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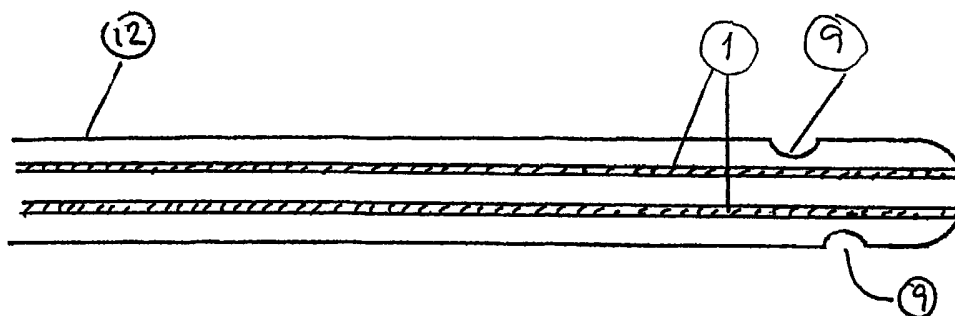
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(54) Title: A URINARY CATHETER DEVICE WITH A PHARMACEUTICALLY ACTIVE COMPOSITION



(57) Abstract: The invention relates to a device for urinary catheterisation comprising a catheter element and a pharmaceutically active composition containing a hormone, an efferent blocking agent, an afferent blocking agent and/or a sympathomimetic agent, the catheter element being adapted to deliver the pharmaceutically active composition in the lower urinary tract system during catheterisation. The invention also relates to the use of said pharmaceutically active composition for the manufacture of a device for the treatment, alleviation or prophylaxis of incontinence in a human and to a method of treating a human suffering from or being susceptible to incontinence. The invention further relates to a device for urinary catheterisation comprising a discrete unit dose comprising a pharmaceutically active composition and a catheter element adapted to shed said pharmaceutically active composition in the lower urinary tract system during catheterisation.

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**TITLE**

A urinary catheter device with a pharmaceutically active composition.

**FIELD OF THE INVENTION**

- 5 The present invention relates to a urinary catheter with a pharmaceutically active composition.

**BACKGROUND OF THE INVENTION**

10 Urinary incontinence is involuntary loss of urine from the bladder and affects millions of people worldwide. It can be caused by a great variety of conditions, including weak pelvic floor and sphincter muscles, estrogen deficiency, traumatic lesions of the urinary system or lesions of peripheral nerves innervating the bladder. Furthermore, spinal cord injury or central nervous diseases or lesions can cause urinary incontinence.

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In some cases, urinary incontinence is seen in combination with overactive bladder and difficulties with complete emptying of the bladder. Intermittent catheterisation is the preferred method of bladder emptying, in the case of over active bladder. Often this method is combined with medical treatment to relax the bladder musculature and increase bladder capacity. In general, systemic drug treatment affects the whole body and has a high risk of side-effects. Local treatment reduces the risk of side-effects, and in some cases increases efficacy.

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25 A special problem applies specifically to women using catheterisation as the method of emptying the bladder. In particular menopausal and postmenopausal women often experience symptoms caused by the estrogen deficiency, including thinning of the urethral mucosa and vaginal mucosa. The uro-genital oestrogen deficiency syndrome includes local urogenital symptoms, appearing in 25-50% of all menopausal women. The symptoms are caused by the lack of oestrogen and they result in atrophy of the epithelium in both vagina and urethra. The symptoms include dryness, discomfort, pain, recurrent urinary tract infections, urge incontinence and stress incontinence (frequent urinations and urinations during night

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time). The problem could be overseen in the group of catheter users, because of their primary bladder dysfunction, impaired sensation and basic incontinence.

Thinning of the urethral mucosa can increase risk of urethral trauma and thereby increase risk of urinary tract infections. The hormonal changes also affects pH to  
5 increase, which contributes to the risk of urinary tract infections. Furthermore, thinning of the urethral mucosa can cause lack of urethral pressure and thus stress incontinence.

Estrogen replacement therapy is often used to control menopause related urinary incontinence, and this treatment is based on the fact, that some estrogens in high  
10 degree stimulate the estrogen receptors in the urethral and bladder wall. By stimulating the estrogen receptors locally, the mucosa lining will increase in thickness and restore urethral pressure, pH and thereby help control urinary incontinence.

The Urogenital Oestrogen Deficiency Syndrome in itself is often solved by treat-  
15 ing with systemic or vaginal administration of oestrogen or oestrogen-derivatives, such as Oestriol or Oestradiol.

It is known that Oestriol or Oestradiol treatment increases the mobility of the urethro-vesical junction (Martan A. et al.. Ceska Gynekol.1999 Jan;64(1):6-9), increases the thickness of urethral mucosa (Henriksson L. et al., Am J Obstet Gynecol.1994 Sep;171(3):624-32), increases urethral vascularisation (Martan A. et al.. Ceska Gynekol.1999 Jan;64(1):6-9), alleviates subjective and objective symptoms (Henriksson L. et al., Am J Obstet Gynecol.1994 Sep;171(3):624-32), restores vaginal pH (Henriksson L. et al., Am J Obstet Gynecol.1994  
20 Sep;171(3):624-32) and decreases leakage episodes and urinary incontinence complaints (Ahlstom K. et al., Gynecol Obstet Invest. 1990;30(1):37-43). The results are, however, varying depending on the administration route, but it can be concluded that vaginal administration bypasses the first liver metabolism and is therefore more potent and shows better results and lesser side effects (Heimer GM. Estriol in the menopause. Acta Obstet Gynecol Scand Suppl 1987;139:1-  
25 30 23).

Agents for treating overactive bladder are used in patients with idiopathic overactive bladder or neurogenic bladder disorders, for instance caused by Spinal Cord Injury. The patients usually have severe detrusor hyperreflexia plus a disorder of bladder emptying, and intermittent catheterisation is the preferred method of  
5 bladder management to minimise residual urine. Catheterisation is often accompanied by treatment to increase bladder capacity and reduce bladder spasms.

