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(54) Benevnelse **A STERILE SOLUTION WITH AN APPLICATION INJECTOR COMPRISING A MEDICAL AGENT AND METHOD FOR PRODUCING SAME**

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A STERILE SOLUTION WITH AN APPLICATION INJECTOR COMPRISING A MEDICAL AGENT AND METHOD FOR PRODUCING SAME

The present invention relates to an application injector containing a sterile solution with a medical agent, in particular for introducing the solution into the bladder of a patient via a urinary tract- and/or bladder catheter. It further relates to a method of providing such an application injector containing a sterile solution with a medical agent.

It is known to make available to doctors, and also to patients for self-medication, solutions for medical treatments containing one or more medical agents filled into application injectors.

Thus, for example, parasympatholytics such as oxybutynin hydrochloride are used for the treatment of overactive bladder. In particular, such parasympatholytics, such as for instance oxybutynin hydrochloride, are used to relax the bladder in patients who are unable to empty their bladder naturally and who need to empty it through a catheter inserted into the urethra. Such patients include, for example and in particular, patients with paraplegia.

Parasympatholytics, such as medicaments containing oxybutynin hydrochloride, are administered orally. The problem with this form of administration is a delayed effect due to delayed absorption via the gastro-intestinal tract, and also the side effects observed with this form of administration. These side effects include dry mouth, constipation, visual disturbances, fatigue and dizziness. In particularly severe cases, there may also be delirium caused by the parasympatholytic such as e.g. oxybutynin hydrochloride.

In this respect, other forms of administration have already been developed that do not involve oral administration but rather transdermal administration of the agent, for example with transdermal patches or gels. Although this method of administering the agent can reduce side effects, it still leads to a delayed effect of the medicament.

There have also been trials and practical applications in which a medicament containing a parasympatholytic, e.g. oxybutynin hydrochloride, is instilled directly into the bladder in the form of a solution, in particular after emptying the bladder via a catheter through the catheter that is already in place for emptying the bladder. This form of administration has the great advantage that not only are the side effects significantly reduced, but above all the medicament is very quick-acting, largely immediate, since it is

administered directly in the region of the bladder and no transport via the bloodstream is necessary. WO 2014/131742 describes a kit consisting of a catheter and a plunger injector containing a medicament.

In previous applications of this type, in which a solution containing a parasympatholytic, e.g. a solution containing oxybutynin hydrochloride, is administered in an application injector, which the user can administer independently via the placed bladder catheter after emptying of the bladder, simple application injectors made of polyethylene (PE) or polypropylene (PP) have been used, with a plunger on the injector plunger made of a simple rubber material. Furthermore, these application injectors were used with a Luer-lock connector surrounding an outlet opening, onto which a matching adapter cone was screwed to connect to the catheter used by the patient to empty their bladder.

In extensive tests, the inventor has discovered that these previously known solutions have various disadvantages. In particular, the inventor was forced to the conclusion that in the application injectors used up to now, in particular when these are subjected to steam pressure treatment for final sterilisation and heated to the customary temperatures of typically at least 120 °C (for example 121 °C), the concentration of the agent, e.g. of oxybutynin hydrochloride, in the solution contained in the application injector changes and this concentration decreases. In further and extensive tests, the inventor was able to attribute this decrease in the concentration of the agent to the fact that the material previously used for the application injectors, on the one hand of the injector body itself, namely the PP and the PE, and on the other hand of the stopper, namely the conventional rubber, absorbs the agent contained in the solution, e.g. oxybutynin hydrochloride, in the course of steam pressure sterilisation and binds it there even after steam pressure treatment.

The inventor had the objective of counteracting this problem and providing an application injector containing a sterile solution with a medical agent, in particular a solution containing parasympatholytics, in particular containing oxybutynin hydrochloride, which can be sterilised in steam pressure process without changing the concentration of the medical agent in the solution.

