5	100,1
Dióxido de titanio (0,2 mg)	96,0	99,8	97,5	92,9
HPMC (1,3 mg)	95,0	100,0	91,8	97,8
PEG (0,3 mg)	96,5	99,8	92,5	96,3

I: Org 12962 cristalino: 92% forma A y 8% forma B;

II: Org 12962 cristalino: 100% forma B;

*: la cantidad (en mg) de excipiente agregado a 5,0 mg de Org 12962 es calibrado en paréntesis

HPC: hidroxipropilcelulosa

HPMC: hidrocipropilmetilcelulosa

PEG: plietilenglicol

Los datos en la tabla II indican que el Org 12962 en mezcla con excipientes farmacéuticos es más estable que en la forma de cristal puro B como se comparó con la forma de cristal puro A. cuando el almacenamiento fue en condiciones de estrés de 60° C, la estabilidad mejoró en la forma pura de cristal B que fue especialmente notable cuando la mezcla con lactosa y con almidón de maíz, dos componentes mayores o principales en las formulaciones farmacéuticas de Org 12962.

Ejemplo 5.

Formulaciones farmacéuticas que comprenden la forma de cristal puro B de Org 12962.

Tabletas de Org 12962, que tienen las siguientes composiciones fueron preparadas:

Ingredientes	mg	mg
Forma B de Org 12962		
Hidroxipropilcelulosa (HPC)		
Almidón de maíz		
Dióxido de silicio coloidal		
Estearato de magnesio		
Lactosa 200 m hasta un total de peso de tableta D		

El Org 12962 es mezclado homogéneamente con el agente de carga lactosa y el desintegrante de almidón de maíz, dando una mezcla que es granulada en una operación de bajo corte con un mucílago del aglomerante hidroxipropilcelulosa. La masa de humedad es tamizada, secada en un lecho fluidizado, tamizada nuevamente y finalmente mezclada con dióxido de silicio coloidal y el lubricante de estearato de magnesio. El granulado resultante es comprimido hasta núcleos de tableta.

~~53~~
54

REIVINDICACIONES

1. El compuesto hidrocloreuro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina (Org 12962), caracterizado en que el compuesto es una forma de cristal puro, que es completa o virtualmente completamente libre de otras formas cristalinas.

2. El compuesto de acuerdo con la reivindicación 1, que tiene una forma de cristal puro A que se caracteriza por un patrón de difracción en polvo de rayos X obtenida con una radiación $\text{CuK}\alpha 1$ con picos en los valores de $2-\theta$ (2θ) de $17,50^\circ$, $17,80^\circ$, $23,85^\circ$, $24,50^\circ$, $25,55^\circ$, $27,75^\circ$ y $29,40^\circ$ y por un espectro de absorción Raman con picos en $82,2 \text{ cm}^{-1}$, $106,6 \text{ cm}^{-1}$, $194,7 \text{ cm}^{-1}$, $211,2 \text{ cm}^{-1}$, $356,5 \text{ cm}^{-1}$, $1037,6 \text{ cm}^{-1}$, $1268,2 \text{ cm}^{-1}$, $2997,0 \text{ cm}^{-1}$, $3006,5 \text{ cm}^{-1}$ y $3122,4 \text{ cm}^{-1}$.

3. El compuesto de acuerdo con la reivindicación 1, que tiene la forma de cristal puro P que es caracterizado por un patrón de difracción en polvo de rayos X obtenido con radiación CuK α 1 con picos en los valores 2- θ (2 θ) 20,40°, 21,05°, 24,80°, 25,80° y 28,10° y por un espectro de absorción Raman con picos en 104,6 cm⁻¹, 147,7 cm⁻¹, 192,8 cm⁻¹, 209,5 cm⁻¹, 360,6 cm⁻¹, 1035,9 cm⁻¹, 1265,3 cm⁻¹, 2997,1 cm⁻¹, 3001,8 cm⁻¹ y 3117,2 cm⁻¹.
4. Un método de preparación del compuesto de acuerdo con la reivindicación 2, caracterizado en que una solución concentrada de una sal de hidrocloruro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina en una mezcla de etanol/agua es rápidamente enfriada a por debajo de 0° C después de lo cual la nucleación espontánea es iniciada.

