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— with amended claims and statement (Art. 19(1))

(54) Title: BIOCOMPATIBLE GRAFT, IN COATED SILICONE, FOR PERMANENT IMPLANT FOLLOWING EXCISION OF THE IPP PLAQUE

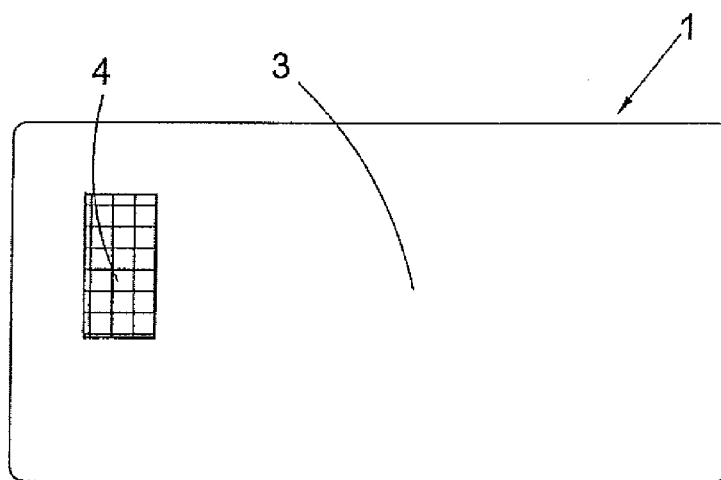


FIG. 2a

(57) Abstract: A description is given of a graft (1) for permanent implant after excision of the IPP (induratio penis plastica) plaque due to Peyronie's disease characterised in that it comprises an elastic and soft membrane (2), in vulcanised silicone, which is coated by a layer (3) of pyrolytic turbostratic carbon or by amorphous diamond-like carbon.

BIOCOMPATIBLE GRAFT, IN COATED SILICONE, FOR PERMANENT IMPLANT FOLLOWING EXCISION OF THE IPP PLAQUE

DESCRIPTION

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The present invention relates to a graft in biocompatible material to be used in the field of urology, in particular as permanent dermic implant in the excision of the IPP (induratio penis plastica) plaque due to Peyronie's disease.

10 Peyronie's disease, whose cause is not yet fully known, affects the male genital organ and causes in it a varyingly accentuated penile deformity due to the presence of one or more hard fibrous plaques, with a nodular appearance, located above the cavernous bodies (corpora cavernosa) of the penis, in particular at the level of the tunica albuginea (the sheath that covers the cavernous bodies of the penis and which represents the bearing
15 structure which determines the rigidity of the penis in erection) with irreversible degeneration of the albugineous elastic component.

The area of fibrosis, defined generically as "plaque", determines a curving of the penis towards the diseased side. This disease is associated with severe pain and erectile
20 dysfunction in that the disappearance of the elastic fibres of the albuginea, which takes place in favour of the growth of the dense fibrous tissue of the plaque, constitutes an alteration of the mechanical characteristics of the cavernous bodies.

When the disease has stabilised (for at least six months) and is such as to jeopardise the
25 sexual function, surgical treatments are required such as surgery on the albuginea or complete excision of the plaque.

The current trend is that of complete excision (removal) of the plaque and a consequent replacement of the removed section with a dermic implant or graft made up of autologous
30 tissue (that of the patient, such as for example the dermis of the patient's thigh) in that a tissue is required which undergoes a natural histological transformation, maintaining the elastic fibres contained therein, to allow the recovery of the function of the organ: in fact in the processes of tissue repair the production of elastic tissue is not foreseen but only of fibrous tissue since only fibroblasts and not elastoblasts exist in the cell matrix.

35

Implants, also known as grafts, allow the restoring of the original length of the side

affected by the scar retraction which shorten the length of the penis, acting at the same time as support for the autologous tissue of the patient which will form with passing time over said graft.

- 5 The synthetic implants in the art of corporoplasty mentioned above are little used in that their physiopathological features of grafting do not allow the reconstruction of a symmetrical and congruous cavernous albugineous membrane.

