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(54) **Botulinum neurotoxint, nem-ionos felületaktív anyagot, nátrium-kloridot és szacharózt tartalmazó gyógyászati készítmények**

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(54) **PHARMACEUTICAL COMPOSITIONS COMPRISING BOTULINUM NEUROTOXIN, A NON IONIC SURFACTANT, SODIUM CHLORIDE AND SUCROSE**

PHARMAZEUTISCHE ZUSAMMENSETZUNG, ENTHALTEND BOTULINUM NEUROTOXIN, EIN NICHTIONISCHES TENSID, NATRIUMCHLORID UND SACCHAROSE

COMPOSITION PHARMACEUTIQUE CONTENANT DE LA NEUROTOXINE BOTULIQUE

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Description

[0001] The invention relates to a pharmaceutical composition containing botulinum neurotoxin.

[0002] The presently most used botulinum neurotoxin is botulinum neurotoxin type A. This neurotoxin is produced during fermentation in the presence of Clostridium botulinum strains. Botulinum neurotoxin type A complexes (which include botulinum neurotoxin type A and at least another non-toxic protein) are active principles widely used in modern medicine. An example of a pharmaceutical composition based on such a complex is the product Dysport® currently sold by the company of the Applicants. Among the most common medical indications for which a botulinum neurotoxin type A complex could be used, one could mention the treatment of a number of muscle disorders (e.g. blepharospasm, hemifacial spasm, torticollis, spasticity, tension headache, back pain or wrinkles), as well as other disorders such as migraine. Alternatively, high purity botulinum toxin (i.e. botulinum neurotoxin free from its complexing non-toxic proteins) may replace the corresponding botulinum toxin complex as disclosed in PCT applications WO 96/11699 or WO 97/35604.

[0003] Currently, the marketed botulinum neurotoxin compositions contain human serum albumin. However, some concerns have been expressed about albumin (see e.g. in PCT application WO 01/58472). For this reason, the pharmaceutical industry is now considering to find alternative stabilising agents to albumin by other stabilising agents in pharmaceutical compositions.

[0004] A possible solution is disclosed in PCT patent application WO 01/58472. In this document, albumin is replaced by a polysaccharide, i.e. a polymer of more than two saccharide molecule monomers, which plays the role of the stabiliser in the botulinum neurotoxin composition.

[0005] An alternative solution is the one described in PCT patent application WO 97/35604 or US patents Nos. 5,512,547 and 5,756,468. In these documents, it is disclosed that pure botulinum neurotoxin (i.e. botulinum neurotoxin free from its complexing non-toxic proteins) can be stabilised by trehalose.

[0006] The Applicant has unexpectedly discovered that a surfactant possesses sufficient stabilising effects to replace albumin, the polysaccharide of PCT patent application WO 01/58472 or the trehalose of PCT patent application WO 97/35604 in botulinum neurotoxin compositions.

[0007] The invention therefore pertains to the use of a surfactant for stabilising a solid or liquid pharmaceutical composition that contains as active principle a botulinum toxin and that does not comprise albumin.

[0008] By botulinum toxin should be understood a naturally occurring botulinum toxin or any recombinantly produced botulinum toxin.

[0009] By naturally occurring botulinum toxin should be understood either a high purity botulinum neurotoxin derived from Clostridium spp or a botulinum neurotoxin complex derived from Clostridium, spp.

[0010] By high purity botulinum neurotoxin (type A, B, C, D, E, F or G) is meant, in the present application, botulinum neurotoxin (type A, B, C, D, E, F or G) outside from complexes including at least another protein. In other words, a high purity botulinum neurotoxin (type A, B, C, D, E, F or G) does not contain significant quantities of any other Clostridium spp derived protein than botulinum neurotoxin (type A, B, C, D, E, F or G).

[0011] Preferably, according to the present invention, botulinum neurotoxin complexes and high purity botulinum neurotoxins will be selected from the group consisting of botulinum neurotoxin complex and high purity botulinum neurotoxin of type A, botulinum neurotoxin complex and high purity botulinum neurotoxin of type B and botulinum neurotoxin complex and high purity botulinum neurotoxin of type F. More preferably, botulinum neurotoxin complexes and high purity botulinum neurotoxins will be selected from the group consisting of botulinum neurotoxin complex and high purity botulinum neurotoxin of type A and botulinum neurotoxin complex and high purity botulinum neurotoxin of type F. More particularly, botulinum neurotoxin complexes and high purity botulinum neurotoxins will be botulinum neurotoxin complexes and high purity botulinum neurotoxins of type A.

[0012] By type A botulinum neurotoxin should be understood any botulinum toxin of type A, and notably botulinum neurotoxins of type A1, A2 or A3. The same applies mutatis mutandis to the other serotypes of toxins.

[0013] The high purity botulinum neurotoxin (type A, B, C, D, E, F or G) used according to the invention or contained in the above described pharmaceutical compositions can easily be obtained from the corresponding botulinum neurotoxin complex, for example as explained in Current Topics in Microbiology and Immunology (1995), 195, p. 151-154. High purity Clostridium botulinum toxin (type A, B, C, D, E, F or G) is obtained, for example, by purification of an adequate fermentation medium (for example, an enriched meat media broth containing Clostridium Botulinum and left for fermentation - this broth may be, for example, the one described in Current Topics in Microbiology and Immunology (1995), 195, p. 150 and DasGupta, "Microbial food toxicants. Clostridium botulinum toxins. CRC handbook of foodborne diseases of biological origin", CRC Boca Raton, p. 25-56) . When including high purity botulinum neurotoxin in a composition according to the instant invention, the purity degree of the toxin should preferably be higher than 80%, more preferably higher than 90 or 95% and in a more particularly preferred manner higher than 98% or 99%. It can be assessed, for example, by using the purity assay described in the present application.

[0014] The instant invention also relates to a solid or liquid pharmaceutical composition comprising:

a) a botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
b) a surfactant as a stabilizing agent,
c) sodium chloride, and
d) a buffer to maintain pH between 5.5 to 7.5

wherein said solid or liquid pharmaceutical composition does not comprise albumin.

[0015] According to a particular variant of the invention, the pharmaceutical composition will be a solid pharmaceutical composition and will essentially consist of:

a) a botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
b) a surfactant as a stabilizing agent,
c) sodium chloride, and
d) a buffer to maintain pH between 5.5 to 7.5.

[0016] According to another particular variant of the invention, the pharmaceutical composition will be a liquid pharmaceutical composition and will essentially consist of

a) a botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
b) a surfactant as a stabilizing agent,
c) sodium chloride,
d) a buffer to maintain pH between 5.5 to 7.5, and
c) water.

