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(54) **Title**: TREATMENT OF LOSS OF SENSE OF TOUCH WITH SAXITOXIN DERIVATIVES

(57) **Abstract**: The invention concerns a sodium channel blocker for the treatment of a reduction or loss of superficial sensitivity or sense of touch of a human being or another mammal.

TREATMENT OF LOSS OF SENSE OF TOUCH WITH SAXITOXIN DERIVATIVES

The invention concerns a sodium channel blocker for the treatment of a human being or another mammal and a pharmaceutical composition comprising that sodium channel blocker as well as method of treatment.

A sodium channel blocker is a compound that specifically binds to a sodium channel in an axon of a neuron and specifically blocks the passage of sodium ions through that sodium channel.

From WO 2006/032459 A1 the use of a sodium channel blocker and/or one of its derivatives for the production of a medicament for the treatment of peripheral-nervously derived neuropathic pain is known.

From WO 2007/110221 A1 the use of a sodium channel blocker and/or its derivatives for the production of a medicament for the treatment of neuropathic pain developing as a consequence of chemotherapy is known.

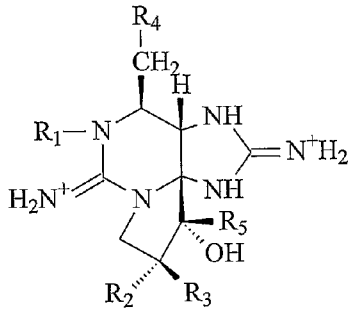
In many diseases such as diabetes mellitus or neuropathy the reduction or loss of superficial sensitivity or sense of touch is a problem. It may lead to painless severe infections and other painless wounds like burns or cuts of which the patients remain unaware.

The problem to be solved by the present invention is to provide a substance and a pharmaceutical composition as well as a method for the treatment of a reduction or loss of

superficial sensitivity or sense of touch of a human being or another mammal.

The problem is solved by the subject-matter of claims 1, 8 and 16. Embodiments of the invention are subject matter of claims 2 to 7, 9 to 15 and 17 to 19.

According to the invention a sodium channel blocker (SCB) for the treatment of a reduction or loss of superficial sensitivity or sense of touch of a human being or another mammal is provided. The SCB is saxitoxin or one of its derivatives, tetrodotoxin or one of its derivatives or a tricyclic 3,4-propinoperhydropurine represented by the following formula (I)



Formula I

wherein R_1 and R_5 are independently selected from the group consisting of -H and -OH; R_2 and R_3 are independently selected from the group consisting of -H, $-OSO_3^-$ and $-SO_3$; and R_4 is selected from the group consisting of -H, -OH, $-COONH_2$, $-COONHSO_3^-$ and $-COOCH_3$.

The sodium channel blocker may be administered over a period of between one to seven days and/or in multiple treatment cycles. By "superficial sensitivity" the ability of the human being or other mammal to register external stimuli like heat,

cold or pressure on its skin or mucosa is meant. By "sense of touch" any ability of the human being or other mammal to register a touch is meant. The sense of touch is a specific superficial sensitivity. A reduction or loss of superficial sensitivity is often felt as numbness. The reduction or loss of superficial sensitivity or sense of touch is a pathological condition that may be caused by a pathogen, by a medical treatment such as chemotherapy or ray treatment, under which it may occur as side effect, by the use of weapons, or by a nuclear accident.

The inventors of the present invention have recognized that a reduction or loss of superficial sensitivity or sense of touch can be treated with an SCB according to the invention such that the superficial sensitivity or the sense of touch is at least partly restored. For example, in diabetes mellitus there is a loss of superficial sensitivity in the extremities. This loss of superficial sensitivity can be treated with an SCB according to the invention such that sensitivity will be restored.

The effect of recovery of sensitivity is independent of the presence of pain such as a neuropathic pain. This means that the effect is not just owing to a possibly also occurring suppression of pain that without treatment drowns out every other feeling. The treatment of a reduction or loss of superficial sensitivity or sense of touch is different from the known treatment of neuropathic pain with SCBs.

