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

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 November 2015 (19.11.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/173154 A9

(51) International Patent Classification:
A61K 31/167 (2006.01) *A61P 11/00* (2006.01)
A61K 31/58 (2006.01) *A61P 11/08* (2006.01)
A61K 9/00 (2006.01) *A61P 43/00* (2006.01)

(21) International Application Number:
PCT/EP2015/060257

(22) International Filing Date:
8 May 2015 (08.05.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1408387.7 12 May 2014 (12.05.2014) GB

(71) Applicant: **TEVA PHARMACEUTICALS EUROPE B.V.** [NL/NL]; Piet Heinkade 107, NL-1019GM Amsterdam (NL).

(72) Inventor: **ULLMANN, Michiel**; Teva Pharmaceuticals Europe B.V., Piet Heinkade 107, NL-1019GM Amsterdam (NL).

(74) Agent: **COTTAM, David, William**; Teva UK Ltd, Global IP Group, Field House, Station Approach, Harlow Essex CM20 2FB (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
3 March 2016

(15) Information about Correction:
see Notice of 3 March 2016

WO 2015/173154 A9

(54) Title: COMBINATIONS OF FORMOTEROL AND BUDESONIDE FOR THE TREATMENT OF COPD

(57) Abstract: This invention provides a fixed-dose composition comprising formoterol or a pharmaceutically acceptable salt thereof and budesonide, for use in the long-term treatment of COPD and the treatment of acute exacerbations of COPD, wherein the composition is administered as a maintenance dose for the long-term treatment of COPD and pro re nata (p.r.n.) as a rescue medication for the treatment of acute exacerbations of COPD.

COMBINATIONS OF FORMOTEROL AND BUDESONIDE FOR THE TREATMENT OF COPD

The present invention relates to the treatment of respiratory disorders, and particularly to a fixed-dose composition comprising formoterol and budesonide for use in the treatment of chronic obstructive pulmonary disease (COPD).

COPD is a leading cause of death worldwide. Global trends indicate that case frequency will continue to rise and by 2030 COPD will become the fourth leading cause of death worldwide. COPD is considered a preventable and treatable disease and is characterised by persistent airflow limitation that is not fully reversible. The limitation is usually progressive, and primarily associated with an abnormal inflammatory response in the lungs to noxious particles or gases.

COPD is a heterogeneous long-term disease comprising chronic bronchitis, emphysema and also involving the small airways. The pathological changes occurring in patients with COPD are predominantly localised to the airways, lung parenchyma and pulmonary vasculature. Phenotypically, these changes reduce the healthy ability of the lungs to absorb and expel gases.

Bronchitis is characterised by long-term inflammation of the bronchi. Common symptoms may include wheezing, shortness of breath, cough and expectoration of sputum, all of which are highly uncomfortable and detrimental to the patient's quality of life. Emphysema is also related to long-term bronchial inflammation, wherein the inflammatory response results in a breakdown of lung tissue and progressive narrowing of the airways. In time, the lung tissue loses its natural elasticity and becomes enlarged. As such, the efficacy with which gases are exchanged is reduced and respired air is often trapped within the lung. This results in localised hypoxia, and reduces the volume of oxygen being delivered into the patient's bloodstream, per inhalation. Patients therefore experience shortness of breath and instances of breathing difficulty.

Patients living with COPD experience a variety, if not all, of these symptoms on a daily basis. Their severity will be determined by a range of factors but most commonly will be correlated to the progression of the disease. These symptoms, independent of their severity, are indicative of stable COPD and this disease state is maintained and managed through the administration of a variety drugs. The treatments are variable, but often include inhaled bronchodilators, anticholinergic agents, long-acting and short-acting β_2-agonists and corticosteroids. The medicaments are often administered as a single therapy or as combination treatments of corticosteroids and long-acting β_2-agonists.