Strategies for treating over active bladder can be to lessen the parasympathetic activity (parasympatolytica) or increasing sympathetic activity locally. Another  
10 principle is blocking the afferent arm of the bladder contraction reflex.

Blocking the parasympathetic activity (block of pelvic nerve-detrusor smooth muscle colinergic transmission) with parasympatolytica is the most widely used treatment principle, using anticholinergic agents, such as oxybutynin, tolterodine  
15 etc. This treatment principle is based on blocking the efferent pathway in the bladder contraction reflex arch. When given systemically, parasympatolytica also affects other organs, such as the mouth, eyes and bowel system. Parasympatolytica in general can have unpleasant side effects on other systems, e.g. dry mouth, accomodation difficulties, tendency of constipation. Parasympatolytica  
20 with specific effect on the bladder is therefore preferable. Furthermore, it is shown that intravesical (local) administration of anticholinergic drugs has very good effect and produces fewer side effects than orally administered anticholinergics.

25 Blocking the afferent arm of the bladder contraction reflex involves blocking of the nerve-pathways from the musculature of the bladder to the spinal cord. This group of drugs include Capsaicin (a chilli peber extract) Resiniferatoxin (RTX) and Local anaesthetic drugs.

30 In summary medical treatment accompanying catheterisations may be beneficial for a number of catheter users. However, systemic administration of a pharmaceutically active composition, often requires a higher dose of active agents, have

more side-effects and is often not as efficient as a local treatment. On the other hand local treatment of the urinary tract system is often performed as a procedure with the only objective of medical treatment, i.e. for catheter users, in addition to the procedure of catheterisation, another procedure must be performed to receive the local medical treatment. It is an object of the present invention to overcome these disadvantages by providing a device for urinary catheterisation, which combines urinary catheterisation with a local medical treatment, in that agents for the medical treatment is delivered by the catheter element during the usual catheterisation process.

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### **SUMMARY OF THE INVENTION**

A first aspect of the invention relates to a device for urinary catheterisation, said device comprising a catheter element adapted to be inserted in the urethra of a human, and a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents , and said catheter element is adapted to deliver at least a part of said pharmaceutically active composition in the lower urinary tract system during catheterisation.

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A second aspect of the invention relates to the use of a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents , for the manufacture of a device for the treatment, alleviation or prophylaxis of incontinence in a human, said device comprising a catheter element adapted to be inserted in the urethra of said human, said catheter element comprising the pharmaceutically active composition, and said catheter element being adapted to deliver said agent in the lower urinary tract system during catheterisation.

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A third aspect of the invention relates to a method of treating a human suffering from or being susceptible to incontinence, the method comprising the steps of catheterisation of said human by arranging a proximal end of a catheter element

of a device for urinary catheterisation in the urethra of said human, said catheter element comprising a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents , and said catheter  
5 element being adapted to deliver said composition in the lower urinary tract system during catheterisation.

A fourth aspect of the invention relates to a kit comprising a device for urinary catheterisation and a pharmaceutically active composition comprising at least  
10 one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents , said device comprising a catheter element adapted to be inserted in the urethra of a human.

A fifth aspect of the invention relates to a device for urinary catheterisation, said  
15 device comprising a catheter element adapted to be inserted in a urinary canal, said device further comprising a discrete unit dose, said discrete unit dose comprising a pharmaceutically active composition and said catheter element being adapted to shed said pharmaceutically active composition in the lower urinary tract system during catheterisation.

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#### **BRIEF DESCRIPTION OF THE DRAWINGS**

The invention is disclosed more in detail with reference to the drawings in which Fig 1-4 shows examples of patterns formed by zones of active ingredients (1) on a tubular catheter element (12) with eyes (9).

25 Fig 5 shows a package with a compartment (5) containing a gel. The compartment has a tip (2), which is removed before use and a sealing (3) which is broken as the catheter element (4) is pushed through the compartment containing the gel (1).

30 Fig 6 shows a cross section (length direction) of a catheter element (6) without eyes and with a discrete unit dose in the shape of a pill (7) placed on the proximal end of the catheter element. The discrete unit dose further comprises a film (8) covering the pill.

Fig 7 shows a cross section (perpendicular to the length direction) of a wing catheter (10) with a substance containing active ingredients in the concave corner (11).

## 5 DETAILED DESCRIPTION OF THE PRESENT INVENTION

### Device for urinary catheterisation

This invention relates to a device for urinary catheterisation, said device comprising a catheter element adapted to be inserted in the urethra of a human, and a  
10 pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents, and said catheter element is adapted to deliver at least a part of said pharmaceutically active composition in the lower urinary tract system during catheterisation.

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A device according to the invention comprises a pharmaceutically active composition, which has an effect on the continence system, and a catheter element for drainage of urine from the bladder and for delivering the pharmaceutically active composition in the urethra during the catheterisation procedure. In addition to  
20 catheterisation, a device according to the invention is thus performing a local medical treatment of the lower urinary tract system, such as urethra or bladder with the aim of treatment, alleviation or prophylaxis of incontinence.

Urinary catheterisation may be performed using an intermittent or an indwelling  
25 catheter. In a preferred embodiment of the invention, a device is provided for intermittent catheterisation. The proximal end of the catheter element is adapted to be inserted in the urethra, typically the catheter element is part of a urinary catheter, the urinary catheter further comprising a handle or connector element attached to the distal end of the catheter element. For most embodiments, the type  
30 of catheter element is not essential to the invention and could be of any type, such as disclosed in PCT/DK02/00449. In addition to tubular catheters for which the drainage canal is defined by the catheter material, preferable embodiments of

the present invention could comprise a catheter element of wing catheter type, for which the urethra form a part of the drainage canals. The catheter element may be adapted to fit the urethra or males, females or children.

- 5 The delivery of the pharmaceutically active composition in the lower urinary tract system may include active delivery mechanisms, such as injection of the active agents through a cavity in the catheter, which may be separated from the cavity used for drainage of urine. Such active delivery mechanisms typically compli-  
10 cates the device and its use, as the pharmaceutically active composition is often provided separately and additional steps in the procedure of catheterisation is introduced due to the delivery of the pharmaceutically active composition.