10 It is in fact known that their mechanism of grafting does not foresee vascular inosculation but only their fibroblast encapsulation: this would entail a structure of replacement of the albuginea without elastic fibres and therefore not extensible, and a fibrous reaction of the erectile tissue below the implant with tendency towards retraction.

15 In the cases of serious erectile deficit another type of surgical technique is used which provides for the use of penile prostheses of various types, soft, malleable, hydraulic, in order to straighten and/or lengthen the organ and reobtain the erection, in combination with autologous dermic grafts. This technique however entails a high percentage of infective complications when dermic grafts of the autologous type are used, due to the presence of staphylococci.

20 Nor does the use of heterologous grafts (SIS) or synthetic grafts (GORETEX), although avoiding the aforesaid complications, guarantee the obtaining of a high elasticity due to their tendency towards retraction and the low quality of the tissue reconstruction around them.

25 Another surgical technique consists of surgery of resection/incision of the plaque, excision of the albuginea and of the cavernous bodies, and implanting of a graft, preferably autologous of saphenous vein, between the albuginea and the cavernous bodies. In this case too, according to the type of graft, the disadvantages stated above may
30 occur.

Neither does the use in the aforesaid techniques of grafts in absorbable materials, which thus do not require removal, guarantee a high quality of the tissue reconstruction since around them a growth occurs of slightly keloid and hypertrophic neotissue having lower
35 quality than the original pre-excision tissue.

Therefore it is highly desirable to have available implants, particularly synthetic implants, of a permanent type which maximise the features of elasticity, almost as much as the original tissue, and which determine a better quality of the tissue reconstruction, similar to the original pre-excision tissue, with the creation of elastoblasts as well as the fibroblasts without granulomas, keloids, hypertrophic tissues and the like, minimising the reaction of retraction at the implant, and infective reactions.

The object of the present invention is to provide a permanent graft for excision of IPP which overcomes the disadvantages stated above and suffered by the prior art, in particular to provide a biocompatible graft, highly elastic, which has a reduced formation of the fibrotic capsule around it, also when replacing an extended IPP plaque, and which can be used in any type of surgical operation, corporoplastic operation or excision, without generating infections, which allows a tissue reconstruction of quality similar to the original pre-excision tissue, with low tendency towards retraction, and which does not need subsequent surgical removal.

Another object of the present invention is that of providing such a graft which is also easily made, economical, reliable, functional and durable.

These objects are achieved by the synthetic graft according to the invention in biocompatible material made from silicone coated with a particular carbonaceous material which has the features of the annexed independent claim 1.

Advantageous embodiments of the invention are disclosed by the dependent claims.

The graft according to the invention for implant after the excision of the plaque of IPP (induratio penis plastica) due to Peyronie's disease is made with a highly biocompatible material made up of a soft and elastic membrane, in vulcanised silicone, having at least both the upper and lower surfaces coated by a layer of pyrolytic turbostratic carbon or amorphous diamond-like carbon, preferably by pyrolytic turbostratic carbon.

"Membrane" here is used to identify a sheet (or slab) in polymeric material (i.e. silicone) obtained by moulding, casting, dipping and the like, and accordingly not in the form of fabrics, gauzes, nets or the like which are instead obtained by spinning of threads/yarns deriving from polymeric fibres.

Amorphous diamond-like carbon is a carbon coating, white or transparent, with layered structure similar to the diamond (defined in fact as "diamond-like carbon" (DLC)) with outstanding features of surface resistance such as hardness and resistance to abrasions, as well as being well tolerated by the skin and resistant to corrosion but elastic.

5

Moreover it is neutral when in contact with cells and micro-organisms: this entails a rapid population by the cells and an accelerated assimilation of the implanted device. At the same time the adhesion is reduced due to the reduced interaction between the coated surface and the biological molecules.

10

Moreover the amorphous diamond-like carbon creates smooth surfaces, without incrustations.

This coating of amorphous diamond-like carbon can also be "doped" with various compounds to achieve oil repellency or water repellency.

15

Said layer of coating preferably covers said membrane completely, including its lateral edges.