According to the invention, this objective is achieved by an application injector containing a sterile solution with a medical agent, in particular for introducing the medicament into the bladder of a patient via a urinary tract- and/or bladder catheter, and

by an application injector with a cylindrical jacket which is closed on one side by an injector lid which is formed integrally with the jacket and has an outlet opening and is formed from a cycloolefin copolymer (COC) and has a plunger made of an, in particular halogenated, isobutene-isoprene rubber (also known as butyl rubber), in which the solution containing the medical agent is arranged in a cavity bounded by the cylindrical jacket with injector lid and the plunger.

In extensive tests, the inventor has established that the materials now proposed by him for the application injector, more precisely for its jacket with injector lid and for the plunger, namely COC and, in particular halogenated, isobutene-isoprene rubber, even under the conditions and in particular temperatures that are used for a final steam pressure sterilisation, do not absorb the medical agent, e.g. a parasympatholytic such as oxybutynin hydrochloride, so that even after the steam pressure sterilisation the concentration of the agent in the solution contained in the application injector so treated and containing the medical agent is not changed.

This means that, for the first time, a finished product can now be offered which meets the required sterility specifications due to the final steam pressure sterilisation, which product contains the sterile solution with the medical agent at the concentration at which it was filled and which can therefore be used with the desired effect by the practitioner or in self-treatment by an affected patient.

The sterile solution may contain as medical agent in particular a parasympatholytic, in particular oxybutynin hydrochloride.

In the application injector according to the invention, the outlet opening is formed in a stepped cone which is formed integrally with the jacket and the injector lid and has at least two, preferably at least three, cylindrical sections with different diameters which become smaller towards a tip of the stepped cone. This design allows e.g. coupling of the application injector with differently designed catheters having different connecting cones, e.g. those for bladder emptying. The integral design of the stepped cone with the jacket and the injector lid is also a significant improvement over the previously known designs with adapter cones fixed to the application injector via a Luer-lock connection. This is because, as the inventor has also established in tests, these cones do not remain sufficiently tight during final steam pressure sterilisation of the filled application injector connected to the adapter cone, so that this can also result in a change in the solution containing the medical agent which is arranged in the application injector. In order to be

able to connect a large number of catheters, e.g. catheters for bladder emptying, as flexibly as possible to the stepped cone, which is designed in the advantageous development according to the invention integrally with the jacket and the injector lid, the stepped cone may have a large number of cylindrical sections with different diameters which become smaller towards the tip of the stepped cone, for example 10 to 15 such cylindrical sections, in particular for example 12.

The material of the plunger may in particular be autoclavable bromobutyl rubber.

In particular, according to the present invention, the medical agent contained in the sterile solution may be a parasympatholytic, in particular oxybutynin hydrochloride. In particular, this agent may be selected for use in relaxing the bladder of a patient and dosed accordingly in the sterile solution.

Sterile solutions containing a parasympatholytic, in particular oxybutynin hydrochloride, with a proportion of the said agent of 0.01 to 1.0% by weight, preferably of 0.05 to 0.5% by weight, in particular of 0.08 to 0.12% by weight, advantageously of 0.1% by weight, have proved to be suitable for a medication for the relaxation of an overactive bladder that is to be carried out with the sterile solution with which the application injector is filled.

The sterile solution that is arranged in the cavity of the application injector may be an oxybutynin hydrochloride containing NaCI solution. In particular, this may be an isotonic NaCI solution containing oxybutynin hydrochloride.

For a single medication, a suitable quantity, a suitable volume, of sterile solution containing a medical agent may in particular be from 1 to 50 ml, to show from 5 to 20 ml, in particular from 8 to 12 ml, may with particular advantage be 10 ml. This also applies in particular to sterile solutions as indicated above, containing a parasympatholytic, in particular oxybutynin hydrochloride, in a proportion as indicated above.

Advantageously, the application injector filled with the sterile solution containing the medical agent is closed at its outlet opening by a closure element, in particular a closure plug or a closure cap, in a delivery condition, this closure element consisting of an, in particular halogenated, isobutene-isoprene rubber. It may in particular be formed from an autoclavable bromobutyl rubber. The closure element prevents premature leakage of the sterile solution containing the medical agent from the cavity of the application injector and ensures that the area around the outlet opening, which is covered by the closure plug or the closure cap, is protected against microbial contamination and thus remains sterile

after a sterilisation process until the application injector is packed in e.g. a blister pack. The choice of material for the closure plug or closure cap again ensures that, in a final steam pressure sterilisation process, the closure element absorbs no agent, e.g. no parasympatholytic, such as e.g. oxybutynin hydrochloride, from the solution, so that the concentration of the agent in the sterile solution is not changed.