The effect of the treatment is also totally different from the effect of a treatment of neuropathic pain with a local anesthetic such as lidocaine which is also an SCB. If pain caused by neuropathy is treated with lidocaine, pain and

sensitivity are lost in the area innervated by nerves affected by the treatment. During treatment with lidocaine the loss of sensitivity lasts as long as the pain relief. The superficial sensitivity and sense of touch restoring activity of the SCB according to the invention is a complete new effect. This effect is totally surprising because in higher dosages SCBs can totally block the propagation of action potentials along axons of neurons.

In an embodiment of the invention either one of R_2 and R_3 is $-OSO_3^-$ or R_4 is $-COONHSO_3^-$. The tricyclic 3,4-propinoperhydropurine may be one of the derivatives of saxitoxin or a gonyautoxin (hereinafter "GTX") according to formula I as set forth in the table below.

Compound	R_1	R_2	R_3	R_4	R_5
Gonyautoxin 1	-OH	-H	$-OSO_3^-$	$-COONH_2$	-OH
Gonyautoxin 2	-H	-H	$-OSO_3^-$	$-COONH_2$	-OH
Gonyautoxin 3	-H	$-OSO_3^-$	-H	$-COONH_2$	-OH
Gonyautoxin 4	-OH	$-OSO_3^-$	-H	$-COONH_2$	-OH
Gonyautoxin 5	-H	-H	-H	$-COONHSO_3^-$	-OH
Neosaxitoxin	-OH	-H	-H	$-COONH_2$	-OH
Descarbamoylsaxitoxin	-OH	-H	-H	-OH	-OH

In one embodiment the SCB according to the invention is in the form of its racemate, pure stereoisomer, especially enantiomer or diastereomer or in the form of a mixture of stereoisomers, especially enantiomers or diastereomers, in neutral form, in the form of an acid or base or in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate.

The reduction or loss of the superficial sensitivity or sense of touch may be a side effect of a drug or of a medical treatment or may be caused by diabetes mellitus, a viral infection, in particular a Herpes virus infection or a Varizella-Zoster virus infection, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, neuralgia, neuritis, neuropathy or other neurologic cause.

In one embodiment the SCB according to the invention is saxitoxin or one of its derivatives, wherein the saxitoxin or the derivative is synthetically synthesised or isolated from a biological source, in particular from cyanobacteria or from contaminated shellfish, especially shellfish contaminated with A. catenella.

The SCB according to the invention may also be tetrodotoxin or one of its derivatives or the tricyclic 3,4-propinoperhydropurine, wherein the tetrodotoxin, the derivative, or the tricyclic 3,4-propinoperhydropurine is synthetically synthesised or isolated from a biological source. In case of tetrodotoxin the biological source may be a puffer fish.

The invention further concerns a pharmaceutical composition comprising at least one sodium channel blocker according to the invention and a pharmacologically acceptable carrier. The carrier may be any material suitable for topical drug administration. Carriers include any such materials known in the art which is non-toxic in the amount used, and does not interact with other components of the composition in deleterious manner.

In an embodiment the SCB according to the invention is contained in the pharmaceutical composition in an amount suitable for an administration of 0.01 to 1000 µg, in particular 0.1 to 100 µg, especially 1 to 10 µg, SCB per day. The SCB according to the invention may be contained in the pharmaceutical composition in a concentration of 0.01 to 1000 µg per ml, in particular 0.1 to 100 µg per ml, especially 1 to 10 µg per ml.

The pharmaceutical composition according to the invention may be a pharmaceutical composition prepared for injection, in particular intramuscular, intravenous, intradermal, or subcutaneous injection, prepared for topical administration, in particular superficial administration, or prepared for systemic administration, in particular oral administration.

The pharmaceutical composition prepared for superficial administration can be a skin-patch, a cream, an ointment, or a spray. The administration may be supported physically in particular by UV light, ultra sound, iontophoresis, phonophoresis, or mechanical modulation.

According to an embodiment of the invention the pharmaceutical composition further comprises at least one analgesic compound. The analgesic compound can be lidocaine or one of its derivatives, bupivacaine or one of its derivatives, fentanyl or one of its derivatives, or acetaminophen or one of its derivatives.