Stable COPD may be indefinitely maintained, however the disease also manifests itself in an acute form, known in the art as an exacerbation. An exacerbation of COPD is an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond the baseline day-to-day variations and can often lead to a change in medication. Exacerbations may be subcategorised as being mild,

moderate or severe, based on, for example, required medications (e.g. oral corticosteroids) and outcomes (e.g. hospitalisation) but are effectively a spectrum of acute worsening of the disorder. Exacerbations can be precipitated by several factors, though it is widely accepted that common causes are respiratory tract infections (viral and bacterial), increased exposure to particulates (air pollution) and poor patient compliance (forgetting or resisting to take medication). These episodes negatively affect the patient's quality of life, accelerate the rate of decline of lung function and are often associated with significant mortality, particularly instances in which hospitalisation is required. During exacerbations patients that seek medical assistance are often treated with short-acting β_2-agonists, corticosteroids and antibiotics, although recent findings have indicated that symptoms persist for several weeks following onset, which suggests that the underlying pathophysiology is not resolved by this approach. Furthermore, it is generally documented that COPD patients frequently experience changeable symptoms. As such, it is estimated that an alarming number of patients endure exacerbations, but choose not to report them, and as a direct result, they suffer irreparable lung damage. These findings highlight an unmet clinical need for improved therapies that manage both stable COPD and offer relief during an exacerbation.

Accordingly, the present invention provides a fixed-dose composition comprising formoterol or a pharmaceutically acceptable salt thereof and budesonide, for use in the long-term treatment of COPD and the treatment of acute exacerbations of COPD, wherein the composition is administered as a maintenance dose for the long-term treatment of COPD and pro re nata (p.r.n.) as a rescue medication for the treatment of acute exacerbations of COPD.

The present invention is based upon a combined treatment of inhaled corticosteroids and β_2-agonists in a single device, which allows patients to receive the benefits of daily maintenance medication and rescue therapy contained within one prescribed dosage (termed a "fixed-dose combination" or "FDC"). Should the patient's symptoms deteriorate (upon experiencing an exacerbation) they will then use the same device as a rescue medication, following secondary (frequency indicating) dosage instructions. Upon multiple actuations of the device, the patient obtains an increased dosage of β_2-agonist that in turn induces bronchodilation and hence provides symptomatic relief. Furthermore, this approach serves to improve patient convenience and compliance through unifying a multi-faceted treatment into a single device. First, the present invention conveniently provides patients with one inhaler to carry, as opposed to two separate inhalers that each contains a different medicament. Secondly, patient compliance is directly addressed and improved, in that, when used as a rescue medication, the patient not only experiences relief from receiving a β_2-agonist but also receives an additional dose of steroid. This feature of the invention is particularly important and beneficial in circumstances where the patient has missed a maintenance dose since it concomitantly provides an increased dose of inhaled corticosteroid to address inflammation that may underlie the worsening of symptoms

It has therefore been found that a combination of budesonide and formoterol may, in a single device, be administered as a maintenance therapy to treat COPD and used also (through increased frequency of actuation) as a rescue medication p.r.n.

Thus, the present invention provides both for the long-term treatment of COPD and the treatment of acute exacerbations of COPD. The long-term treatment involves the administration of a maintenance dose every day. The treatment is typically over a period of more than 6 months, and usually more than 12 months. Many patients will receive the treatment palliatively. This aspect of the disease may be termed "stable COPD". The acute treatment is for exacerbations, as defined hereinabove. Exacerbations are treated p.r.n., that is, as required. The present invention improves patient care and maintains positive patient prognoses. It particularly provides a therapy that can offer daily symptomatic relief and reduces patient distress in the early stages of, and during, an exacerbation presenting in the home. For this reason, it is often termed a "rescue medication". It combats persistent inflammation with directed treatment at the appropriate location in the lungs.

Formoterol is a long-acting β_2-agonist that displays a rapid onset of action. It can be synthesised as four independent stereoisomers, and the present invention can include each of these individual forms. Typically it is administered as (R,R)-formoterol, or a racemic mixture of (R,R)- and (S,S)-formoterol. Suitable pharmaceutically acceptable salts of formoterol include those known in the art, and they are commonly derived from the addition of inorganic or organic acids to the medicament. Non-exhaustive examples include hydrochloride, hydrobromide, acetate, formate, halo and alkyl benzoate, tartrate, citrate, fumarate, triflate or salicylate. An example of particular interest is formoterol fumarate, e.g. formoterol fumarate dihydrate.

It is preferable that substantially all of the particles of formoterol fumarate are less than 10 μm in size. This is also to ensure that the particles are effectively entrained in the air stream and deposited in the lower lung, which is the site of action. Preferably, the particle size distribution of the formoterol is d10 <1 μm, d50 = <5 μm, d90 = <10 μm and NLT 99% <10 μm; more preferably, the particle size distribution of the formoterol fumarate is d10 <1 μm, d50 = 1-3 μm, d90 = 3.5-6 μm and NLT 99% <10 μm.