- More preferred is a passive delivery mechanism, i.e. the catheter element carries the pharmaceutically active composition on the outside surface of the insertable  
15 part of the catheter element, i.e. the surface adapted to contact the urethra. At least a part of the pharmaceutically active composition is deposited in the urinary tract system during catheterisation as a result of the friction, body heat, humid environment, osmosis etc. encountered in the body. Preferably the pharmaceuti-  
20 cally active composition is delivered in the urinary tract system solely by such passive mechanism, eliminating the need for additional steps in the procedure of catheterisation due to the delivery of a pharmaceutically active composition. This also simplifies the device, as the pharmaceutically active composition is typically an integrated part of the catheter element.

- 25 The part of the pharmaceutically active composition to be delivered in the urinary tract system may be placed on the outer surface of a proximal part of the catheter element prior to insertion, in accordance with a passive delivery mechanism, as the outer surface is brought in contact with the cavities of the urinary tract sys-  
30 tem, so that the pharmaceutically active composition can be passively delivered from the catheter element.



In a preferred embodiment of the invention, a major part of said pharmaceutically active composition is present on an outer surface of the catheter element before insertion of said catheter element. Typically substantially all of the pharmaceutically active composition may be present on an outer surface of the catheter element prior to insertion of the catheter element.

In a further embodiment of the invention the device is provided in a sealed package, wherein a major part of said pharmaceutically active composition is present on an outer surface of the catheter element, i.e. the catheter element is pre-treated with the pharmaceutically active composition prior to opening the package to expose said catheter element.

In one embodiment of the invention the catheter element is adapted for intermittent catheterisation. In this case the catheter element should be able to deliver the pharmaceutically active composition very quickly, i.e. in less than 2 minutes, which is the average normal time for intermittent catheterisation. The active ingredient should preferably work in the urethra for approx. 2-4 hours, in between catheterisations. In another embodiment of the invention the active substance is released more slowly and the time spend by the catheter element in the urethra by intermittent catheterisation is extended. In a further embodiment the release of the active agents is adapted to take place with the catheter element permanently placed in the urethra.

In one embodiment of the invention, the catheter element is comprised in a female catheter. Accordingly the catheter element is adapted to fit the female urethra, i.e. it has a length in the range of 50-200mm, such as 130-180mm, such as in a length in the size of 150mm or even as short as 50-90 mm, such as in the range of 55-85 mm, such as in the range of 60-80 mm, such as a length in the size of 70 mm.

In one embodiment of the invention, at least a part of the active composition is provided in a coating covering at least a portion of the outer surface of a proximal part of the catheter element and the coating is adapted to release said pharma-

ceutically active composition within the lower urinary tract system. The coating could be a polymer coating, of which at least a portion is impregnated with at least a part of the pharmaceutically active composition. At least a portion of the catheter could have a hydrophilic coating adapted to reduce friction between the catheter element and urethra for a more comfortable insertion. In one embodiment of the present invention this hydrophilic coating and/or the swelling medium for swelling the hydrophilic coating may contain at least a part of the pharmaceutically active composition. In another embodiment of the present invention a hydrophilic coating and a coating containing the active ingredients could be applied to the catheter element in an alternating pattern to create zones adapted to deliver active ingredients alternating with zones adapted to reduce friction. Examples of patterns of distribution are shown in Fig 1-4. The zones of active ingredients could be constrained to a part of the catheter element such as the tip. The coating containing active ingredients could have hydrophobic properties, e.g. for resistance to a liquid swelling medium.

In one embodiment of the invention the pharmaceutically active composition is distributed over a section of the catheter element having a length of at least 50% of the total length of the catheter element. A section of the catheter element is a part of the catheter element bounded by one or two cross sections perpendicular to the long axis of the catheter element. This drug delivering section may constitute a major section of the catheter element having a length of at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% of the total length of the catheter element, such as essentially the full insertable length of the catheter element. Thus the treatment may be extended to a major part of the urethra.

Also a high-viscosity coating may be provided by means of a gel or crême or alternatively liquid, solution or spray may be used. In one embodiment at least a part of the active composition is provided in a gel or crême adapted for application to at least a portion of the catheter element. In a preferred embodiment the active composition is integrated in a gel that pre-lubricates the catheter element

to reduce friction between the catheter element and urethra for a more comfortable insertion. In this case there is no need for a hydrophilic coating, since the gel in itself would provide the lubricating effect. In one embodiment of the present invention the gel is applied in the production procedure, i.e. the catheter is provided in a pre-treated condition. In another embodiment the gel and the catheter element is provided in a catheter assemblage adapted for application of the gel to the catheter element prior to use by the person performing the catheterisation. An example is a catheter package including an Oestriol-containing gel. In an embodiment of the invention the gel is provided in a separate container adapted for application of the gel to the catheter element by squeezing the container. In another embodiment the package hosting the catheter element has a compartment adapted to hold the gel. In a further embodiment the gel is applied to the catheter element by pressing the catheter element through the compartment containing the gel. An example of this solution is shown in Fig 5.

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In another embodiment the catheter element has depressions on the outer surface, which are adapted to hold at least a part of the active agents. In case of a wing catheter active ingredients could be provided in the concave corners of the catheter as shown in Fig 7. Fig 1-4 gives examples of a tubular catheter with depressions forming a pattern of zones containing at least one active ingredient. In a further embodiment of the invention, release of the active ingredients in the urethra is promoted by a consistency regulating agent, which e.g. become more viscous when warmed to body temperature, and is either used in the matrix or as a slip layer between catheter element and the pharmaceutical composition or as a cover on top of the active ingredients which is melted or dissolved by contact with urine and/or body heat.

The catheter element may be provided with a capping covering at least a part of the pharmaceutically active composition. Preferably the capping comprises a material, which is dissolved or melted by contact with urine and/or body heat, e.g. PVA.