56

5. Un método de preparación de un compuesto de acuerdo con la reivindicación 3, caracterizado en que una solución concentrada de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina en una solución de etanol-agua es tratada a temperatura de reflujo con un exceso de ácido clorhídrico mientras que la nucleación es iniciada en la temperatura de reflujo, después de lo cual la solución es enfriada lentamente a temperatura ambiente.
6. Un método de preparación del compuesto de acuerdo con la reivindicación 3, caracterizado que una suspensión de hidrocloruro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina polimorfo en una mezcla de etanol/agua se mantiene hasta que la conversión a la forma B sea completa.
7. El método de acuerdo con la reivindicación 6 en donde la suspensión es mantenida a temperatura de reflujo.

~~18~~
57

8. Una composición farmacéutica que comprende un excipiente farmacéuticamente aceptable y Org 12962, caracterizado en que Org 12962 está en la forma de cristal puro sustancialmente que tiene un patrón de difracción en polvo de rayos X obtenido con radiación CuK α 1 con picos en valores de 2θ (2 θ) de 20,40°, 21,05°, 24,80°, 25,80° y 28,10° y un espectro de absorción Raman con picos de absorción en 104,6 cm⁻¹, 147,7 cm⁻¹, 192,8 cm⁻¹, 209,5 cm⁻¹, 360,6 cm⁻¹, 1035,9 cm⁻¹, 1265,3 cm⁻¹, 2997,1 cm⁻¹, 3001,8 cm⁻¹ y 3117,2 cm⁻¹.
9. Un método para tratar depresión, ansiedad, obesidad o incontinencia urinaria en un mamífero que comprende administrar una cantidad terapéuticamente efectiva de hidrocloruro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina en la forma de cristal puro B de la reivindicación 3.