The delivered dose of formoterol, is preferably 1-20 μg per actuation, with specific examples being 4.5 and 9 μg per actuation. The doses are based on the amount formoterol present (i.e. the amount is calculated without including contribution to the mass of the counterion, where present). The actual prescribed dosage will be dependent upon patient age and weight, severity of disease and response to therapy.

The present invention also comprises the corticosteroid budesonide as a second pharmaceutically active ingredient.

It is preferable that substantially all of the particles of the corticosteroid are less than 10 μm in size. This is to ensure that, when administered with a DPI, the particles are effectively entrained in the air stream and deposited in the lower lung, which is the site of action. Preferably, the particle size distribution of the corticosteroid is d10 <1 μm, d50 = <5 μm, d90 = <10 μm and NLT 99% < 10 μm.

The delivered dose of budesonide (the amount actually delivered to the patient) is preferably 50-500 μg per actuation, with specific examples being 80, 160 and 320 μg per actuation. Again, the actual prescribed dosage will be dependent upon patient age and weight, severity of disease and response to therapy.

Particularly preferred delivered doses of budesonide/formoterol in μg are 80/4.5, 160/4.5 and 320/9. Particularly preferred molar ratios of budesonide/formoterol are within the range of 40:1 to 10:1, wherein the moles of formoterol are based on the amount present (i.e. the amount is calculated without including contribution to the mass of the counterion).

The formulation may be administered via inhalation devices known in the art. These can include but are not limited to dry powder inhalers (DPIs) and pressurised metered dose inhalers (pMDIs).

The composition is preferably a dry powder formulation, further comprising a coarse carrier. The carrier can be selected from polysaccharides e.g. glucose or lactose. The carrier is preferably lactose, more preferably lactose monohydrate (α-lactose monohydrate) and may be prepared by standard techniques, e.g. sieving. The lactose carrier preferably has a particle size distribution of d10 = 20-65 μm, d50 = 80-120 μm, d90 = 130-180 μm and <10 μm = <10%. Preferably, the particle size distribution of the lactose is d10 = 20-65 μm, d50 = 80-120 μm, d90 = 130-180 μm and <10 μm = <6%.

A suitable inhaler for working the present invention is the Spiromax® DPI available from Teva Pharmaceuticals.

The delivered dose of the active agent is measured as per the USP <601>, using the following method. A vacuum pump (MSP HCP-5) is connected to a regulator (Copley TPK 2000), which is used for adjusting the required drop pressure P_1 in a DUSA sampling tube (Dosage Unit Sampling Apparatus, Copley). The inhaler is inserted into a mouthpiece adaptor, ensuring an airtight seal. P_1 is adjusted to a pressure drop of 4.0 KPa (3.95-4.04 KPa) for the purposes of sample testing. After actuation of the inhaler, the DUSA is removed and the filter paper pushed inside with the help of a transfer pipette. Using a known amount of solvent (acetonitrile:methanol:water (40:40:20)), the mouthpiece adaptor is rinsed into the DUSA. The DUSA is shaken to dissolve fully the sample. A portion of the sample solution is transferred into a 5 mL syringe fitted with Acrodisc PSF 0.45 μm filter. The first few drops from the filter are discarded and the filtered solution is transferred into a UPLC

vial. A standard UPLC technique is then used to determine the amount of active agent delivered into the DUSA. The delivered doses of the inhaler are collected at the beginning, middle and end of inhaler life, typically on three different days.

In one embodiment the composition is administered 2-4 times per day as a maintenance dose, more preferably the composition is administered twice-per-day (i.e. b.i.d.) as a maintenance dose. B.i.d. administration is typically every morning and every evening as a maintenance dose and the required dose may be administered in one or two puffs of the inhaler.

The composition is preferably administered no more than ten times p.r.n as a rescue medication, more preferably no more than eight times p.r.n as a rescue medication. In a particularly preferred embodiment, the composition is administered twice-per-day as a maintenance dose and no more than eight times p.r.n as a rescue medication. Ideally, the patient should not exceed 120 µg of formoterol over any 24 hour period and 3,200 µg of budesonide over any 24 hour period.

The present invention will now be described with reference to the examples, which are not intended to be limiting.