[0017] In the abovementioned pharmaceutical compositions, the surfactant will be such that it stabilises the botulinum toxin.

[0018] Preferably, the surfactant will be a non-ionic surfactant. Non- ionic surfactants include notably polysorbates and block copolymers like poloxamers (i.e. copolymers of polyethylene and propylene glycol). According to a preferred variant of the invention, the surfactant will be a polysorbate. More preferably, a polysorbate included in a composition according to the instant invention will have a mean polymerisation degree of from 20 to 100 monomer units (preferably about 80) , and may for example be polysorbate 80. Preferably also, the polysorbate should be vegetable-derived.

[0019] According to the invention, the solid or liquid pharmaceutical composition will also contain a crystalline agent which is sodium chloride.

[0020] By crystalline agent is meant an agent which, inter alia, would maintain a mechanically strong cake structure to lyophilised botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) . When included in solid formulations, crystalline agents also have a bulking effect. Crystalline agents notably include sodium chloride. Contrarily to what was taught in the prior art (see e.g. Goodnough, M.C. and Johnson, E.A., Applied and Environmental Microbiology (1992), 58(10), 3426-3428), the use of sodium chloride for this type of compositions further improves the stability of the botulinum toxin composition.

[0021] According to the invention, the solid or liquid pharmaceutical composition will also contain a buffer to maintain pH from 5.5 to 7.5.

[0022] The buffer can be any buffer able to maintain the adequate pH. Preferably, the buffer for compositions according to the invention will be chosen from the group consisting of succinate 5 and an amino acid like histidine. In particular, the buffer will be histidine. Preferably, the pH will be at least equal to 5.5 or 5.8, and most preferably at least equal to 6.0 or 6.5. Preferably also, the pH will be equal to or less than 7.5 or 7.0, more preferably equal to or less than 6.8.

[0023] Preferably, the solid or liquid pharmaceutical composition of the invention may also contain a disaccharide.

[0024] The disaccharide used in compositions according to the invention will preferably be chosen from the group consisting of sucrose, trehalose, mannitol and lactose. The disaccharide used in compositions according to the invention will more preferably be chosen from the group consisting of sucrose and trehalose. In particular, the disaccharide used in compositions according to the invention will be sucrose. Preferably, the disaccharide will be present in the pharmaceutical compositions of the instant invention, particularly when the compositions are in a solid form.

[0025] Preferably, a disaccharide will also be included in the pharmaceutical compositions according to the present invention, especially when they are in a solid form.

[0026] According to the invention, a solid pharmaceutical composition can be obtained by lyophilising a sterile water solution containing the components (a) to (d) as mentioned previously. A liquid pharmaceutical composition according to the invention will be obtained by mixing a solid (e.g. lyophilized) mixture of said components (a) to (d) with sterile water.

[0027] According to the invention, the concentrations of said components (a) to (d) in the solution to be lyophilised or the liquid pharmaceutical composition will preferably be as follows:

- the solution will contain from 50 to 10,000 LD50 units of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) per ml of solution, preferably [the solution will contain] from 50 to 3,000 LD50 units of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) per ml of solution, more preferably from 100 to 2,500 LD50 units of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) per ml of solution and most preferably from 100 to 2,000 LD50 units of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) per ml of solution;

- the concentration of surfactant will be from above critical micellar concentration to a concentration of 1% v/v, and notably from about 0.005% to 0.02% v/v in the case of polysorbate 80;

- the concentration of crystalline agent will be from 0.1 to 0.5 M, more preferably from 0.1 to 0.4 M, notably about 0.15 to 0.3 M; and

- the concentration of buffer will be from 1 to 50 mM, more preferably from 5 to 20 mM, notably about 10 mM.

[0028] As mentioned earlier, the solid or liquid pharmaceutical formulation according to the invention may contain a disaccharide. In that case, the concentration of disaccharide in the solution to be lyophilised / the liquid pharmaceutical composition will be for example from 5 to 50 mM, preferably from 5 to 25 mM, more preferably from 10 to 20 mM, and notably about 11.7 mM.

[0029] According to a preferred execution mode of the invention, the mixture of the different components of the pharmaceutical composition (i.e. botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G), the surfactant, the crystalline agent, the buffer, and the optional excipients such as the disaccharide) is lyophilised. The solid compositions thus obtained, which are also part of this invention, should preferably be stable for at least 12 months, more preferably for at least 18 months and in a more particularly preferred manner for at least 24 or even 36 months.

[0030] A composition according to the invention is considered stable during a certain period of time if at least 70% of the initial toxicity, as evaluated by assessing the LD50 in mice or by any method validated with respect to the LD50 mouse assay (i.e. a method allowing a conversion of its results into LD50 units), is maintained over said period of time (cf. the part entitled "mouse toxicity assay" concerning the LD50 mouse assay).

[0031] Pharmaceutical compositions according to the invention can be used for preparing medicaments intended to treat a disease / a condition / a syndrome chosen from the following:

- ophtalmological disorders selected from the group consisting of blepharospasm, strabismus (including restrictive or myogenic strabismus), amblyopia, oscillopsia, protective ptosis, therapeutic ptosis for corneal protection, nystagmus, estropia, diplopia, entropion, eyelid retraction, orbital myopathy, heterophoria, concomitant misalignment, nonconcomitant misalignment, primary or secondary esotropia or exotropia, internuclear ophthalmoplegia, skew deviation, Duane' s syndrome and upper eyelid retraction;

- movement disorders including hemifacial spasm, torticollis, spasticity of the child or of the adult (e.g. in cerebral palsy, post-stroke, multiple sclerosis, traumatic brain injury or spinal cord injury patients), idiopathic focal dystonias, muscle stiffness, Writer's cramp, hand dystonia, VI nerve palsy, oromandibular dystonia, head tremor, tardive dyskinesia, tardive dystonia, occupational cramps (including musicians' cramp), facial nerve palsy, jaw closing spasm, facial spasm, synkinesia, tremor, primary writing tremor, myoclonus, stiff-person-syndrome, foot dystonia, facial paralysis, painful-arm-and-moving-fingers-syndrome, tic disorders, dystonic tics, Tourette' s syndrome, neuromyotonia, trembling chin, lateral rectus palsy, dystonic foot inversion, jaw dystonia, Rabbit syndrome, cerebellar tremor, III nerve palsy, palatal myoclonus, akasthesia, muscle cramps, IV nerve palsy, freezing-of- gait, extensor truncal dystonia, post-facial nerve palsy synkinesis, secondary dystonia, Parkinson's disease, Huntington' s chorea, epilepsy, off period dystonia, cephalic tetanus, myokymia and benign cramp-fasciculation syndrome;