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In another embodiment of the invention, at least a part of the pharmaceutically active composition is provided in a separate discrete unit dose, such as a pill or ampoule, and the catheter device is adapted to insert this discrete unit dose in the lower urinary tract system. In one embodiment a pill could be placed on the tip of the catheter and capped with a film, which is dissolved or melted by contact with urine and/or body heat, such as PVA. An example of this embodiment is shown in Fig 6. This solution has the advantage that a tubular catheter element does not need eyes, i.e. drainage holes in the side of the tubular member, since the pill provide a rounded end of the catheter element for comfortable insertion. Hence the catheter can be made about 2 cm shorter and discomfort due to the eyes is avoided.

A further aspect of the invention is to provide a kit comprising a device for urinary catheterisation and a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents , said device comprising a catheter element adapted to be inserted in the urethra of a human.

In particular the catheter element and the pharmaceutically active composition may be provided separately. This may in particular be the case when the pharmaceutically active composition is provided in the form of a gel or crème for application to the catheter element.

#### **Pharmaceutically active composition**

The present invention allows for medical treatment of the continence system. In a first embodiment of the invention, the pharmaceutically active composition contains active agents for treatment of the urethral mucosa, such as agents effective against urethral atrophy. Certain hormones have proven valuable for preventing and treating urethral atrophy. Examples include oestrogens and oestrogen derivatives such as oestriol or oestradiol.

In one embodiment of the invention the pharmaceutically active composition comprises at least one hormone. In a further embodiment of the invention the hormone is a female sex hormone. This embodiment of the device is especially suitable for treating incontinence in women, e.g. by treatment with a pharmaceutically active composition effective against urethral atrophy. Also in women with imperative urge to urinate and possibly accompanying urge incontinence because of postmenopausal changes in the urethral mucosa, estrogens (e.g. estradiol and estriol) have a positive effect on these symptoms.

10 In a further embodiment of the invention the hormone is estrogen or an estrogen derivative. Estrogens may increase urethral pressure by increasing the thickness of the urethral mucosa. Moreover, estrogens may increase the number of adrenergic receptors on urethral smooth muscle. The estrogen can have several different forms including natural, synthetic, or semi-synthetic compounds. Examples of  
15 estrogens include estradiol, diethyl stilbestrol, estrone, estrone sodium sulfate, sodium equilin sulfate, ethinyl estradiol, quinestrol, diethylstilbestriol, mestranol, estriol, and chlorotrianisene. In a preferred embodiment of the invention the pharmaceutically active composition comprises oestriol or oestradiol.

By coating an intermittent catheter with a hormone such as Oestriol or Oestradiol,  
20 the active ingredient is delivered to the urethral mucosa directly and this treatment could alleviate the symptoms caused by urethral atrophy in between the catheterisations.

The primary effect of the device is drainage of urine, the secondary effect is supplying the urethral epithelium with oestriol to achieve better continence in between catheterisations by mucosal proliferation and additional effects as described above.  
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Compared to known treatments, the purpose of urethral administration is to achieve better effect on urological symptoms than vaginal or oral administration, and to avoid the side effects seen by systemic administration.  
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In another embodiment of the present invention at least a part of the pharmaceutically active composition could be selected to have an effect on the unstriated musculature or the neuromuscular junction. Examples of such active ingredients with a desired effect comprise anticholinergical drugs and capsaicin.

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The pharmaceutically active composition may comprise efferent blocking agents for lessening the parasympathetic efferent activity (blocking the pelvic nerve-detrusor smooth muscle colinergic transmission), and/or agents for increasing sympathetic activity and/or afferent blocking agents for blocking the afferent arm of the reflex causing the bladder contraction may also be used.

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Efferent blocking agents includes parasympatolytica or spasmolytica, such as anticholinergica. Examples are Cetiprin (Emepron), Detrusitol (Tolterodin), Urispadol (Flavoxat), Atropine, oxybutynin and Spasmo-Lyt (Trospiumchlorid).

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In one embodiment of the invention the pharmaceutically active composition comprises an efferent blocking agent selected from the group consisting of anticholinergical agents, sympathomimetics agents, alfa-adrenergic agonists and nicotinic cholinergic agonists.

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In a preferred embodiment of the invention the pharmaceutically active composition comprises oxybutynin or trospiumchlorid.

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In another embodiment of the invention the pharmaceutically active composition comprises an afferent blocking agent, such as Capsaicin, RTX and Local anaesthetic drugs.

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When treating detrusor hyperreflexia, the group of parasympatolytica or spasmolytica can be used to relax the bladder wall musculature. Parasympatolytica in general can have unpleasant sideeffects on other systems, e.g. dry mouth, accommodation difficulties, tendency of constipation. Parasympatolytica with specific

effect on the bladder is therefore preferable. It is shown that intravesical (local) administration of anticholinergic drugs has very good effect and produces fewer sideeffects than orally administered anticholinergics.

- 5 The pharmaceutically active composition may also comprise sympathomimetic agents (agents increasing sympathetic activity). Sympathomimetic agents generate urethral pressure by increasing the tone of the internal sphincter. The sympathomimetic agent will stimulate the .alpha.-adrenergic receptors in the internal sphincter, which will increase its tone. The internal sphincter will then tighten  
10 around the urethra and the neck of the bladder.