The application injector filled with the solution containing the medical agent is, in particular, sterilised at the end of the process and subsequently packaged, e.g. in a blister pack, so that when the user removes the application injector from the packaging immediately before use, the injector contents are sterile and germ-free, thus preventing germs from being introduced into the urethral and bladder tract, e.g during treatment of the bladder.

The invention also makes available a method for providing an application injector containing a sterile solution with a medical agent, in particular for introducing the sterile solution into the bladder of a patient via a urinary tract- and/or bladder catheter, which application injector is formed as described above. The method comprises the following steps:

A sterile application injector is provided, comprising a cylindrical jacket made of a cycloolefin copolymer (COC) which is closed on one side by an injector lid which is formed integrally with the material and has an outlet opening, and a plunger made of an, in particular halogenated, isobutene-isoprene rubber. A solution containing the medical agent, e.g. a parasympatholytic, such as oxybutynin hydrochloride, is also provided. This solution containing the medical agent may be formed in particular in accordance with the above information given in the description of the application injector, i.e. with an, in particular isotonic, NaCl solution and/or in the above-mentioned concentrations of a parasympatholytic, such as oxybutynin hydrochloride, as the agent. A cavity of the application injector, which is bounded by the cylindrical jacket with injector lid and the plunger, is filled with the solution containing the agent. This may be, in particular, a filling of the cavity with a volume of the solution as set out above in the description of the application injector. The outlet opening of the application injector is closed with a closure element made of an, in particular halogenated, isobutene-isoprene rubber, e.g. an autoclavable bromobutyl rubber. The unit thus formed, i.e. the application injector filled with the solution containing the agent and closed at its outlet opening, is finally steam pressure sterilised in an autoclave.

After steam pressure sterilisation, the application injector filled with the sterilised solution containing the active substance and sealed with the closure element may be packaged for delivery, storage and transport to the patient and, if necessary, safekeeping there.

In particular, an application injector as described above may be provided with an outlet opening in a stepped cone that is formed integrally with the jacket and the injector lid and has at least two, preferably at least three, cylindrical sections with different diameters which decrease towards a tip of the stepped cone. The stepped cone can again be designed in a way that it is shown and explained above in the description of the application injector.

The steam pressure sterilisation may be carried out in the autoclave for at least 10 minutes, in particular at least 15 minutes, in particular for 20 minutes, and proceeds preferably at least 115°C, in particular at least 120°C, in particular at exactly 121°C.

Further advantages and features of the invention are evident from the following description of an exemplary embodiment with reference to the accompanying Figures, in which:

Fig. 1 shows a three-dimensional view of an application injector according to the invention (without the injector plunger with piston);

Fig. 2 shows a sectional view of the application injector shown in Fig. 1 (again without the injector plunger with piston); and

Fig. 3 shows an enlarged view of the area marked III in Fig. 2.

In the Figures, a possible exemplary embodiment of an application injector according to the invention is shown in principle. The Figures are thereby not to scale and also do not contain all the elements required for the design of the application injector. In particular, the Figures do not show an injector plunger with the piston attached to it, as belongs to the application injector. However, the shape of such an injector plunger is sufficiently familiar to the skilled person so that reference can be made to the known designs. The special feature of the application injector according to the invention is not its shape, but rather the material of the plunger.

An application injector (shown, as mentioned, without the injector plunger with piston) is generally designated in the Figures by the reference sign 1. This application injector 1 includes a jacket 2, with which an injector lid 3 is integrally formed. Also integrally formed on the injector lid 3 is, in the exemplary embodiment shown, a stepped

cone 4 which is composed of a large number of cylindrical sections 8 placed one on top of the other with diameters decreasing from the injector lid 3 to the tip of the stepped cone 4. In the exemplary embodiment shown, these are a total of twelve such sections 8, which merge integrally via a neck into the injector lid 3.