- otorhinolaryngological -disorders including spasmodic dysphonia, hypersalivation, sialorrhoea, otic disorders, hearing impairment, ear click, tinnitus, vertigo, Meniere's disease, cochlear nerve dysfunction, stuttering, cricopharyngeal dysphagia, bruxism, closure of larynx in chronic aspiration, vocal fold granuloma, ventricular dystonia, ventricular dysphonia, mutational dysphonia, trismus, snoring, voice tremor, aspiration, tongue protrusion dystonia, palatal tremor, deep bite of - lip and laryngeal dystonia;

- gastrointestinal disorders including achalasia, anal fissure, constipation, temperomandibular joint dysfunction, sphincter of Oddi dysfunction, sustained sphincter of Oddi hypertension, intestinal muscle disorders, puborectalis syndrome, anismus, pyloric spasm, gall bladder dysfunction, gastrointestinal or oesophageal motility dysfunction, diffuse oesophageal spasm and gastroparesis;

- urogenital disorders including detrusor sphincter dyssynergia, detrusor hyperreflexia, neurogenic bladder dysfunction (e.g. in Parkinson's disease, spinal cord injury, stroke or multiple sclerosis patients), bladder spasms, urinary incontinence, urinary retention, hypertrophied bladder neck, voiding dysfunction, interstitial cystitis, vaginismus, endometriosis, pelvic pain, prostate gland enlargement (Benign Prostatic Hyperplasia), prostatodynia, prostate cancer and priapism;

- dermatological disorders including hyperhidrosis (including axillary hyperhidrosis, palmar hyperhidrosis and Frey' s syndrome), bromhidrosis, cutaneous cell proliferative disorders (including psoriasis), skin wounds and acne;

- pain disorders including back pain (upper back pain,. lower back pain), myofascial pain, tension headache, fibromyalgia, painful syndromes, myalgia, migraine, whiplash, joint pain, post-operative pain, pain not associated with a muscle spasm and pain associated with smooth muscle disorders;

- inflammatory disorders including pancreatitis, neurogenic inflammatory disorders (including gout, tendonitis, bursitis, dermatomyositis and ankylosing spondylitis);

- secretory disorders such as excessive gland secretions, mucus hypersecretion and hyperlacrimation, holocrine gland dysfunction;

- respiratory disorders including rhinitis (including allergic rhinitis), COPD, asthma and tuberculosis;

- hypertrophic disorders including muscle enlargement, masseteric hypertrophy, acromegaly and neurogenic tibialis anterior hypertrophy with myalgia;

- articular disorders including tennis elbow (or epicondilytis of the elbow), inflammation of joints, coxarthrosis, hip osteoarthritis, rotator muscle cap pathology of the shoulder, rheumatoid arthritis and carpal tunnel syndrome;

- endocrine disorders like type 2 diabetes, hyperglucagonism, hyperinsulinism, hypoinsulinism, hypercalcemia, hypocalcemia, thyroid disorders (including Grave's disease, thyroiditis, Hashimoto's thyroiditis, hyperthyroidism and hypothyroidism), parathyroid disorders (including hyperparathyroidism and hypoparathyroidism), Gushing's syndrome and obesity;

- autoimmune diseases like systemic lupus erythemotosus;

- proliferative diseases including paraganglioma tumors, prostate cancer and bone tumors;

- traumatic injuries including sports injuries, muscle injuries, tendon wounds and bone fractures; and

- veterinary uses (e.g. immobilisation of mammals, equine colic, animal achalasia or animal muscle spasms).

[0032] Pharmaceutical compositions according to the invention can also be used for cosmetic treatments including cosmetic treatments of the following cosmetic disorders :

- skin defects;

- facial asymmetry;

- wrinkles including glabellar frown lines and facial wrinkles;

- downturned mouth;

- hair loss; and

- body odours.

[0033] Preferably, pharmaceutical compositions according to the invention will be used for preparing medicaments intended to treat a disease / a condition / a syndrome chosen from the following:

- ophtalmological disorders selected from the group consisting of blepharospasm, strabismus (including restrictive or myogenic strabismus), amblyopia, protective ptosis, therapeutic ptosis for corneal protection and upper eyelid retraction;

- movement disorders selected from the group consisting of hemifacial spasm, torticollis, cerebral palsy spasticity of the child, spasticity of the adult in post-stroke, multiple sclerosis, traumatic brain injury or spinal cord injury patients, idiopathic focal dystonias, muscle stiffness, Writer's cramp, hand dystonia, VI nerve palsy, oromandibular dystonia, head tremor, tardive dyskinesia, tardive dystonia, occupational cramps (including musicians' cramp) , facial nerve palsy, jaw closing spasm, facial spasm, synkinesia, tremor, primary writing tremor, myoclonus, stiff-person-syndrome, foot dystonia, facial paralysis, painful-arm-and-moving-fingers-syndrome, tic disorders, dystonic tics, Tourette's syndrome, neuromyotonia, trembling chin, lateral rectus palsy, dystonic foot inversion, jaw dystonia, Rabbit syndrome, cerebellar tremor, III nerve palsy, palatal myoclonus, akasthesia, muscle cramps, IV nerve palsy, freezing-of- gait, extensor truncal dystonia, post-facial nerve palsy synkinesis, secondary dystonia, off period dystonia, cephalic tetanus, myokymia and benign cramp-fasciculation syndrome;

- otorhinolaryngological disorders selected from the group consisting of spasmodic dysphonia, hypersalivation, sialorrhoea, ear click, tinnitus, vertigo, Meniere's disease, cochlear nerve dysfunction, stuttering, cricopharyngeal dysphagia, bruxism, closure of larynx in chronic aspiration, vocal fold granuloma, ventricular dystonia, ventricular dysphonia, mutational dysphonia, trismus, snoring, voice tremor, aspiration, tongue protrusion dystonia, palatal tremor and laryngeal dystonia;

- gastrointestinal disorders selected from the group consisting of achalasia, anal fissure, constipation, temperomandibular joint dysfunction, sphincter of Oddi dysfunction, sustained sphincter of Oddi hypertension, intestinal muscle disorders, puborectalis syndrome, anismus, pyloric spasm, gall bladder dysfunction, gastrointestinal or oesophageal motility dysfunction, diffuse oesophageal spasm, oesophageal diverticulosis and gastroparesis;