alpha-Adrenergic agonists are one type of sympathomimetic agent that can be effective. Various types of alpha-adrenergic agents include phenylephrine HCl, pseudoephedrine HCl, phenylpropanolamine HCl, ephedrine sulfate, norephedrine HCl, xylometazoline HCl, oxymetazoline HCl, naphazoline HCl, norepinephrine HCl, and privine HCl. Examples of other sympathomimetic agents include norepinephrine uptake inhibitors such as desipramine HCl, amitriptyline HCl, desmethylimipramine HCl, and imipramine HCl. Yet another sympathomimetic agent includes norepinephrine releasing agents such as tyramine.  
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Nicotinic cholinergic agonists and acetylcholinesterase inhibitors increase the tone of the external sphincter. Additionally, either of these types of agents can be combined with muscarinic cholinergic antagonist such as atropine, scopolamine, or glycopyrrolate. In this type of treatment, the agent will stimulate the nicotinic cholinergic receptors in the external sphincter, which will increase its tone and cause it to tighten around the urethra. Examples of nicotinic cholinergic agonists include choline, acetylcholine, methacholine, carbachol, bethanechol, arecoline, and 1,1-dimethyl-4-phenylpiperazinium iodide. Examples of acetylcholinesterase inhibitors include physostigmine salicylate, neostigmine bromide, ambenonium chloride, edrophonium chloride, demecarium bromide, and pyridostigmine bromide.  
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Additionally, estrogens and sympathomimetics such as an alpha-adrenergic agonist can be used in combination. Current medical research indicates that estrogens may increase the number of alpha-adrenergic receptors in the internal sphincter. Thus, the alpha-adrenergic agonists will stimulate both the preexisting and newly developed alpha-adrenergic receptors. The increased number of alpha-adrenergic receptors will cause the sphincter muscles to respond more efficiently to the alpha-adrenergic agonists and have an even greater increase in tone.

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The pharmaceutically active composition may in addition to the therapeutic agents for medical treatment of incontinence also comprise enhancing agents for enhanced penetration of the therapeutic agents through the urothelium lining of the urethra and into the tissue of the urethral wall. Examples of penetration enhancers include 1->2-(decylthio)ethylazacyclopentan-2-one; 1-dodecylazacycloheptan-2-one; dimethylsulfoxide; 1-menthol; and 1-lauryl-2-pyrrolidone.

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### **Medical treatment**

A further aspect of the invention relates to the use of a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents, for the manufacture of a device for the treatment, alleviation or prophylaxis of incontinence in a human, said device comprising a catheter element adapted to be inserted in the urethra of said human, said catheter element comprising the pharmaceutically active composition, and said catheter element being adapted to deliver said agent in the lower urinary tract system during catheterisation.

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The catheter element comprises the pharmaceutically active composition, in the form of an impregnation, coating, substance distributed over the catheter or in

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any other way previously disclosed. Also the device may have any features previously described.

In one embodiment of the invention the use in particular relates to females.

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A further aspect of the invention is to provide a method of treating a human suffering from or being susceptible to incontinence, the method comprising the steps of catheterisation of said human by arranging a proximal end of a catheter element of a device for urinary catheterisation in the urethra of said human, said  
10 catheter element comprising a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents, and said catheter element being adapted to deliver said composition in the lower urinary tract system during catheterisation.

15

The catheter element comprises the pharmaceutically active composition, in the form of an impregnation, coating, substance distributed over the catheter or in any other way previously disclosed. Also the device may have any features previously described.

20

In one embodiment of the invention the method in particular relates to females.

#### **Device comprising discrete unit dose**

A second objective of the invention is to provide a device for urinary catheterisation, comprising a catheter element with a proximal end adapted for insertion in a  
25 urinary canal, and a discrete unit dose containing a pharmaceutically active composition. The catheter element is adapted to shed the discrete unit dose in the lower urinary tract system during catheterisation.

30 The urinary canal is in particular the natural urethra of men, women or children, but the invention may in some cases be useful even for delivering a pharmaceutically active composition through an artificial urinary canal to the bladder. The

catheter element may be e.g. a tubular catheter for draining urine through an internal duct or a wing catheter for draining urine in external ducts partly bounded by the urinary canal, the catheters being provided in dimensions to fit the urinary canals in males, females or children.

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The pharmaceutically active composition may comprise any active agents suitable for administration in the lower urinary tract system e.g. antibacterial agents, or active agents for treatment of incontinence, such as disclosed in this document regarding the first aspect of the invention.

10

The discrete unit dose may be a pill, tablet, capsule, ampoule etc, containing a pharmaceutically active element comprising a pharmaceutically active composition. The pharmaceutically active element may be in solid form, shaped to constitute the discrete unit dose. The discrete unit dose may also comprise a capping, in the shape of a film or coating, covering at least a part of the pharmaceutical active element. This is e.g. advantageous when the pharmaceutically active element is not in solid form. The discrete unit dose may be attached to the catheter by means of the capping. Preferably the capping is made of a material, which is dissolved or melted by contact with urine and/or body heat, e.g. PVA. In this manner the discrete unit dose is released by the insertion into the urinary tract system. In one embodiment of the invention the pharmaceutically active element is placed in contact with the catheter element and a capping, such as a film covers the discrete unit dose and a proximal part of the catheter element. In another embodiment the capping extends at least between the catheter element and the discrete unit dose. In this case the discrete unit dose may adhere to the catheter element by means of the capping material. As an alternative the discrete unit dose may be unattached to the catheter element. According to this alternative the catheter element may have a depression, wherein the discrete unit dose may be seated. As an example the catheter element may have a depression at the tip, wherein the discrete unit dose may be seated, to be pushed through the urinary in front of the catheter element.

30

The pharmaceutically active element may be deposited in the urethra during catheterisation, e.g. during insertion of the catheter. Typically, however, the pharmaceutically active element composition is delivered in the bladder.

- 5 In a preferred embodiment of the invention the discrete unit dose is placed on the tip of the catheter. Usually, urinary catheters have a rounded tip, to allow comfortable insertion of the catheter and avoid damaging urethra and bladder. The opening or openings in a tubular catheter for drainage of urine are thus placed as 'eyes' in the side wall a small distance, e.g. in the order of one or a few cm from
- 10 the tip. In a preferred embodiment of the present invention, the catheter has a tubular proximal section, the proximal end of said tubular proximal section having an opening for draining urine from the outside of the catheter to the inside of the tubular section. The discrete unit dose may then be placed proximally at the tip of the catheter element, to provide a smooth tip thereby preventing the edges of the
- 15 opening from cutting in the urinary canal. Evidently the unit dose may also be used in combination with a wing catheter to provide a smooth tip on the catheter element. For a tubular catheter element a further advantage is that the catheter element does not need eyes, i.e. drainage openings in the side of the tubular member, since a drainage opening is provided in the proximal end of the tubular
- 20 section, with the discrete unit dose providing a rounded, smooth tip on the catheter, to support comfortable and non-traumatic insertion of the catheter. Hence the catheter can be made about 2 cm shorter. Furthermore the eyes typically present in known catheters must be carefully rounded and smoothed to prevent cutting in the urethra and even then the eyes may still cause discomfort and damage to the
- 25 tissue, as the urethra in some cases tends to be sucked into the eyes of the catheter, especially during withdrawal of the catheter from the bladder.