The SCB in the pharmaceutical composition according to the invention may be contained in a liposome or a microemulsion. A microemulsion is a stable, isotropic liquid mixture of oil, water and surfactant, frequently in combination with a

cosurfactant. The mixture is an emulsion with oil dispersed in water or water dispersed in oil the dispersed phase of which is forming such small domains that visible light is not scattered by the dispersed phase. Therefore, the microemulsion is clear.

Alternatively or in addition the pharmaceutical composition comprising the SCB may further comprise at least one substance facilitating the transport of the SCB through the skin. Such substances are known in the art as permeation enhancers. The substance may be a substance selected from the group consisting of: alcohols, amines, amides, amino acids, amino acid esters, 1-substituted azacycloheptan-2-ones, pyrrolidones, terpenes, fatty acids, fatty acid esters, macrocyclic compounds, tensides, sulfoxides, liposomes, transferomes, lecithin vesicles, ethosomes, anionic, cationic and non-ionic surfactants, polyols, essential oils, dimethylsulfoxide, decylmethylsulfoxide, diethylene glycol monoethyl ether, diethylene glycol monomethyl ether, sodium laurate, sodium lauryl sulfate, cetyltrimethylammonium bromide, benzalkonium chloride, a poloxamer, polysorbate 20 (Tween 20 = polyoxyethylene sorbitan monolaurate), polysorbate 40 (Tween 40 = polyoxyethylene sorbitan monopalmitate), polysorbate 60 (Tween 60 = polyoxyethylene sorbitan monostearate), polysorbate 80 (Tween 80 = polyoxyethylene sorbitan monooleate), lecithin, 1-n-dodecylcyclazacycloheptan-2-one, ethanol, propanol, octanol, benzyl alcohol, lauric acid, oleic acid, valeric acid, isopropyl myristate, isopropyl palmitate, methylpropionate, ethyl oleate, sorbitan sesquioleate, propylene glycol, ethylene glycol, glycerol, butanediol, polyethylene glycol, polyethylene glycol monolaurate, urea, dimethylacetamide, dimethylformamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone,

ethanol amine, diethanol amine, triethanolamine, alkanones, salicylic acid, salicylates, citric acid and succinic acid.

The poloxamer (polyethylene-polypropylene glycol, molecular formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$, wherein a and b are integers) is a synthetic nonionic triblock block copolymer composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). It is available in several types such as Poloxamer 231, Poloxamer 182, or Poloxamer 184.

The invention further concerns a method of treatment of a reduction or loss of superficial sensitivity or sense of touch of a human being or another mammal, wherein the SCB or the pharmaceutical composition according to the invention is administered to the human being or other mammal.

EXAMPLE

The following cream composition was used for all therapeutic applications described below:

Ingredient	**Concentration**
Aqua	70,400
Persea Gratissima Oil	6,000
Propylene Glycol	5,000
Squalane	3,500
Active Ingredient	xx
Petrolatum	3,500
Dimethicone	3,000
PEG-20 Methyl Glucose Sesquistearate	2,500

Cetyl Acetate and Acetylated Lanolin Alcohol	2,000 (total concentration of the mentioned ingredients)
Diazolinidyl Urea and Methylparaben and Propylparaben and Propylene Glycol	1,500 (total concentration of the mentioned ingredients)
Glyceryl Stearate	1,000
Methyl Glucose Sesquistearate	0,500
Triethanolamine	0,300
Ozokerite	0,300
Carbomer	0,050
Acrylate(s)	0,200
Parfum	0,150
Tocopherol and Ascorbyl Palmitate and Lecithin and Glyceryl Stearate and Glyceryl Oleate and Citric Acid	0,100

The concentrations in the above table are given in grams of a total of 100 g. The acrylate(s) may be C 10-30 alkyl acrylate crosspolymer(s)

1. Active Ingredient: 10 µg/ml of a mixture of the epimers GTX-2 and GTX-3

Three patients (2 female, 1 male) used a pharmaceutical composition according to the invention containing 10 µg/ml of a mixture of the epimers GTX-2 and GTX-3. The mixture of GTX-2 and GTX-3 was contained in liposomes in the above-specified cream composition. All three patients were AIDS patients with drug-related neuropathy. All patients were receiving a drug

combination including a nucleoside reverse-transcriptase inhibitor, didanosine. It is well-known that patients on didanosine may develop toxic peripheral neuropathy, usually characterised by bilateral symmetrical distal numbness, tingling, and pain in feet and, less frequently, hands.