Examples

Example 1

Three formulations of Budesonide/Formoterol (BF) Spiromax (Teva Pharmaceuticals) were prepared: low strength (120 inhalations, each delivering 80 µg budesonide and 4.5 µg formoterol), middle strength (120 inhalations, 160 µg budesonide and 4.5 µg formoterol per inhalation), and high strength (60 inhalations, 320 µg budesonide and 9 µg formoterol per inhalation).

The compositions of the three strengths of BF Spiromax per container are set out in Tables 1-3.

Table 1. Composition per container of BF Spiromax 80/4.5 µg 120 inhalation product

Material	Weight	Function	Quality Standard
Budesonide (micronised)	12.0 mg	Drug substance	Ph. Eur.
Formoterol fumarate dihydrate (micronised)	0.645 mg	Drug substance	Ph. Eur.
Lactose monohydrate	1.487 g	Excipient	Ph. Eur.
Target fill weight per device	1.500 g		

Table 2. Composition per Container of BF Spiromax 160/4.5 μg 120 inhalation product

Material	Weight	Function	Quality Standard
Budesonide (micronised)	31.6 mg	Drug substance	Ph. Eur.
Formoterol fumarate dihydrate (micronised)	0.914 mg	Drug substance	Ph. Eur.
Lactose monohydrate	0.838 g	Excipient	Ph. Eur.
Target fill weight per device	0.870 g		

Table 3. Composition per Container of BF Spiromax 320/9 μg 60 inhalation product

Material	Weight	Function	Quality Standard
Budesonide (micronised)	28.7 mg	Drug substance	Ph. Eur.
Formoterol fumarate dihydrate (micronised)	0.870 mg	Drug substance	Ph. Eur.
Lactose monohydrate	0.840 g	Excipient	Ph. Eur.
Target fill weight per device	0.870 g		

Example 2

This is a two-arm parallel study investigating whether symptom-driven maintenance and reliever/rescue therapy with budesonide/formoterol is more effective as a single device dual treatment regimen that manages and also concomitantly reduces the number of exacerbations of COPD compared to a multiple device fixed maintenance dose of fluticasone/salmeterol and salbutamol as a rescue medication.

Patient group A (invention)

Participants are receiving Spiromax® budesonide/formoterol 160/4.5 μg, two inhalations, twice daily and additionally, Spiromax® budesonide/formoterol 160/4.5 μg as needed, with a maximum of eight additional inhalations per day for rescue use.

Patient group B (comparative)

Participants are receiving Diskus® fluticasone/salmeterol (steroid/long-acting β_2-agonist) 500/50 μg, one inhalation, twice daily and additionally, salbutamol (short-acting β_2-agonist) 100 μg as needed with a maximum of eight additional inhalations per day. The comparative study represents an example of the current standard treatment for COPD.

Patients are being subjected to constant evaluation throughout the investigation. Key parameters that are being assessed include; but are not limited to, reduction in the number of exacerbations (moderately severe and severe exacerbations combined), reductions in hospitalisation during exacerbations, improvement in patient compliance and convenience, general lung function (PEF, FEV1, FEV1/FVC, FEV25-75%, RV, TLC, RV/TLC, RV/TLC %, predicted).

Claims

1. A fixed-dose composition comprising formoterol or a pharmaceutically acceptable salt thereof and budesonide, for use in the long-term treatment of COPD and the treatment of acute exacerbations of COPD, wherein the composition is administered as a maintenance dose for the long-term treatment of COPD and pro re nata (p.r.n.) as a rescue medication for the treatment of acute exacerbations of COPD.

2. The composition as claimed in claim 1, wherein the composition is a dry powder formulation, further comprising a coarse carrier.

3. The composition as claimed in claim 2, wherein the carrier is lactose.

4. The composition as claimed in claim 1, wherein formoterol is present as formoterol fumarate.

5. The composition as claimed in any preceding claim, wherein the delivered dose of formoterol, based on the amount of formoterol, is 1-20 µg.

6. The composition as claimed in any preceding claim, wherein the delivered dose of budesonide is 5-500 µg.

7. The composition as claimed in claims 5 and 6, wherein the delivered doses of formoterol/budesonide in µg are 80/4.5, 160/4.5 or 320/9.

8. The composition as claimed in any preceding claims, wherein the composition is administered 2-4 times per day as a maintenance dose.

9. The composition as claimed in claim 7, wherein the composition is administered twice-per-day as a maintenance dose.

10. The composition as claimed in any preceding claim, wherein the composition is administered no more than ten times p.r.n as a rescue medication.