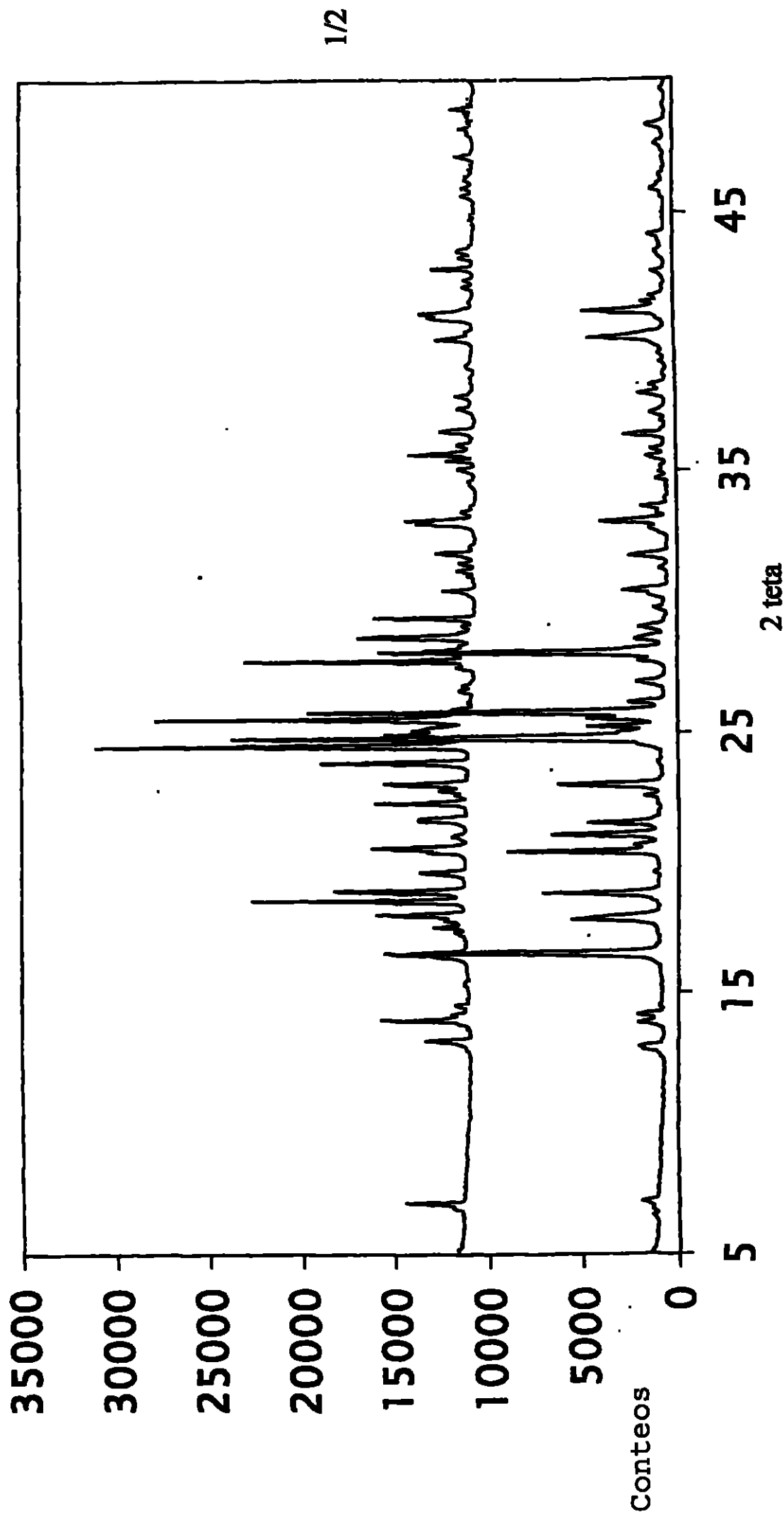
A7

58

RESUMEN

La invención se relaciona con formas cristalinas A y B de hidrocloruro de 1-[6-cloro-5-(trifluorometil)-2-piridinil]piperazina (Org 12962) a métodos para la preparación de estas formas de cristal y a composiciones farmacéuticas que comprenden la forma de cristal útil en el tratamiento de depresión, ansiedad, obesidad, o incontinencia urinaria.

Figura 1: Difractogramas de polvo rayos X de formas A
(superior) y B (inferior) de Org 12962.