This stepped cone 4, which is formed integrally on the injector lid 3 and is thus connected to the jacket 2, allows the application injector 1 to be connected to conical connection openings of catheters, e.g. those for emptying of bladders, with very different shapes.

The special feature of the application injector 1 according to the invention is that it is on the one hand made, e.g. by injection-moulding, integrally with the jacket 2, the injector lid 3 and the stepped cone 4 and of a particular material, namely a cycloolefin copolymer (COC), and has a plunger (not shown in the Figures, inserted in the usual manner into the jacket 2 from a rear end 7) that is made of a particular rubber, namely an, in particular halogenated, isobutene-isoprene rubber, e.g. an autoclavable bromobutyl rubber. Furthermore, what is special is that this application injector 1 is filled, in a cavity 6 formed in the jacket 2 and bounded by the jacket 2, the injector lid 3 and the plunger that is not described in detail, with a sterile solution containing a medical agent, in particular a solution containing a parasympatholytic, such as in particular oxybutynin hydrochloride, in particular an oxybutynin hydrochloride containing NaCl solution, in particular an oxybutynin hydrochloride containing isotonic NaCl solution. In the course of preparation, the application injector 1 according to the invention, the outlet opening 5 of which has in particular previously been closed by a cap placed on the stepped cone 4 and consisting of an, in particular halogenated, isobutene-isoprene rubber, preferably of autoclavable bromobutyl rubber, has been sterilised in a final step, in particular in a steam pressure sterilisation in an autoclave, for example for 20 minutes at 121 °C.

The concentration of a sterile solution containing a parasympatholytic such as e.g. oxybutynin hydrochloride in the cavity 6 may in particular be between 0.01 % by weight and 1.0 % by weight. In the exemplary embodiment described here, it is preferably 0.1 % by weight. The volume of the sterile solution in the cavity 6 may in particular be between 1 ml and 50 ml, but in the exemplary excursion shown it is preferably 10 ml.

The advantage that the stepped cone 4 is formed integrally with the injector lid 3 is that a leakage which may be observed at this point with application injectors known from the prior art cannot occur, so that in the final steam pressure sterilisation step there can

be no influence on the solution in cavity 6, in particular on the medical agent dissolved in it, e.g. in the form of a parasympatholytic, such as oxybutynin hydrochloride.

From the above description of the exemplary embodiment, it has once again become clear what special advantages the design according to the invention brings with it, in particular by enabling a final sterilisation of the application injector 1 filled with the solution containing the medical agent in a steam pressure sterilisation step in an autoclave, without this leading to an adverse effect on the solution filled into the application injector 1 and the agent dissolved in it.

List of reference signs

1	Application injector
2	Jacket
3	Injector lid
4	Stepped cone
5	Outlet opening
6	Cavity
7	Rear end
8	Cylindrical section

PATENTKRAV

1. Applikasjonsinjektor (1) inneholdende en steril løsning med et medisinsk middel for å innføre den aktive substans-holdige løsningen i blæren til en pasient via et urinveis- og/eller blærekateteret, hvor

• applikasjonsinjektoren (1) har en sylindrisk kappe (2) som er lukket av et injektorlokk (3) som er dannet i ett stykke med kappen (2) og har en utløpsåpning (5), og er dannet av en sykloolefin-kopolymer (COC), og har et stempel laget av en, spesielt halogenert, isobuten-isopren-gummi, og

• den sterile løsningen som inneholder det medisinske middelet er anordnet i et hulrom (6) begrenset av den sylindriske kappen (2) med injektorlokket (3) og stempelet,

karakterisert ved at utløpsåpningen (5) er dannet i en trinnkjegle (4) som er utformet i ett stykke med kappen (2) og injektorlokket (3) og som har minst to, fortrinnsvis minst tre, sylindriske seksjoner (8) med forskjellige diametere som avtar mot spissen av trinnkjeglen (4).

2. Applikasjonsinjektoren (1) ifølge krav 1, *karakterisert ved at* et parasympatolytisk middel, spesielt oksybutyninhydroklorid, er inneholdt i den sterile løsningen som medisinsk middel.