All three patients presented numbness and loss of superficial sensitivity in addition to an intense neuropathic pain in their inferior limbs (ankles and feet). They described the pain as the worst pain ever experienced preventing them to have a normal sleep and complained that they could not feel hot and/or cold in their feet.

The first patient (female, age: 45) presented numbness and loss of sensitivity in both her feet. She had been treated with an antidepressant drug associated with analgesics. She reported that the pain was poorly controlled with the drugs she received. She began to use the pharmaceutical composition in the numb area using it once a day then up to three times a day. She reported feeling better (i.e. a decrease in her symptoms) after using the pharmaceutical composition three times daily for three days. After one week of application she reported a complete relief of the initials symptoms.

The second patient (male, age: 51) presented numbness, loss of sensitivity and neuropathic pain in both feet and his right calf. He has been treated with antidepressant drug, analgesics and vitamins for his condition. He reported no relief of the symptoms with this treatment. He used the pharmaceutical composition in topical application on the affected areas four times a day. After four days of application he felt a decrease in the symptoms, reporting a

complete relief nine days after he began to use the composition.

The third patient (female, age: 47) presented loss of sensitivity and neuropathic pain in both feet and calfs. She had been treated with anticonvulsant drug, analgesics, vitamins and acupuncture. The symptoms were so intense that she attempted to stop her AIDS medication. She used the pharmaceutical composition on her painful and numb areas three times daily. After two days of treatment she reported less pain and numbness in the affected areas and relief of symptoms ten days after she began. In the meanwhile she resumed her AIDS medications. She attempted to stop the application of the pharmaceutical composition and reported that the pain and numbness came back within a few days. Resuming the application of the pharmaceutical composition resulted in pain relief and superficial sensitivity recovery within one week.

All three patients had been treated for their conditions with different drugs or drug associations including analgesics, antidepressant or anticonvulsant drugs, vitamins, or physical treatment (acupuncture) with no or few positive results.

They applied the pharmaceutical composition on the numb areas one to four times per day. They reported a decrease of the symptoms after about two to four days of use and a complete relief within seven to nine days.

A further patient (female, age: 56) used the same cream composition as specified above containing 10 µg/ml of a mixture of the epimers GTX-2 and GTX-3 contained in liposomes.

This patient's history is remarkable by the existence of a grade IIb/III cervicouterine cancer in the past years, treated with chemotherapy and radiotherapy. The patient first presented with local pain on the internal side of the right arm. This pain was described as severe and unbearable, and she reported she almost could not wear clothes. This was followed by a typical zoster distributed skin eruption of an entire dermatoma (posterior and anterior T6). The eruption resolved in about two weeks. The pain lasted about six weeks from the beginning of the clinical presentation. This patient could not be treated with antidepressant or anticonvulsivant agents since she was already treated with bupropion for a post-traumatic depression. She was given NSAID (ketoprofen 200 mg twice daily), and acetaminophen (1000 mg three times daily). No opiod-like drug (tramadol) could be used due to a patient history of intolerance to this drug. She intended to use a topical preparation of lidocaine 5% with no or poor relief of the pain.

She began to use the GTX-2 and GTX-3 containing cream composition topically about one week after the onset of the symptoms. Relief of the pain and recovery of a normal superficial sensitivity was noted between 15 and 30 min after the application, lasting for about 4 to 6 hours. She continued to use the topical GTX preparation three to four times a day with the same results. In absence of application the patient noted a recurrence of the pain.