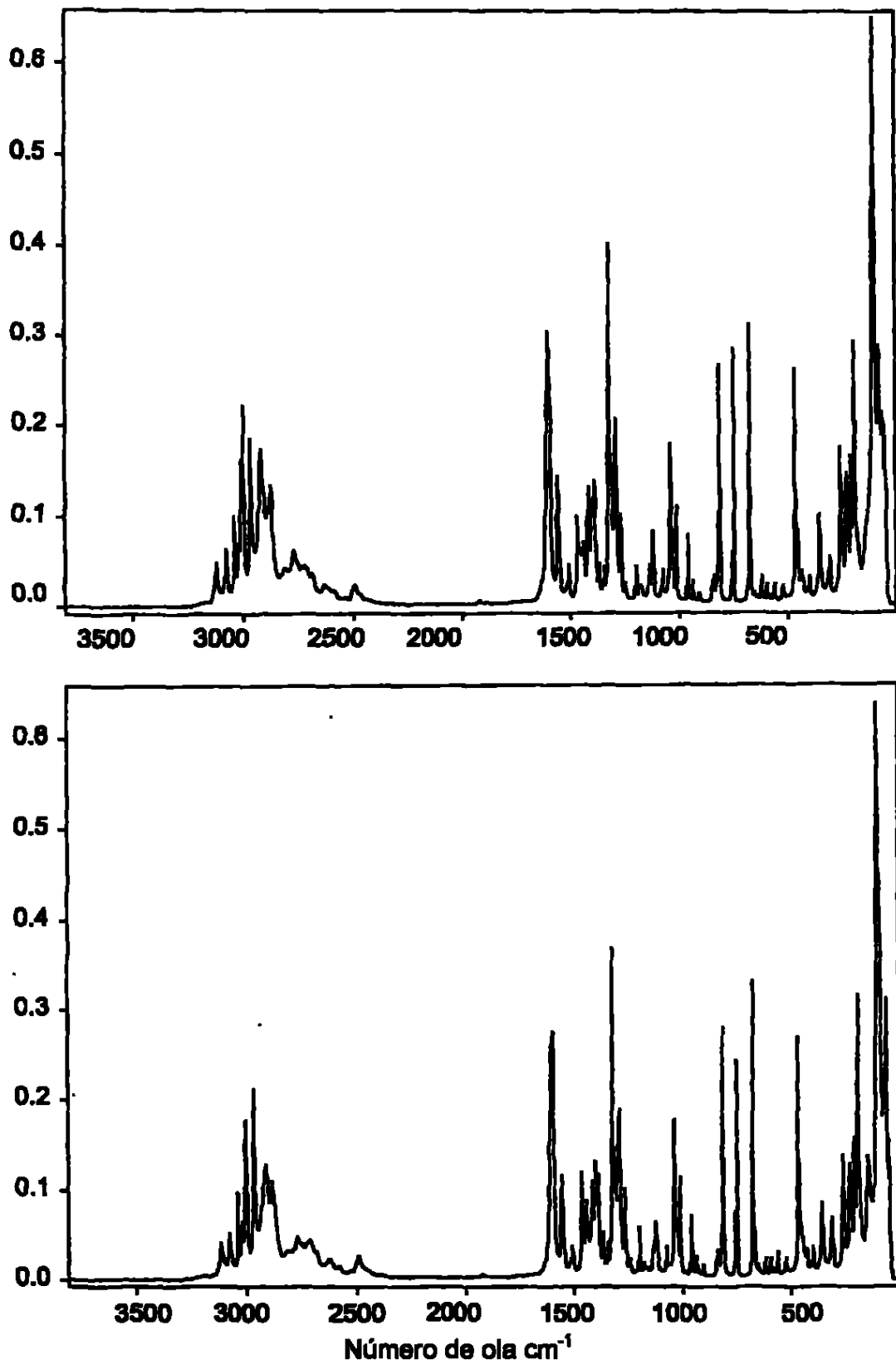


✓

60

2/2

Figura 2: Espectro Raman de formas de cristal A (superior) y B (inferior).



**FORMATO DE DIGITALIZACION
RELACION DE ANEXOS**

61

Expediente No		D 30.306 39	No de Follo
Item		No de unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	7	
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

one final

CAVELIER

ABOGADOS

CAR:

BOGOTÁ

REPRESENTACION Y PODER

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTATION AND
POWER OF ATTORNEY

I (we), the undersigned / Yo (nosotros), abajo firmado (s)

AKZO NOBEL N.V.

of/domiciliado (s) en Velperweg 76, 6824

BM Arnhem, THE NETHERLANDS

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contencioso-administrative and judicial, before Arbitration Court, in all matters relating to the following: a) Obtainment of patents, utility models, industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative and judicial, nullity, infringement, granting of licenses, the actions for writ mandamus, the protection of trade secrets and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this Day and Month of 6 AUG 1998

F.G.M. Hermans

In/en

Director Patents Pharma

Signature

AKZO NOBEL N.V.

E.H. Reerink

Deputy Director
Legal AffairsCAVELIER ABOGADOS
WPPODERE-179 (MINUTA N° 12.1.12.5)

TRADUCCION No. 18.11.98
MARIA ELVIRA MAFIELLO
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Res. No. 2679 Min. Justicia

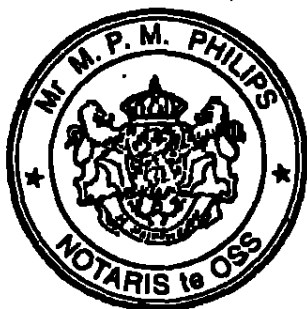
LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate* on (1) the legal existence of the company; (2) that it is in accordance with the Power-of-Attorney, (2) that it is in accordance with the company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

Seen for legalization of the signatures of Mr. F.G.M. Hermans and Mr. E.H. Reerink by me, Mr. Martinus Petrus Maria Philips, notary public at Oss, the Netherlands, on this 26th day of August 1998.