- In one embodiment the drainage openings of the catheter are covered by the discrete unit dose and the drainage openings are uncovered as the discrete unit
- 30 dose is delivered in the body of a human.

## Claims

1. A device for urinary catheterisation, said device comprising a catheter element adapted to be inserted in the urethra of a human, c h a r a c t e r i s e d i n that  
5 said device is comprising a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents, and said catheter element is adapted to deliver at least a part of said pharmaceutically active composition in the lower urinary tract system during catheterisation.  
10
2. A device according to claim 1, wherein a major part of said pharmaceutically active composition is present on an outer surface of the catheter element before insertion of said catheter element.
- 15 3. A device according to claim 1 or 2, said device being provided in a sealed package, wherein a major part of said pharmaceutically active composition is present on an outer surface of the catheter element.
- 20 4. A device according to any of the preceding claims, wherein the pharmaceutically active composition is distributed over a section of the catheter element having a length of at least 50% of the total length of the catheter element.
5. A device according to any of the preceding claims, wherein the catheter element is adapted for intermittent catheterisation.
- 25 6. A device according to any of the preceding claims, wherein said catheter element is comprised in a female catheter.
- 30 7. A device according to any of the preceding claims, wherein said catheter element has a coating covering at least a portion of the outer surface of the catheter element and said coating contains at least a part of said pharmaceutically active composition and is adapted to release said pharmaceutically active composition within the lower urinary tract system.

8. A device according to any of the preceding claims, wherein at least a part of said catheter element has a polymer coating, and at least a portion of said polymer coating is impregnated with at least a part of said pharmaceutically active composition.
- 5
9. A device according to any of the preceding claims, wherein at least a portion of said catheter element has a hydrophilic coating.
- 10
10. A device according to claim 12, wherein said hydrophilic coating is impregnated with at least a part of said pharmaceutically active composition.
11. A device according to any of the preceding claims, wherein said catheter element has depressions on the outer surface, which are adapted to hold at least a part of said pharmaceutically active composition.
- 15
12. A device according to any of the preceding claims, wherein at least a part of said pharmaceutically active composition is provided in a gel or crème.
- 20
13. A device according to any of the preceding claims, wherein said device is comprising a lubricating gel adapted to reduce friction between the catheter element and urethra, and said gel is containing at least a part of said pharmaceutically active composition.
- 25
14. A device according to any of the preceding claims, wherein said device is comprising a discrete unit dose containing said pharmaceutically active composition said device is adapted to shed said discrete unit dose in the lower urinary tract system.
- 30
15. A device according to any of the preceding claims, wherein said pharmaceutically active composition comprises a hormone.

16. A device according to claim 15, wherein said hormone is a female sex hormone or a derivative thereof.
17. A device according to any of the preceding claims, wherein said hormone is selected from oestrogen or an oestrogen derivative.
18. A device according to claim 16 or 17, wherein said hormone is oestriol or oestradiol.
19. A device according to any of the preceding claims, wherein said pharmaceutically active composition comprises an efferent blocking agent selected from the group consisting of anti-cholinergical agents, sympathomimetics agents, alfa-adrenergic agonists and nicotinic cholinergic agonists.
20. A device according to claim 19, wherein said efferent agent is oxybutynin or trospiumchlorid.
21. A device according to any of the preceding claims, wherein said pharmaceutically active composition comprises an afferent blocking agent.
22. Use of a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sympathomimetic agents , for the manufacture of a device for the treatment, alleviation or prophylaxis of incontinence in a human, said device comprising a catheter element adapted to be inserted in the urethra of said human, said catheter element comprising the pharmaceutically active composition, and said catheter element being adapted to deliver said agent in the lower urinary tract system during catheterisation.
23. The use according to claim 22, wherein the human is a female.

24. The use according to any of the claims 22-23, wherein the device is as defined in any of claims 1-21.
- 5 25. A method of treating a human suffering from or being susceptible to incontinence, the method comprising the steps of catheterisation of said human by arranging a proximal end of a catheter element of a device for urinary catheterisation in the urethra of said human, said catheter element comprising a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and  
10 sympathomimetic agents , and said catheter element being adapted to deliver said composition in the lower urinary tract system during catheterisation.
26. The method according to claim 25, wherein the human is a female.
- 15 27. The method according to any of claim 24-25, wherein the device is as defined in any of claim 1-21.
28. A kit comprising a device for urinary catheterisation and a pharmaceutically active composition comprising at least one agent selected from the group consisting of hormones, efferent blocking agents, afferent blocking agents and sym-  
20 pathomimetic agents , said device comprising a catheter element adapted to be inserted in the urethra of a human.
29. A device for urinary catheterisation, said device comprising a catheter element with a proximal end adapted to be inserted in a urinary canal, c h a r a c t e  
25 r i s e d i n that said device is comprising a discrete unit dose, said discrete unit dose comprising a pharmaceutically active composition and said catheter element being adapted to shed said pharmaceutically active composition in the lower urinary tract system during catheterisation.  
30
30. A device according to claim 29, wherein said discrete unit dose is placed at the tip of the catheter.

31. A device according to claim 29 or 30, wherein said catheter has a tubular proximal section, the proximal end of said tubular proximal section having an opening for draining urine from the outside of the catheter to the inside of the tubular section.  
5

32. A device according to any of claims 29-31, wherein said discrete unit dose comprises a capping, covering at least a part of the pharmaceutically active composition, said capping being dissolved or melted by contact with urine and/or body heat.  
10

33. A device according to claim 32, wherein said discrete unit dose is attached to the catheter by means of said capping.

15 34. A device according to claim 32 or 33, wherein said capping is provided as a film covering at least a part of the pharmaceutically active element and at least a part of the catheter element.