3. Applikasjonsinjektor (1) ifølge krav 2, *karakterisert ved at* det parasympatolytiske middel, spesielt oksybutyninhydroklorid, er inneholdt i den sterile løsningen i en andel på 0,01 til 1,0 vekt%, fortrinnsvis på 0,05 til 0,5 vekt%, spesielt på 0,1 vekt%.

4. Applikasjonsinjektoren (1) ifølge et av de foregående kravene, *karakterisert ved at* den sterile løsningen som inneholder det medisinske middelet er en oksybutyninhydrokloridholdig NaCl-løsning.

5. Applikasjonsinjektoren (1) ifølge krav 4, *karakterisert ved at* den sterile løsningen som inneholder det medisinske midlet er en isoton NaCl-løsning som inneholder oksybutyninhydroklorid.

6. Applikasjonsinjektoren (1) ifølge et av de foregående krav, *karakterisert ved at* trinnkjeglen (4) har 10 til 15 sylindriske seksjoner (8) med forskjellige diametere som blir mindre mot spissen av trinnkjeglen (4).

7. Applikasjonsinjektoren (1) ifølge et av de foregående kravene, *karakterisert ved at* stempelet er laget av en autoklaverbar brombutylgummi.

8. Applikasjonsinjektoren (1) ifølge et av de foregående krav, *karakterisert ved at* løsningen som inneholder oksybutyninhydroklorid med et volum på 1 til 50 ml, fortrinnsvis 5 til 25 ml, spesielt 10 ml, er anordnet i hulrommet (6).

9. Applikasjonsinjektoren (1) ifølge et av de foregående krav, *karakterisert ved at* utløpsåpningen (5) er lukket med et lukkeelement, spesielt en lukkekork, fremstilt av en, spesielt halogenert, isobuten-isoprengummi.

10. Applikasjonsinjektoren (1) ifølge et av de foregående krav, *karakterisert ved at* den er sterilisert.

11. Fremgangsmåte for å tilveiebringe en applikasjonsinjektor (1) inneholdende et medikament for å innføre medikamentet i blæren til en pasient via et urinveis- og/eller blærekateteret, ifølge et av de foregående kravene, omfattende følgende trinn å:
• tilveiebringe en steril kappe (2) omfattende en sylindrisk kappe (2) som er lukket på den ene siden av et injektorlokk (3) dannet integrert med kappen (2) og som har en utløpsåpning (5) og som består av en sykloolefin-kopolymer (COC), og et stempel som består av en applikasjonsinjektor (1), spesielt en halogenert applikasjonsinjektor (1) omfattende isobuten-isoprengummi,
• tilveiebringe en løsning som inneholder oksybutyninhydroklorid som medisinering,
• fylle et hulrom (6) av applikasjonsinjektoren (1), hvilket hulrom er avgrenset av den sylindriske kappen (2) med injektorlokket (3) og stempelet, med løsningen som inneholder oksybutyninhydroklorid,
• tette utløpsåpningen (5) på applikasjonsinjektoren (1) med et lukkeelement laget av isobuten-isoprengummi,
• damptrykksterilisere applikasjonsinjektoren (1) fylt med løsningen som inneholder oksybutyninhydroklorid og lukket med lukkeelementet i en autoklav.

12. Fremgangsmåten ifølge krav 11, *karakterisert ved at* trinnet å tilveiebringe den sterile, sylindriske kappen (2), som er lukket på den ene siden av injektorlokket (3), som er dannet integrert med kappen (2) og har en utløpsåpning (5), og som består av en sykloolefin-kopolymer (COC) og et stempel laget av en, spesielt halogenert, isobuten-isopren-gummi-applikasjonsinjektor (1) omfatter tilveiebringelse av en slik

applikasjonsinjektor (1) med en utløpsåpning (5) dannet i en trinnkjegle (4) utformet i ett stykke med kappen (2) og injektorlokket (3) og har minst to, fortrinnsvis minst tre, sylindriske seksjoner (8) med forskjellige diametere som avtar mot en spiss av trinnkjeglen (4).