15499

TRADUCCION No.: 18.11/98

MARIA ELVIRA MARTELLO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

CHAMBER OF COMMERCE AND INDUSTRY
FOR OOST-BRABANT (NETHERLAND)

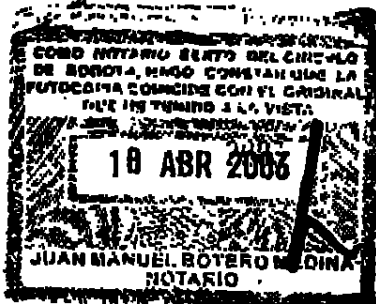
EXCLUSIVE PLACE FOR LEGALIZATION OF
THE ABOVE MENTIONED SIGNATURE(S)



27 AUG 1998

KAMER VAN KOOP- EN
OOST-BRABANT
's-HERTOGENBOSCH

J. Schellekens



Gezien voor legalisatie van de handtekening
van dhr/mw J. Schellekens

's-Gravenhage,

9 SEP 1998



De Minister van
Buitenlandse Zaken
voor deze,

Leges f 20,= H.H. van POORTEN

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



CONSULADO DE COLOMBIA

C 20 112 11-201-001-3

62
63

El suscrito Cónsul de Colombia en La Haya, Holanda,
vistos los documentos presentados por los interesados,

CERTIFICA:

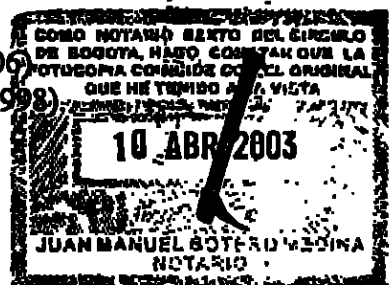
Que el Señor Martinus Petrus Maria PHILIPS, quien como Notario Público de Oss, Países Bajos, autenticó las firmas de los signatarios del poder precedente, ejercía en la fecha las funciones indicadas, y su firma corresponde a la registrada en este Consulado.

Que la Compañía AKZO NOBEL N.V. es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número 09007809;

Que los Señores Franciscus Guilielmus Maria HERMANS y Engbert Harmen REERINK, signatarios del presente documento, quienes en su carácter de Apoderados de la Empresa AKZO NOBEL N.V., conjuntamente tienen facultad para ello, y cuyas firmas fueron autenticadas ante el Notario Público de Oss, Señor Martinus Petrus Maria PHILIPS, son los representantes legales de la citada Empresa en este País.

El Cónsul de Colombia en La Haya, Países Bajos, no asume responsabilidad alguna por el contenido del documento.

Esta certificación se expide en La Haya, Países Bajos, a los seis (06) días del mes de Noviembre de mil novecientos noventa y ocho (1998).



Impuesto de Timbre	US\$	6.00.
Derechos Consulares	US\$.	100.00
Costo Total Pagado	US\$.	106.00

Certificación No. 206

JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

TRADUCCION No. 18.11/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

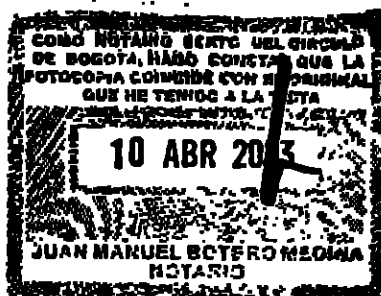
90 NOV 19 AM 11:56

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERIORES

300803

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS



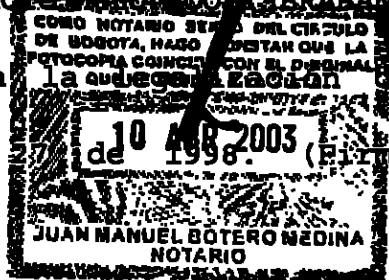
63
64

TRADUCCIÓN OFICIAL No. 18.11/98 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual AKZO NOBEL N.V. otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER). Dado y firmado el 6 de agosto de 1998. (Firma ilegible) F.G.M. Hermans, Director de Patentes Farmacéuticas. (Firma ilegible) E.H. Reerink, Subdirector de Asuntos Jurídicos. (Sello Corporativo) AKZO NOBEL N.V.

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 26 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

(Legalización) CAMARA DE INDUSTRIA Y COMERCIO PARA COSTA BRABANT (PAÍSES BAJOS). Visto exclusivamente para la(s) firma(s) que antecede(n). Agosto 10 de 1998. (Firma ilegible) J. Schellenkens.