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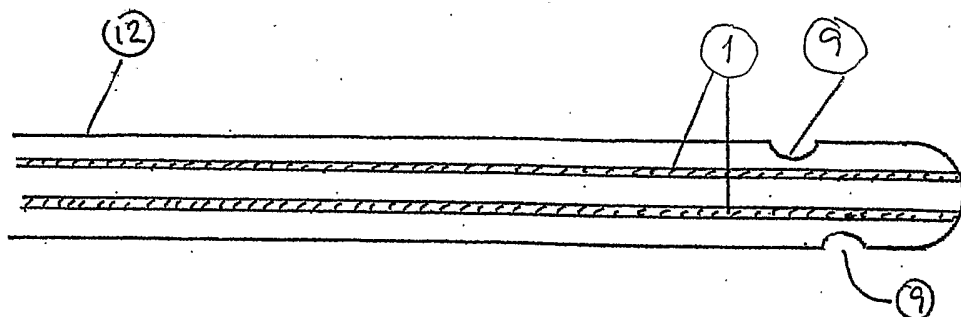


Fig. 1

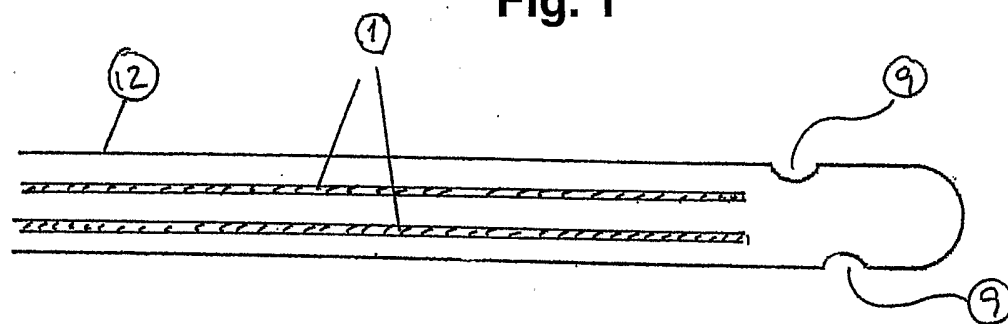


Fig. 2

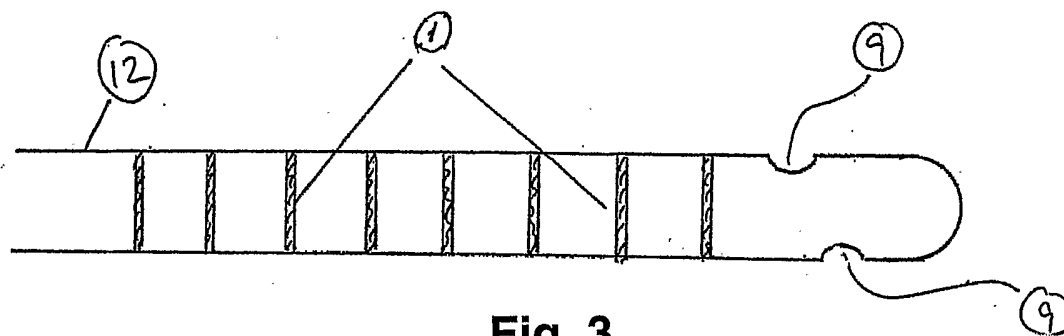


Fig. 3

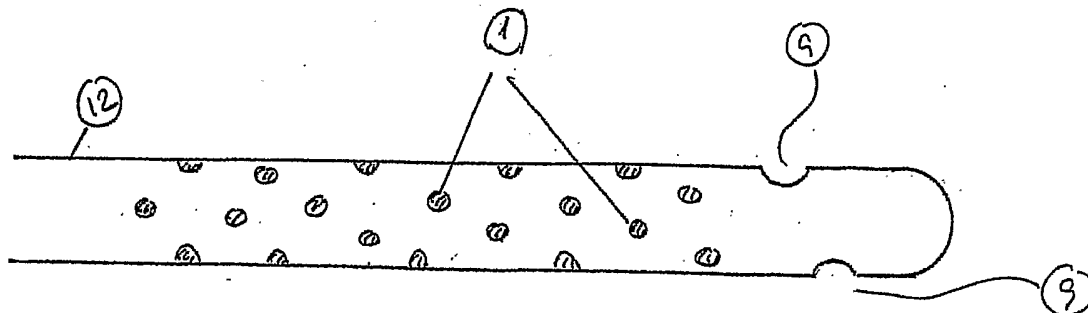


Fig. 4

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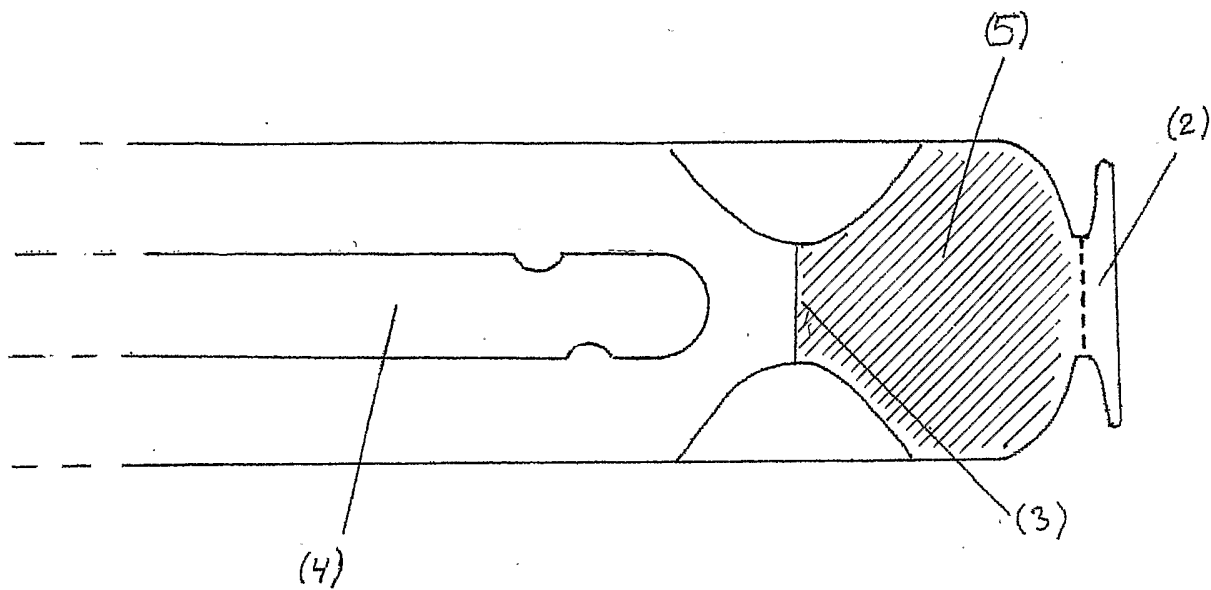