- urogenital disorders selected from the group consisting of detrusor sphincter dyssynergia, detrusor hyperreflexia, neurogenic bladder dysfunction in Parkinson's disease, spinal cord injury, stroke or multiple sclerosis patients, bladder spasms, urinary incontinence, urinary retention, hypertrophied bladder neck, voiding dysfunction, interstitial cystitis, vaginismus, endometriosis, pelvic pain, prostate gland enlargement (Benign Prostatic Hyperplasia), prostatodynia, prostate cancer and priapism;

- dermatological disorders selected from the group consisting of axillary hyperhidrosis, palmar hyperhidrosis, Frey' s syndrome, bromhidrosis, psoriasis, skin wounds and acne;

- pain disorders selected from the group consisting of upper back pain, lower back pain, myofascial pain, tension headache, fibromyalgia, myalgia, migraine, whiplash, joint pain, post-operative pain and pain associated with smooth muscle disorders;

- inflammatory disorders selected from the group consisting of pancreatitis, gout, tendonitis, bursitis, dermatomyositis and ankylosing spondylitis;

- secretory disorders selected from the group consisting of excessive gland secretions, mucus hypersecretion and hyperlacrimation and holocrine gland dysfunction;

- respiratory disorders selected from the group consisting of non-allergic rhinitis, allergic rhinitis, COPD and asthma;

- hypertrophic disorders selected from the group consisting of muscle enlargement, masseteric hypertrophy, acromegaly and neurogenic tibialis anterior hypertrophy with myalgia;

- articular disorders selected from the group consisting of • tennis elbow (or epicondilytis of the elbow) , inflammation of joints, coxarthrosis, hip osteoarthritis, rotator muscle cap pathology of the shoulder, rheumatoid arthritis and carpal tunnel syndrome;

- endocrine disorders selected from the group consisting of type 2 diabetes, hypercalcemia, hypocalcemia, thyroid disorders, Cushing' s syndrome and obesity;
- prostate cancer; and
- traumatic injuries selected from the group consisting of sports injuries, muscle injuries, tendon wounds and bone fractures; or for performing cosmetic treatments wherein the cosmetic disorder to be treated is selected from the group consisting of
- skin defects;
- facial asymmetry;
- wrinkles selected from glabellar frown lines and facial wrinkles;
- downturned mouth; and
- hair loss.

[0034] More preferably, pharmaceutical compositions according to the invention will be used for preparing medicaments intended to treat a disease / a condition / a syndrome chosen from the following:

- ophtalmological disorders selected from the group consisting of blepharospasm and strabismus;
- movement disorders selected from the group consisting of hemifacial spasm, torticollis, cerebral palsy spasticity of the child and arm or leg spasticity of the adult in post-stroke, multiple sclerosis, traumatic brain injury or spinal cord injury patients;
- otorhinolaryngological disorders selected from the group consisting of spasmodic dysphonia, hypersalivation, sialorrhoea, cricopharyngeal dysphagia, bruxism, closure of larynx in chronic aspiration, ventricular dystonia, ventricular dysphonia, mutational dysphonia, trismus, snoring, voice tremor, tongue protrusion dystonia, palatal tremor and laryngeal dystonia;
- gastrointestinal disorders selected from the group consisting of achalasia, anal fissure, constipation, temporomandibular joint dysfunction, sphincter of Oddi dysfunction, sustained sphincter of Oddi hypertension, intestinal muscle disorders, anismus, pyloric spasm, gall bladder dysfunction, gastrointestinal or oesophageal motility dysfunction and gastroparesis;
- urogenital disorders selected from the group consisting of detrusor sphincter dyssynergia, detrusor hyperreflexia, neurogenic bladder dysfunction in Parkinson's disease, spinal cord injury, stroke or multiple sclerosis patients, bladder spasms, urinary incontinence, urinary retention, hypertrophied bladder neck, voiding dysfunction, interstitial cystitis, vaginismus, endometriosis, pelvic pain, prostate gland enlargement (Benign Prostatic Hyperplasia), prostatodynia, prostate cancer and priapism;
- dermatological disorders selected from the group consisting of axillary hyperhidrosis, palmar hyperhidrosis, Frey' s syndrome, bromhidrosis, psoriasis, skin wounds and acne;
- pain disorders selected from the group consisting of upper back pain, lower back pain, myofascial pain, tension headache, fibromyalgia, myalgia, migraine, whiplash, joint pain, post-operative pain and pain associated with smooth muscle disorders;
- inflammatory disorders selected from the group consisting of pancreatitis and gout;
- hyperlacrimation;
- respiratory disorders selected from the group consisting of non-allergic rhinitis, allergic rhinitis, COPD and asthma;
- masseteric hypertrophy;

- articular disorders selected from the group consisting of tennis elbow (or epicondilytis of the elbow) , inflammation of joints, coxarthrosis, hip osteoarthritis, rotator muscle cap pathology of the shoulder, rheumatoid arthritis and carpal tunnel syndrome;
- obesity;
- traumatic injuries selected from the group consisting of muscle injuries, tendon wounds and bone fractures;

or for performing cosmetic treatments wherein the cosmetic disorder to be treated is selected from the group consisting of:

- skin defects;
- facial asymmetry;
- wrinkles selected from glabellar frown lines and facial wrinkles;
- downturned mouth; and
- hair loss.

[0035] In a particularly preferred manner, pharmaceutical compositions according to the invention will be used for preparing medicaments intended to treat a disease / a condition / a syndrome chosen from the following: blepharospasm, hemifacial spasm, torticollis, cerebral palsy spasticity of the child and arm or leg spasticity of the adult in post-stroke, multiple sclerosis, traumatic brain injury or spinal cord injury patients, axillary hyperhidrosis, palmar hyperhidrosis, Frey' s syndrome, skin wounds, acne, upper back pain, lower back pain, myofascial pain, migraine, tension headache, joint pain, tennis elbow (or epicondilytis of the elbow), inflammation of joints, coxarthrosis, hip osteoarthritis, rotator muscle cap pathology of the shoulder, muscle injuries, tendon wounds and bone fractures;
or for performing cosmetic treatments wherein the cosmetic disorder to be treated is selected from the group consisting of

- skin defects;
- facial asymmetry; and
- wrinkles selected from glabellar frown lines and facial wrinkles.

[0036] The dose of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) which shall be needed for the treatment of the diseases / disorders mentioned above varies depending on the disease / disorder to be treated, administration mode, age and body weight of the patient to be treated and health state of the latter, and it is the treating physician or veterinary that will eventually make the decision. Such a quantity determined by the treating physician or veterinary is called here "therapeutically efficient quantity".