11. The composition as claimed in claim 9, wherein the composition is administered no more than eight times p.r.n as a rescue medication.

12. The composition as claimed in any preceding claim, wherein the composition is administered twice-per-day as a maintenance dose and no more than eight times p.r.n as a rescue medication.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/060257

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/167 A61K31/58 A61K9/00 A61P11/00 A61P11/08 A61P43/00
ADD.
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)
A61K

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 practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Astra Zeneca: "Symbicort Prescribing Information: Symbicort Turbohaler 200/6", , 18 February 2013 (2013-02-18), XP055193843, Retrieved from the Internet: URL:http://www.symbicort.com/content/dam/website-services/global/symbicort-com/SmPC 160. 4.5 v2.pdf [retrieved on 2015-06-05]	1-12
Y	the whole document	1-12

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2015	12/06/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Taylor, Mark

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/060257

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Astrazeneca: "Symbicort Prescribing Information: Symbicort Turbohaler 400/12", , 18 February 2013 (2013-02-18), XP055193849, Retrieved from the Internet: URL:http://www.symbicort.com/content/dam/website-services/global/symbicort-com/SmPC 320. 9 v2.pdf [retrieved on 2015-06-05]	1-12
Y	the whole document	1-12

X	P.M. CALVERLEY ET AL: "Maintenance therapy with budesonide and formoterol in chronicobstructive pulmonary disease", EUROPEAN RESPIRATORY JOURNAL, vol. 22, no. 6, 1 December 2003 (2003-12-01), pages 912-919, XP055193835, ISSN: 0903-1936, DOI: 10.1183/09031936.03.00027003 abstract	1-12

X	EP 2 682 102 A2 (SANOVEL ILAC SANAYI VE TICARET [TR] ARVEN ILAC SANAYI VE TICARET A S [) 8 January 2014 (2014-01-08)	1-6
Y	abstract paragraph [0035] - paragraph [0049] paragraphs [0052], [0055], [0065] examples B-44 to B-48 claims 1-27 paragraph [0031] paragraph [0122]	1-12

X	US 2005/042175 A1 (NILSSON THOMAS [SE] ET AL) 24 February 2005 (2005-02-24) abstract paragraphs [0001], [0004], [0015], [0016] paragraph [0018] - paragraph [0020] table 1	1,4-12

X	EP 1 086 697 A2 (ASTRAZENECA AB [SE]) 28 March 2001 (2001-03-28) abstract paragraphs [0009], [0016], [0017] paragraph [0020] - paragraph [0023] examples 1-3 claims 1-32	1-12

A	WO 93/11773 A1 (ASTRA AB) 24 June 1993 (1993-06-24) abstract examples 1-3 claims 1-7	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/060257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2682102 A2	08-01-2014	EP 2682102 A2	08-01-2014
		WO 2014007770 A2	09-01-2014
US 2005042175 A1	24-02-2005	NONE	
EP 1086697 A2	28-03-2001	EP 0613371 A1	07-09-1994
		EP 1086697 A2	28-03-2001
		EP 1101493 A2	23-05-2001
		LU 90941 I2	30-09-2002
		NL 300094 I1	02-09-2002
WO 9311773 A1	24-06-1993	AT 213946 T	15-03-2002
		AU 673660 B2	21-11-1996
		CA 2123909 A1	24-06-1993
		CA 2356145 A1	24-06-1993
		CZ 291455 B6	12-03-2003
		CZ 9401434 A3	15-12-1994
		DE 10299033 I1	23-01-2003
		DE 69232462 D1	11-04-2002
		DE 69232462 T2	10-10-2002
		DK 0613371 T3	13-05-2002
		ES 2172510 T3	01-10-2002
		HK 1010339 A1	02-08-2002
		HR P921445 A2	31-12-1994
		HU 227519 B1	28-07-2011
		IS 3959 A	19-06-1993
		JP 3342484 B2	11-11-2002
		JP H07502036 A	02-03-1995
		NO 942116 A	07-06-1994
		NZ 246050 A	21-12-1995
		PT 613371 E	31-07-2002
		SG 48301 A1	17-04-1998
		SI 9200403 A	30-06-1993
		SK 73394 A3	08-03-1995
		SK 285910 B6	04-10-2007
		US 5674860 A	07-10-1997
		US 5972919 A	26-10-1999
		WO 9311773 A1	24-06-1993
		YU 106192 A	08-01-1996