Fig. 5

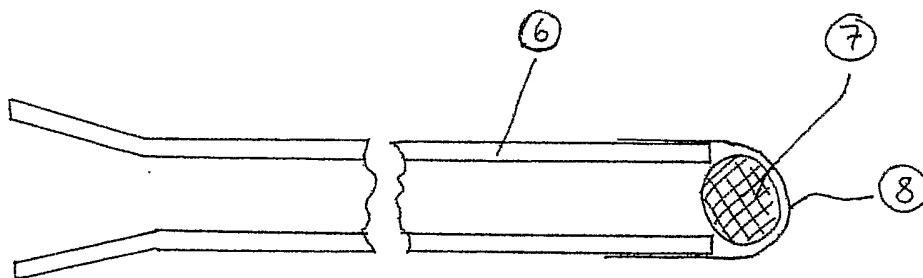


Fig. 6

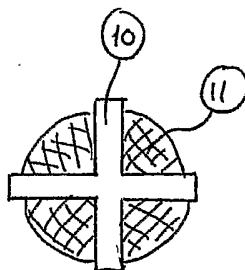


Fig. 7

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK 03/00853

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61M25/00 A61M25/01 A61L29/16

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61M A61L

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, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91/00074 A (NILSSON LEIF) 10 January 1991 (1991-01-10) page 8, line 2 - line 20; figures -----	1,2,5,6, 15-22,28
X	US 6 048 332 A (DUFFY NIAL ET AL) 11 April 2000 (2000-04-11)  column 3, line 10 - column 4, line 42; figures -----	1,6,11, 12, 15-22,28
X	WO 02/24246 A (HUNTER GARY FRANCIS) 28 March 2002 (2002-03-28)  the whole document -----	1-10,12, 13, 15-22,28
X	US 4 603 152 A (LAURIN DEAN ET AL) 29 July 1986 (1986-07-29) column 3, line 55 - line 62; figures -----	1-8, 15-22,28

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents:

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

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

Date of the actual completion of the international search

14 April 2004

Date of mailing of the international search report

21/04/2004

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Authorized officer

Kousouretas, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00853

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 053 905 A (WALLS JAMES A ET AL) 25 April 2000 (2000-04-25) abstract; figures	29-31
X	US 6 050 934 A (JOHNSON SHELLEY N ET AL) 18 April 2000 (2000-04-18)  column 12, line 64 - column 13, line 9; figures	1,2,5,6, 12,22, 24,28
A	US 3 598 127 A (WEPSIC JAMES G) 10 August 1971 (1971-08-10) the whole document	1,2,4-6, 11
A	US 4 834 711 A (GREENFIELD ALBERT R ET AL) 30 May 1989 (1989-05-30) abstract; figures	1-22,24, 28

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 03/00853

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 23, 25-27  
because they relate to subject matter not required to be searched by this Authority, namely:  
Article 34(4)(a)(i) and Rule 67.1(ii) PCT for claim 23  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery for claims 25-27
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00853

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9100074	A	10-01-1991	SE 465999 B 02-12-1991
			AT 102814 T 15-04-1994
			AU 5939590 A 17-01-1991
			BR 9007479 A 16-06-1992
			CA 2063257 A1 29-12-1990
			DE 69007483 D1 21-04-1994
			DE 69007483 T2 23-06-1994
			DK 479935 T3 30-05-1994
			EP 0479935 A1 15-04-1992
			ES 2049993 T3 01-05-1994
			JP 2947610 B2 13-09-1999
			JP 4506468 T 12-11-1992
			KR 157987 B1 15-12-1998
			SE 8902333 A 29-12-1990
			WO 9100074 A1 10-01-1991
			SE 9002267 A 29-12-1990
			SE 9002268 A 29-12-1990
<hr/>			
US 6048332	A	11-04-2000	NONE
<hr/>			
WO 0224246	A	28-03-2002	AU 9006001 A 02-04-2002
			EP 1324785 A1 09-07-2003
			WO 0224246 A1 28-03-2002
			US 2004030301 A1 12-02-2004
<hr/>			
US 4603152	A	29-07-1986	AU 582796 B2 13-04-1989
			AU 4861885 A 17-04-1986
			EP 0197068 A1 15-10-1986
			JP 62500432 T 26-02-1987
			WO 8602006 A1 10-04-1986
			US 4677143 A 30-06-1987
			ZA 8507530 A 28-05-1986
			AU 2039883 A 22-05-1984
			CA 1224717 A1 28-07-1987
			EP 0124536 A1 14-11-1984
			ES 8504464 A1 16-07-1985
			WO 8401721 A1 10-05-1984
			<hr/>
US 6053905	A	25-04-2000	AU 3306299 A 06-09-1999
			CA 2287187 A1 26-08-1999
			EP 0977610 A2 09-02-2000
			JP 2001517136 T 02-10-2001
			WO 9942155 A2 26-08-1999
<hr/>			
US 6050934	A	18-04-2000	NONE
<hr/>			
US 3598127	A	10-08-1971	NONE
<hr/>			
US 4834711	A	30-05-1989	NONE
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