13. Fremgangsmåte ifølge et av kravene 11 eller 12, *karakterisert ved at* damptrykkssterilisering utføres i autoklaven i minst 10 minutter, spesielt i minst 15 minutter, spesielt i 20 minutter, ved minst 115 °C, spesielt ved minst 120 °C, spesielt ved 121 °C.

14. Fremgangsmåte ifølge et av kravene 11 til 13, *karakterisert ved at* det omfatter videre trinnet med å pakke den damptrykkssteriliserte applikasjonsinjektoren (1) fylt med løsningen inneholdende oksybutyninhydroklorid og lukket med lukkeelementet.

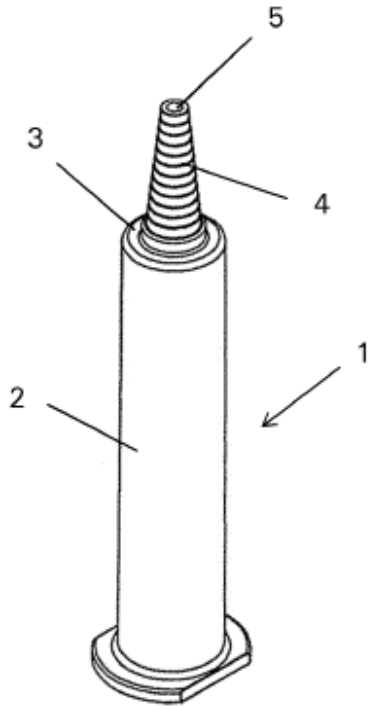

Fig. 1

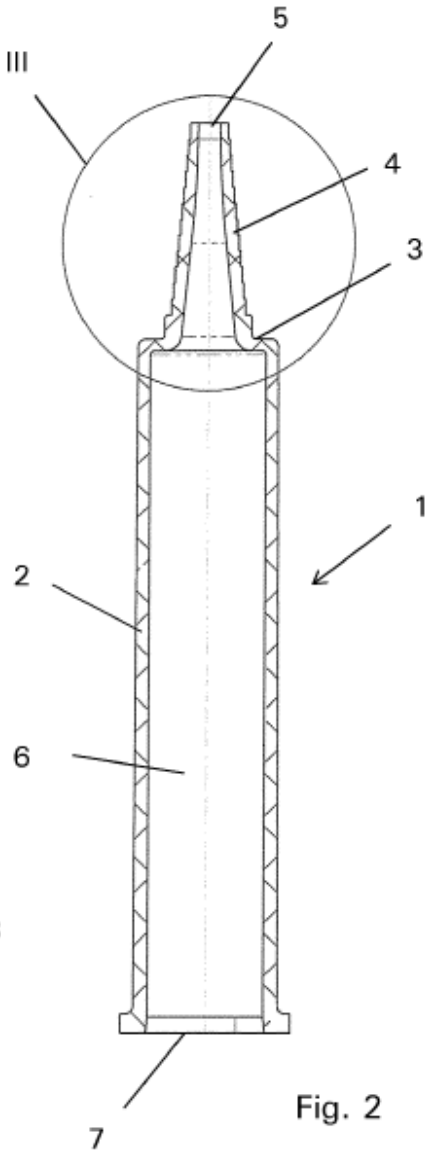

Fig. 2

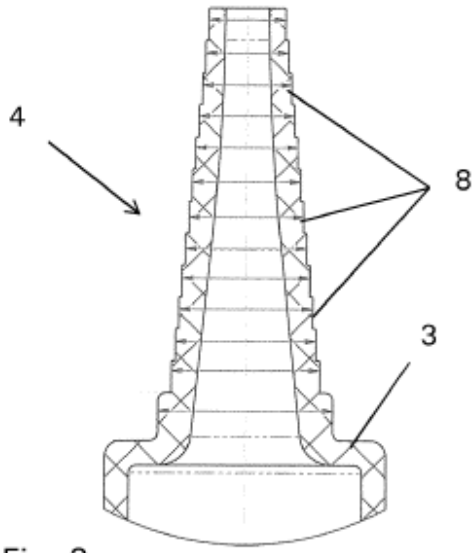

Fig. 3