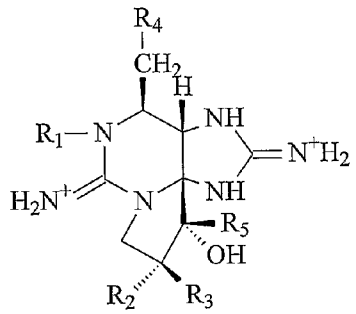
2. Active Ingredient: 10 µg/ml Neosaxitoxin

A further patient (male, age: 70) used the same cream composition as specified above containing 10 µg/ml neosaxitoxin contained in liposomes.

This patient has COPD (Chronic Obstructive Pulmonary Disease) of several years of evolution. Its current treatment includes prednisone (corticoid) 5 mg per day, plus inhalers. The patient presented a typical ophthalmic herpes zoster on the right side. The pain was severe and unbearable. He was given NSAID and acetaminophen because no opiods and opiods-like drugs could be used due to his respiratory condition. He began to apply the neosaxitoxin containing cream composition topically three days after the onset of the symptoms. He used it three to four times a day obtaining a relief of the pain and a recovery of the superficial sensitivity within half an hour after the application. He used the preparation during two weeks.

Claims

1. Sodium channel blocker (SCB) for the treatment of a reduction or loss of superficial sensitivity or sense of touch of a human being or another mammal, wherein the SCB is saxitoxin or one of its derivatives, tetrodotoxin or one of its derivatives or a tricyclic 3,4-propinoperhydropurine represented by the following formula (I),



Formula I

wherein R_1 and R_5 are independently selected from the group consisting of -H and -OH; R_2 and R_3 are independently selected from the group consisting of -H, $-OSO_3^-$ and $-SO_3$; and R_4 is selected from the group consisting of -H, -OH, $-COONH_2$, $-COONHSO_3^-$ and $-COOCH_3$.

2. The SCB according to claim 1, wherein either one of R_2 and R_3 is $-OSO_3^-$ or R_4 is $-COONHSO_3^-$.

3. The SCB according to claim 1 or 2, wherein the tricyclic 3,4-propinoperhydropurine is neosaxitoxin, descarbamoylsaxitoxin, or a gonyautoxin (GTX), in particular GTX-1, GTX-2, GTX-3, GTX-4, or GTX-5.

4. The SCB according to any of the preceding claims, wherein the SCB is in the form of its racemate, pure stereoisomer, especially enantiomer or diastereomer or in the form of a mixture of stereoisomers, especially enantiomers or diastereomers, in neutral form, in the form of an acid or base or in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate.

5. The SCB according to any of the preceding claims, wherein the reduction or loss of the superficial sensitivity or sense of touch is a side effect of a drug or of a medical treatment or is caused by diabetes mellitus, a viral infection, in particular a Herpes virus infection or a Varizella-Zoster virus infection, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, neuralgia, neuritis, neuropathy or other neurologic cause.

6. The SCB according to any of the preceding claims, wherein the SCB is saxitoxin or one of its derivatives, wherein the saxitoxin or the derivative is synthetically synthesised or isolated from a biological source, in particular from cyanobacteria or from contaminated shellfish, especially shellfish contaminated with A. catenella.

7. The SCB according to any of the preceding claims, wherein the SCB is tetrodotoxin or one of its derivatives or the tricyclic 3,4-propinoperhydropurine, wherein the tetrodotoxin, the derivative, or the tricyclic 3,4-propinoperhydropurine is synthetically synthesised or isolated from a biological source.

8. Pharmaceutical composition comprising at least one SCB according to any of the preceding claims and a pharmacologically acceptable carrier.

9. The pharmaceutical composition according to claim 8, wherein the SCB is contained in an amount suitable for an administration of 0.01 to 1000 µg, in particular 0.1 to 100 µg, especially 1 to 10 µg, SCB per day.

10. The pharmaceutical composition according to claim 8 or 9, wherein the SCB is contained in a concentration of 0.01 to 1000 µg per ml, in particular 0.1 to 100 µg per ml, especially 1 to 10 µg per ml.

11. The pharmaceutical composition according to any of claims 8 to 10, wherein the pharmaceutical composition is prepared for injection, in particular intramuscular, intravenous, intradermal, or subcutaneous injection, prepared for topical administration, in particular superficial administration, or prepared for systemic administration, in particular oral administration.