(Sello en holandés).

(En español) Certificación de las firmas que anteceden y de la existencia legal de AKZO NOBEL N.V. expedida por el Consulado de Colombia en La Haya el día 6 de noviembre de 1998, bajo el No.

64
65

**ITINERARIO DE EMILIO FERRERO Y SEÑORA
29 Abril al 11 Mayo, 2003**

**INTA 125 ANNUAL MEETING AMSTERDAM, 2003
Amsterdam, Holanda, 02-10 Mayo, 2003 (COLO 03774-008-012-4)**

Martes 29 Abril BOGOTA – PARIS
Vuelo : AF 423
Salida : 17:25
Llega : 11:05 (30 Abril)

Miércoles 30 Abril PARIS – AMSTERDAM
Vuelo : AF1740
Salida : 12:35
Llega : 13:50

HOTEL OKURA AMSTERDAM
Ferdinand Bolstraat 333
Amsterdam 1072, Holanda
Tel.: 009 (31-20) 678-7111
Fax.: 009 (31-20) 671-2344

Sábado 10 Mayo AMSTERDAM – PARIS
Vuelo : AF 2041
Salida : 18:05
Llega : 19:20

HOTEL HOLIDAY INN - PARIS-CHARLES DE GAULLE AIRPORT
1 Allée du Verger
Roissy, 95700
Francia
Tel.: 009 (33-1) 342-93000
Fax.: 009 (33-1) 342-99052

Domingo 11 Mayo PARIS – BOGOTA
Vuelo : AF 422
Salida : 11:00
Llega : 15:00

65
66

206. Firmado JOSE IGNACIO VILLEGAS CORTES, Cónsul de Colombia, La Haya.. Pagado impuesto de timbre.

(Al dorso) Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 300803 del 19 de NOVIEMBRE de 1998, firmado por el Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

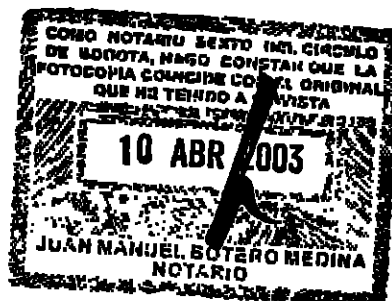
COLO 11214-801-001-3

Id. 6

Nov. 20/98

Maria E. Marto
TRADUCCION No. 11198
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LAS ANTERIORES(S) FIRMAS(S) FUERON POR *[Firma]* IDENTIFICADOS CON C.C. No.(s) *[Firma]* ES(SON) AUTENTICA(S) SANTAFE DE BOGOTA, 23 NOV. 1998



MINISTERIO DE RELACIONES EXTERIORES
198457
Maria Marto
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPENA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
98 NOV 24 PM 12:06
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

66
67

SUPERINDUSTRIA Y COMERCIO
Radicacon : 03030679 00000000 Folios: 66
Fecha (AMB): 2003-04-10 17:19:45
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE MARCAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 23,236
FECHA : ABRIL 1 DE 2003

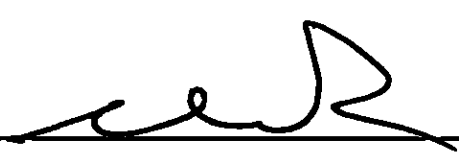
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	12169297	01/04/2003	17,514,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	7 TRAMITES DE SOL. DE DISENOS INDUS	400,000.00
		TOTAL :	\$ 400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 11214-B41-008-0

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION		
MODELO DE UTILIDAD	()	(X)
- Indicación de que se solicita la concesión de una patente.	()	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	(X)
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	(X)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA (X)	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial.	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Eduar Navarino

10-04-2003

Fecha:



70
69

2020
Bogotá, D.C.,

Doctor:
EMILIO FERRERO
Apoderado
AKZO NOBEL N.V

Oficio N° 08077

ASUNTO:	Radicación N°	03-30679
	Solicitud internacional	PCT/EP01/11714-
	Fecha inicio fase nacional	13/05/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 24 OCT. 2003.