[0037] For botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) , this therapeutically efficient dose is often expressed as a function of the corresponding LD50- By LD50 should be understood in the present application the median intraperitoneal dose in mice injected with botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) that causes death of half of said mice within 96 hours.

[0038] The term "about" refers to an interval around the considered value. As used in this patent application, "about X" means an interval from X minus 10% of X to X plus 10% of X, and preferably an interval from X minus 5% of X to X plus 5% of X.

[0039] Unless they are defined differently, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. The following examples are presented by way of illustration and should in no way be considered to limit the scope of the invention.

EXAMPLES

Example 1: A liquid pharmaceutical composition containing the following components is prepared:

[0040]

Clostridium botulinum type A1 neurotoxin complex	2,000 LD_{50} units/ml
Sucrose	11.7 mM
Histidine	10 mM
Sodium chloride 0.3 M	0.3 M
Polysorbate 80	0.01% v/v
pH	6.5

[0041] The mixture containing nominally 2,000 LD_{50} units of botulinum toxin per ml is lyophilised in a sterilised vial, which is then sealed. The solid composition obtained is stable for at least 18 months when stored at a temperature between 2 and 8°C and at least 6 months at 23 to 27°C.

Example 2: A liquid pharmaceutical composition containing the following components is prepared:

[0042]

Clostridium botulinum type A1 neurotoxin complex	500 LD_{50} units/ml
Sucrose	11.7 mM
Histidine	10 mM
Sodium chloride 0.3 M	0.3 M
Polysorbate 80	0.01% v/v
pH	6.5

[0043] The liquid composition thus prepared is sealed in a syringe type device with no liquid/gaseous interface. Stored in these conditions, it is stable for at least six months at 23 to 27°C and at least twelve months at 2-8°C.

Example 3: A liquid pharmaceutical composition, containing the following components is prepared:

[0044]

Clostridium botulinum type A1 neurotoxin complex	500 LD_{50} units/ml
Sucrose	11.7 mM
Histidine	10 mM
Sodium chloride 0.3 M	0.15 M
Polysorbate 80	0.01% v/v
pH	6.5

[0045] The liquid composition composition thus prepared is sealed in a syringe type device with no liquid/gaseous interface. Stored in these conditions, it is stable for at least six months at 23 to 27°C and at least twelve months at 2-8°C.

ANALYTICAL METHODS

Mouse toxicity assay

[0046] A mouse toxicity assay can be used to measure the toxicity of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G) . In the assay, a standard diluent will be used to prepare a range of dilutions at or about the estimated LD50 value. The range and scale of dilutions is arranged so as to establish an accurate LD50 value.

[0047] Mice are injected intraperitoneally with a known and standardised volume of diluted toxin. After 96 hours, the

number of deaths and survivors in each dilution group will be recorded. The LD 50 value is the median dose which kills half of the injected animals within 96 hours.

[0048] A composition according to the invention is considered stable over a cert ain period of time if at least 70% of the initial toxicity is maintained over said period of time relative to a reference preparation.

Claims

1. A solid or liquid pharmaceutical composition comprising:

   a) botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
   b) a surfactant as a stabilizing agent,
   c) sodium chloride, and
   d) a buffer to maintain pH between 5.5 to 7.5

   wherein said solid or liquid pharmaceutical composition does not comprise albumin.

2. A solid or liquid pharmaceutical composition according to claim 1, wherein said composition consists of:

   a) botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
   b) a surfactant,
   c) sodium chloride,
   d) a buffer to maintain pH between 5.5 to 7.5,
   optionally
   e) water, and
   optionally
   f) a disaccharide.

3. A solid or liquid pharmaceutical composition according to claim 1 or 2 wherein the buffer is maintaining a pH from 5.8 to 7.0.

4. A solid or liquid pharmaceutical composition according to claim 1 further comprising a disaccharide.

5. A solid or liquid pharmaceutical composition according to claim 4 wherein the disaccharide is chosen from the group consisting of sucrose, trehalose, lactose and mannitol.

6. A solid or liquid pharmaceutical composition according to any of claims 1 to 5 which contains botulinum neurotoxin complex type A.

7. A pharmaceutical composition according to any of claims 1 to 5 which contains high purity botulinum neurotoxin type A.

8. A pharmaceutical composition according to any of claims 1 to 7 claims in which the surfactant is a non-ionic surfactant.

9. A pharmaceutical composition according to claim 8 in which the non-ioninc surfactant is a polysorbate, e.g. polysorbate 80, or a block polymer, in particular a poloxamer.

10. A pharmaceutical composition according to any of claims 1 to 9 wherein

    - said surfactant is Polysorbate 80,
    - said buffer is Histidine,
    - the pH is maintained at about 6.5,
    wherein said composition comprises a disaccharide, and
    wherein said disaccharide is sucrose.

11. A pharmaceutical composition according to any one of claims 1 to 10 which is liquid and which is sealed in a syringe

type device with no liquid/gaseous interface.

12. A pharmaceutical composition according to any of claims 1 to 11 for use in the treatment of a disease selected from ophtalmological disorders, movement disorders, otorhinolaryngological disorders, gastrointestinal disorders, urogenital disorders, dermatological disorders, pain disorders, inflammatory disorders, secretory disorders, respiratory disorders, hypertrophic disorders, articular disorders, endocrine disorders, autoimmune diseases, proliferative disease and traumatic injuries.

13. Use of a pharmaceutical composition according to any one of claims 1 to 11 in cosmetics.

14. Use of a surfactant for stabilising a solid or liquid pharmaceutical composition that contains as active principle a botulinum toxin and that does not comprise albumin.

15. Use according to claim 14, wherein said surfactant is a non-ionic surfactant.

16. Use according to claim 15, wherein said non-ionic surfactant is a polysorbate, e.g. polysorbate 80, or a block polymer, in particular a poloxamer.

17. A pharmaceutical composition according to any of claims 1 to 11, wherein said botulinum neurotoxin is botulinum neurotoxin of type A1, A2 or A3.

18. A pharmaceutical composition according to any of claims 1 to 11, wherein said pharmaceutical composition comprises 50 to 10,000 LD50 units/ml, preferably 50 to 3,000 LD50 units/ml, of botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F or G).

19. A pharmaceutical composition according to any of claims 1 to 11, wherein the concentration of surfactant will be from above critical micellar concentration to a concentration of 1% v/v.