12. The pharmaceutical composition according to claim 11, wherein the pharmaceutical composition prepared for superficial administration is a skin-patch, a cream, an ointment, or a spray.

13. The pharmaceutical composition according to any of claims 8 to 12, wherein the pharmaceutical composition further comprises at least one analgesic compound.

14. The pharmaceutical composition according to claim 13, wherein the analgesic compound is lidocaine or one of its

derivatives, bupivacaine or one of its derivatives, fentanyl or one of its derivatives, or acetaminophen or one of its derivatives.

15. The pharmaceutical composition according to any of claims 8 to 14, wherein the SCB is contained in a liposome or a microemulsion and/or wherein the pharmaceutical composition further comprises at least one substance facilitating the transport of the SCB through the skin, in particular a substance selected from the group consisting of: alcohols, amines, amides, amino acids, amino acid esters, 1-substituted azacycloheptan-2-ones, pyrrolidones, terpenes, fatty acids, fatty acid esters, macrocyclic compounds, tensides, sulfoxides, liposomes, transferomes, lecithin vesicles, ethosomes, anionic, cationic and non-ionic surfactants, polyols, essential oils, dimethylsulfoxide, decylmethylsulfoxide, diethylene glycol monoethyl ether, diethylene glycol monomethyl ether, sodium laurate, sodium lauryl sulfate, cetyltrimethylammonium bromide, benzalkonium chloride, a poloxamer, polysorbate 20 (polyoxyethylene sorbitan monolaurate), polysorbate 40 (polyoxyethylene sorbitan monopalmitate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 80 (polyoxyethylene sorbitan monooleate), lecithin, 1-n-dodecylcycla-zacycloheptan-2-one, ethanol, propanol, octanol, benzyl alcohol, lauric acid, oleic acid, valeric acid, isopropyl myristate, isopropyl palmitate, methylpropionate, ethyl oleate, sorbitan sesquioleate, propylene glycol, ethylene glycol, glycerol, butanediol, polyethylene glycol, poly-ethylene glycol monolaurate, urea, dimethylacetamide, dimethylformamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, ethanol amine, diethanol amine, triethanolamine, alkanones, salicylic acid, salicylates, citric acid and succinic acid.

16. Method of treatment of a reduction or loss of superficial sensitivity or sense of touch of a human being or another mammal, wherein the SCB according to any of claims 1 to 7 or the pharmaceutical composition according to any of claims 8 to 15 is administered to the human being or other mammal.

17. The method according to claim 16, wherein the SCB or the pharmaceutical composition is administered by way of injection, in particular intramuscular, intravenous, intradermal, or subcutaneous injection, by way of topical administration, in particular superficial administration, or by way of systemic administration, in particular oral administration.

18. The method according to claim 16 or 17, wherein administration is supported physically, in particular by UV light, ultra sound, iontophoresis, phonophoresis, or mechanical modulation.

19. The method according to any of claims 16 to 18, wherein the SCB or the pharmaceutical composition is administered over a period of between one to seven days and/or in multiple treatment cycles.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/051992

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/519 A61P25/00
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 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)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/110417 A1 (PHYTOTOX LTD; WILSON NESTOR ANTONIO LAGOS [CL]; MICRO ALGAE CORP [US]) 24 November 2005 (2005-11-24) page 10, line 12 - line 21 claims 1-51	8-15
X	WO 2006/032481 A1 (ESTEVE LABOR DR [ES]; BUSCHMANN HELMUT [DE]; HAYKONG FRANK [CA]; NOELF) 30 March 2006 (2006-03-30) claims 1-17	8-12
X	US 2003/100574 A1 (WILSON NESTOR ANTONIO LAGOS [CL]) 29 May 2003 (2003-05-29) examples 1-8 claims 1-54	8-12

☐ Further documents are listed in the continuation of Box C.

☒ 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 document 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

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2011	20/04/2011

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	Albayrak, Timur

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005110417 A1	24-11-2005	AU 2005244105 A1	24-11-2005
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