20. A pharmaceutical composition according to any of claims 1 to 11, wherein said pharmaceutical composition is liquid, has a PH of 6. 5, and comprises:

- 2, 000 LD50 units/ml of Clostridium botulinum neurotoxin type A 1 complex
- 11.7 mM Sucrose
- 10 mM Histidine
- 0.3 M Sodium chloride
- 0.01 % v/v Polysorbate 80

21. A pharmaceutical composition according to any of claims 1 to 11, wherein said pharmaceutical composition is liquid, has a PH of 6. 5, and comprises:

- 500 LD50 units/ml of Clostridium botulinum neurotoxin type A 1 complex
- 11 .7 mM Sucrose
- 10 mM Histidine
- 0.3 M Sodium chloride
- 0.01 % v/v Polysorbate 80

22. A pharmaceutical composition according to any of claims 1 to 11, wherein said pharmaceutical composition is liquid, has a PH of 6. 5, and comprises:

- 500 LD50 units/ml of Clostridium botulinum neurotoxin type A1 complex
- 11.7 mM Sucrose
- 10 mM Histidine
- 0.15 M Sodium chloride
- 0.01% v/v Polysorbate 80

23. A pharmaceutical composition according to claim 12 for use in the treatment of a disease selected from blepharospasm, hemifacial spasm, torticollis, spasticity of the child or of the adult, detrusor hyperreflexia, neurogenic bladder dysfunction, bladder spasms, urinary incontinence and hyperhidrosis.

Patentansprüche

1. Eine feste oder flüssige pharmazeutische Zusammensetzung, umfassend:

   a) einen Botulinum-Neurotoxin-Komplex (Typ A, B, C, D, E, F oder G) oder ein hochreines Botulinum-Neurotoxin (Typ A, B, C, D, E, F oder G),
   b) ein Tensid als Stabilisierungsmittel,
   c) Natriumchlorid und
   d) einen Puffer, um den pH-Wert zwischen 5,5 und 7,5 zu halten,

   wobei die feste oder flüssige pharmazeutische Zusammensetzung kein Albumin umfasst.

2. Eine feste oder flüssige, pharmazeutische Zusammensetzung gemäß Anspruch 1, wobei die Zusammensetzung besteht aus:

   a) einem Botulinum-Neurotoxin-Komplex (Typ A, B, C, D, E, F oder G) oder einem hochreinen Botulinum-Neurotoxin (Typ A, B, C, D, E, F oder G),
   b) einem Tensid,
   c) Natriumchlorid,
   d) einem Puffer, um den pH-Wert zwischen 5,5 und 7,5 zu halten,
   gegebenenfalls
   e) Wasser und
   gegebenenfalls
   f) einem Disaccharid.

3. Eine feste oder flüssige pharmazeutische Zusammensetzung gemäß Anspruch 1 oder 2, wobei der Puffer einen pH-Wert von 5,8 bis 7,0 aufrechterhält.

4. Eine feste oder flüssige pharmazeutische Zusammensetzung gemäß Anspruch 1, die ferner ein Disaccharid umfasst.

5. Eine feste oder flüssige pharmazeutische Zusammensetzung gemäß Anspruch 4, wobei das Disaccharid ausgewählt ist aus der Gruppe, bestehend aus Saccharose, Trehalose, Laktose und Mannit.

6. Eine feste oder flüssige pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 5, die Botulinum-Neurotoxin-Komplex vom Typ A enthält.

7. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 5, die hochreines Botulinum-Neurotoxin vom Typ A enthält.

8. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 7, bei der das Tensid ein nichtionisches Tensid ist.

9. Eine pharmazeutische Zusammensetzung gemäß Anspruch 8, wobei das nichtionische Tensid ein Polysorbat ist, z.B. Polysorbat 80, oder ein Blockpolymer, insbesondere ein Poloxamer.

10. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 9, wobei

    - das Tensid Polysorbat 80 ist,
    - der Puffer Histidin ist,
    - der pH-Wert bei etwa 6,5 gehalten wird,
    wobei die Zusammensetzung ein Disaccharid umfasst, und
    wobei das Disaccharid Saccharose ist.

11. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 10, die flüssig ist und die in einer Vorrichtung vom Typ Spritze ohne Flüssig/Gas-Grenzfläche versiegelt ist.

12. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11 zur Verwendung bei der Behand-

lung einer Erkrankung, ausgewählt aus ophthalmologischen Störungen, Bewegungsstörungen, otorhinolaryngologischen Störungen, gastrointestinalen Störungen, urogenitalen Störungen, dermatologischen Störungen, Schmerzstörungen, entzündlichen Störungen, sekretorischen Störungen, Atemstörungen, hypertrophischen Störungen, Gelenkstörungen, endokrinen Störungen, Autoimmunerkrankungen, proliferativer Erkrankung und traumatischen Verletzungen.

13. Verwendung einer pharmazeutischen Zusammensetzung gemäß einem der Ansprüche 1 bis 11 in der Kosmetik.

14. Verwendung eines Tensids zur Stabilisierung einer festen oder flüssigen pharmazeutischen Zusammensetzung, die als Wirkprinzip ein Botulinumtoxin enthält und die kein Albumin umfasst.

15. Verwendung gemäß Anspruch 14, wobei das Tensid ein nichtionisches Tensid ist.

16. Verwendung gemäß Anspruch 15, wobei das nichtionische Tensid ein Polysorbat ist, z.B. Polysorbat 80, oder ein Blockpolymer, insbesondere ein Poloxamer.

17. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei das Botulinum-Neurotoxin ein Botulinum-Neurotoxin vom Typ A1, A2 oder A3 ist.

18. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei die pharmazeutische Zusammensetzung 50 bis 10000 LD50-Einheiten/ml, vorzugsweise 50 bis 3000 LD50-Einheiten/ml, Botulinum-Neurotoxin-Komplex (Typ A, B, C, D, E, F oder G) oder hochreines Botulinum-Neurotoxin (Typ A, B, C, D, E, F oder G) umfasst.

19. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei die Konzentration des Tensids von oberhalb der kritischen Mizellkonzentration bis zu einer Konzentration von 1% Vol./Vol. beträgt.

20. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei die pharmazeutische Zusammensetzung flüssig ist, einen pH-Wert von 6,5 besitzt und umfasst:

- 2000 LD50-Einheiten/ml Clostridium-botulinum-Neurotoxin-Typ-A1-Komplex
- 11,7 mM Saccharose
- 10 mM Histidin
- 0,3M Natriumchlorid
- 0,01% Vol./Vol. Polysorbat 80

21. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei die pharmazeutische Zusammensetzung flüssig ist, einen pH-Wert von 6,5 besitzt und umfasst:

- 500 LD50-Einheiten/ml Clostridium-botulinum-Neurotoxin-Typ-A1-Komplex
- 11,7 mM Saccharose
- 10 mM Histidin
- 0,3M Natriumchlorid
- 0,01 % Vol./Vol. Polysorbat 80

22. Eine pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 11, wobei die pharmazeutische Zusammensetzung flüssig ist, einen pH-Wert von 6,5 besitzt und umfasst:

- 500 LD50-Einheiten/ml Clostridium-botulinum-Neurotoxin-Typ-A1-Komplex
- 11,7 mM Saccharose
- 10 mM Histidin
- 0,15M Natriumchlorid
- 0,01 % Vol./Vol. Polysorbat 80

23. Eine pharmazeutische Zusammensetzung gemäß Anspruch 12 zur Verwendung bei der Behandlung einer Erkrankung, ausgewählt aus Blepharospasmus, hemifazialem Spasmus, Tortikollis, Spastik beim Kind oder beim Erwachsenen, Detrusorhyperreflexie, neurogener Blasendysfunktion, Blasenspasmus, Harninkontinenz und Hyperhidrose.

Revendications

1. Composition pharmaceutique solide ou liquide comprenant :

   a) une neurotoxine botulique (type A, B, C, D, E, F ou G) sous forme complexée ou une neurotoxine botulique hautement purifiée (type A, B, C, D, E, F ou G),
   b) un surfactant en tant qu'agent de stabilisation,
   c) du chlorure de sodium, et
   d) un tampon pour maintenir le pH entre 5,5 et 7,5
   où ladite composition pharmaceutique solide ou liquide ne comprend pas d'albumine.

2. Composition pharmaceutique solide ou liquide selon la revendication 1, où ladite composition consiste en :

   a) une botulique (type A, B, C, D, E, F ou G) sous forme complexée ou d'une neurotoxine botulique hautement purifée (type A, B, C, D, E, F ou G),
   b) un surfactant,
   c) du chlorure de sodium,
   d) un tampon pour maintenir le pH entre 5,5 et 7,5,
   éventuellement
   e) de l'eau, et
   éventuellement
   f) un disaccharide.

3. Composition pharmaceutique solide ou liquide selon la revendication 1 ou 2, dans laquelle le tampon maintient un pH entre 5,8 et 7,0.

4. Composition pharmaceutique solide ou liquide selon la revendication 1, comprenant en outre un disaccharide.

5. Composition pharmaceutique solide ou liquide selon la revendication 4, dans laquelle le disaccharide est choisi dans le groupe constitué de sucrose, de tréhalose, de lactose et de mannitol.

6. Composition pharmaceutique solide ou liquide selon l'une quelconque des revendications 1 à 5 qui contient une neurotoxine botulique de type A sous forme complexée.

7. Composition pharmaceutique solide ou liquide selon l'une quelconque des revendications 1 à 5 qui contient une neurotoxine botulique heutement purifiée de type A.

8. Composition pharmaceutique solide ou liquide selon l'une quelconque des revendications 1 à 7 dans laquelle le surfactant est un surfactant non ionique.

9. Composition pharmaceutique solide ou liquide selon la revendication 8 dans laquelle le surfactant non ionique est un polysorbate, par exemple du polysorbate 80, ou un polymère séquencé, en particulier un poloxamère.

10. Composition pharmaceutique selon l'une quelconque des revendications 1 à 9, dans laquelle

    - ledit surfactant est du polysorbate 80,
    - ledit tampon est de l'histidine,
    - le pH est maintenu à environ 6,5,
    dans laquelle ladite composition comprend un disaccharide, et
    dans laquelle ledit disaccharide est du sucrose.

11. Composition pharmaceutique selon l'une quelconque des revendications 1 à 10 qui est liquide et qui est hermétiquement enfermée dans un dispositif de type seringue sans interface liquide/gazeuse.

12. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11 à utiliser dans le traitement d'une maladie sélectionnée parmi les troubles ophtalmologiques, les troubles du mouvement, les troubles oto-rhino-laryngologiques, les troubles gastro-intestinaux, les troubles urogénitaux, les troubles dermatologiques, les troubles de la douleur, les troubles inflammatoires, les troubles des sécrétions, les troubles respiratoires, les troubles hyper-

trophiques, les troubles de l'articulation, les troubles endocriniens, les maladies auto-immunes, les maladies prolifératives et les blessures traumatiques.

13. Utilisation d'une composition pharmaceutique selon l'une quelconque des revendications 1 à 11 en cosmétique.

14. Utilisation d'un surfactant pour stabiliser une composition pharmaceutique solide ou liquide qui contient comme principe actif une toxine botulique et qui ne contient pas d'albumine.

15. Utilisation selon la revendication 14, dans laquelle ledit surfactant est un surfactant non ionique.

16. Utilisation selon la revendication 15, dans laquelle ledit surfactant non ionique est un polysorbate, par exemple du polysorbate 80, ou un polymère séquencé, en particulier un poloxamère.

17. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle ladite neurotoxine botulique est une neurotoxine botulique de type A1, A2 ou A3.

18. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle ladite composition pharmaceutique comprend entre 50 et 10 000 unités LD50/ml, de préférence entre 50 et 3 000 d'unités LD50/ml, de neurotoxine botulique (type A, B, C, D, E, F ou G) sous forme complexée ou de neurotoxine botulique hautement purifiée (type A, B, C, D, E, F ou G).

19. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle la concentration de surfactant est comprise entre la concentration micellaire critique et une concentration de 1 % v/v.

20. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle ladite composition pharmaceutique est liquide, a un pH de 6,5 et comprend :

- 2 000 unités LD50/ml de neurotoxine botulique clostridiale de type A1 sous forme complexée,
- 11,7 mM de sucrose
- 10 mM d'histidine
- 0,3 M de chlorure de sodium
- 0,01 % v/v de polysorbate 80

21. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle ladite composition pharmaceutique est liquide, a un pH de 6,5 et comprend :

- 500 unités LD50/ml de neurotoxine botulique clostridiale de type A1 sous forme complexée,
- 11,7 mM de sucrose
- 10 mM d'histidine
- 0,3 M de chlorure de sodium
- 0,01 % v/v de polysorbate 80

22. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle ladite composition pharmaceutique est liquide, a un pH de 6,5 et comprend :

- 500 unités LD50/ml de neurotoxine botulique clostridiale de type A1 sous forme complexée,
- 11,7 mM de sucrose
- 10 mM d'histidine
- 0,15 M de chlorure de sodium
- 0,01 % v/v de polysorbate 80

23. Composition pharmaceutique selon la revendication 12 à utiliser dans le traitement d'une maladie sélectionné parmi le blépharospasme, le spasme hémifacial, le torticolis, la spasticité de l'enfant ou de l'adulte, l'hyper-réflectivité du détrusor, le dysfonctionnement neurogène de la vessie, les spasmes de la vessie, l'incontinence urinaire et l'hyperhidrose.

REFERENCES CITED IN THE DESCRIPTION

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Szabadalmi igénypontok

1. Szilárd vagy folyékony gyógyászati készítmény

amely tartalmaz:

a) botulinum neurotoxin komplexet (A, B, C, D, E, F vagy G típus) vagy nagy tisztaságú botulinum neurotoxint (A, B, C, D, E, F, vagy G típus),

b) felületaktív anyagot stabilizálószerként,

c) nátrium-kloridot, és

d) puffert a pH 5,5 és 7,5 között tartására

ahol a szilárd vagy folyékony gyógyászati készítmény nem tartalmaz albumint.

2. Az 1. igénypont szerinti szilárd vagy folyékony gyógyászati készítmény, ahol a készítmény a következőkből áll:

a) botulinum neurotoxin komplex (A, B, C, D, E, F vagy G típus) vagy nagy tisztaságú botulinum neurotoxin (A, B, C, D, E, F, vagy G típus),

b) felületaktív anyag,

c) nátrium-klorid,

d) puffer a pH 5,5 és 7,5 között tartására,

adott esetben

e) víz, és

adott esetben

f) diszaccharid.

3. Az 1. vagy 2. igénypont szerinti szilárd vagy folyékony gyógyászati készítmény, ahol a puffer 5,8 és 7,0 között tartja a pH-t.

4. Az 1. igénypont szerinti szilárd vagy folyékony gyógyászati készítmény, amely továbbá diszaccharidot is tartalmaz.

5. A 4. igénypont szerinti szilárd vagy folyékony gyógyászati készítmény, ahol a diszaccharid a következők által alkotott csoportból van kiválasztva: szacharóz, trehalóz, laktóz és mannitol.

6. Az 1-5. igénypontok bármelyike szerinti szilárd vagy folyékony gyógyászati készítmény, amely A típusú botulinum neurotoxin komplexet tartalmaz.

7. Az 1-5. igénypontok bármelyike szerinti gyógyászati készítmény, amely nagy tisztaságú A típusú botulinum neurotoxint tartalmaz.

8. Az 1-7. igénypontok bármelyike szerinti gyógyászati készítmény, amelyben a felületaktív anyag nem-ionos felületaktív anyag.

9. A 8. igénypont szerinti gyógyászati készítmény, amelyben a nem-ionos felületaktív anyag poliszorbát, például poliszorbát 80, vagy blokk-polimer, előnyösen poloxamer.

10. Az 1-9. igénypontok bármelyike szerinti gyógyászati készítmény, ahol

- a felületaktív anyag poliszorbát 80,
- a puffer hisztidin,
- a pH körülbelüli 6,5 értéken van tartva,

ahol a készítmény diszaccharidot tartalmaz, és

ahol a diszaccharid szacharóz.

11. Az 1-10. igénypontok bármelyike szerinti gyógyászati készítmény, amely folyékony és amely fecskendő típusú eszközbe van leforrasztva folyadék/gáz határfelület nélkül.

12. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény a következők által alkotott csoportból kiválasztott betegség kezelésben történő alkalmazásra: szemészeti rendellenességek, mozgási rendellenességek, fül-orr-gégészeti rendellenességek, gyomor-bélrendszeri rendellenességek, húgyivari rendellenességek, bőrgyógyászati rendellenességek, fájdalom rendellenességek, gyulladásos rendellenességek, szekréciós rendellenességek, légzőszervi rendellenességek, hipertrófiás rendellenességek, izületi rendellenességek, endokrin rendellenességek, autoimmun betegségek, proliferatív betegség és traumás sérülések.

13. Az 1-1. igénypontok bármelyike szerinti gyógyászati készítmény alkalmazása kozmetikumokban.

14. Felületaktív anyag alkalmazása olyan szilárd vagy folyékony gyógyászati készítmény stabilizálására, amely hatóanyagként botulinum toxint tartalmaz és nem tartalmaz albumint.

15. A 14. igénypont szerinti alkalmazás, ahol a felületaktív anyag nem-ionos felületaktív anyag.

16. A 15. igénypont szerinti alkalmazás, ahol a nem-ionos felületaktív anyag poliszorbát, például poliszorbát 80, vagy blokk-polimer, előnyösen poloxamer.

17. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény, ahol a botulinum neurotoxin A1, A2 vagy A3 típusú botulinum neurotoxin.

18. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény, ahol a gyógyászati készítmény 50 - 10000 LD50 egység/ml, előnyösen 50 - 3000 LD50 egység /ml botulinum neurotoxin komplexet (A, B, C, D, E, F vagy G típus) vagy nagy tisztaságú botulinum neurotoxint (A, B, C, D, E, F, vagy G típus) tartalmaz.

19. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény, ahol a felületaktív anyag koncentrációja a kritikus micellaképző koncentráció felettitől 1 térfogat% koncentrációig terjedhet.

20. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény, ahol a gyógyászati készítmény folyékony, a pH-ja 6,5, és tartalmaz:

- 2000 LD50 egység/ml A1 típusú Clostridium botulinum neurotoxin komplexet
- 11,7 mM szacharózt
- 10 mM hisztidint
- 0,3 M nátrium-kloridot
- 0,01 térfogat% poliszorbát 80-at.

21. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény, ahol a gyógyászati készítmény folyékony, a pH-ja 6,5, és tartalmaz:

- 500 LD50 egység/ml A1 típusú Clostridium botulinum neurotoxin komplexet
- 11,7 mM szacharózt
- 10 mM hisztidint
- 0,3 M nátrium-kloridot
- 0,01 térfogat% poliszorbát 80-at.

22. Az 1-11. igénypontok bármelyike szerinti gyógyászati készítmény, ahol a gyógyászati készítmény folyékony, a pH-ja 6,5, és tartalmaz:

- 500 LD50 egység/ml A1 típusú Clostridium botulinum neurotoxin komplexet

• 11,7 mM szacharózt

• 10 mM hisztidint

• 0,15 M nátrium-kloridot

• 0,01 térfogat% polioxorbát 80-at.

23. A 12. igénypont szerinti gyógyászati készítmény a következők közül választott betegség kezelésére: szemhéjgörcs, arcfél-görcs, nyakmerevség, gyermek vagy felnőtt görcsre való hajlama, detrusor hiperreflexia, neurogén hólyagzavar, hólyag görcsök, vizelettartási problémák és hiperhidrózis.