The DLC (diamond-like carbon) coating process can take place according to a known technique, such as for example PVD.

20

The coating in pyrolytic turbostratic carbon also has features of surface resistance, resistance to abrasions, resistance to corrosion. Moreover said pyrolytic turbostratic carbon is neutral when in contact with cells and micro-organisms: this entails a rapid population by the cells and an accelerated assimilation of the implanted device.

25

At the same time the adhesion of the pyrolytic turbostratic carbon to the tissues is almost totally absent due to the reduced interaction between the coated surface and the biological molecules. In this way a substantial absence is obtained of the phenomenon of fusion to the surrounding tissues which takes place instead when other materials are used, for example a membrane of only silicone such as that described in WO 2009/131682.

30

The silicone in fact has the tendency to co-penetrate with the polyprotein fibrotic growth (red blood cells) and to fuse with the neotissues: therefore a graft in silicone can be used for a temporary implant or graft, up to 30 days, and then has to be removed as

35

subsequently the silicone starts to graft with the fibrotic capsule and the neotissues.

The tissues which are reconstructed around the present membrane in coated silicone are moreover of similar quality to the original pre-excision tissue, both that of the cavernous
5 bodies placed below the graft and that of the tunica albuginea placed over said graft, in particular they show substantially the same original elasticity. More particularly the aforesaid coated membrane allows the tissue which goes to form over it (tunica albuginea) to grow symmetrical and congruous in that this membrane has a low tendency towards retraction.

10 The aforesaid coating materials make the synthetic membrane in silicone highly biocompatible, conferring to the graft of the present invention a series of advantages as will be described herein below.

15 The Applicant has unexpectedly found that the membrane in coated silicone as described above is able to withstand high expansions and/or elongations, both in a longitudinal and transverse direction, of approximately 2-3 times its dimensions, which enables its use as permanent implant in the excision of the IPP plaque.

20 This could not be inferred from the prior art in that coated silicone membranes are used currently for the temporary replacement of a portion of bladder wall which, as is known, has to withstand dilations, due to its expanding and emptying, of a much smaller extent compared to the dilations (elongation and expansion) which a graft for permanent implant in the excision of the IPP plaque has to withstand.

25 In fact the carbon coating described above, more particularly pyrolytic turbostratic carbon, has been found to be capable of not reducing the elasticity of the underlying silicone membrane.

30 The graft in accordance with the present invention is in general planar, rectangular or square in shape, with variable dimensions according to the possible approximate dimensions of the plaque.

A dimensional example of this graft is 5 cm x 10 cm.

35 Said graft is in the form of a membrane and can be sutured to the incision by means of

suture yarn with diameter of 3/0 or 4/0, in absorbable material, for example PGA, or a non-absorbable one.

As mentioned, the graft of the invention has at least the two upper and lower surfaces
5 coated with pyrolytic turbostratic carbon or amorphous diamond-like carbon, and the layer of said coating appears smooth without any surface texturisation.

Further features of the invention will be made clearer by the following detailed description referred to some of its embodiments purely by way of a non-limiting
10 example, illustrated in the accompanying drawings, in which:

Fig. 1a is a plan view from above of a first embodiment of the graft;

Fig. 1b is a side view of the graft illustrated in Fig. 1a;

Fig. 2a is a plan view from above of a second embodiment of the graft;

Fig. 2b is a frontal side view of the graft of Fig. 2a;

15 Figs. 3a-3c are views illustrating the possible positionings of the graft of Fig. 1 on the penile organ in ventral, dorsal, lateral position respectively;

Fig. 4 is a view in cross section of a penile organ which has the IPP plaque.

Referring to Figures 1a and 1b, the body of the graft 1 is formed by a multilayer
20 membrane 2, in silicone, provided with sufficient flexibility and elasticity, in such a way as to ensure the proper functioning of the penile organ after having applied said graft.

The overall thickness of said membrane in silicone is not binding for the purposes of the present invention even if an example can be constituted by a value of around 600
25 microns.

The thickness of the layer of coating 3 in pyrolytic turbostratic carbon or in amorphous diamond-like carbon is also not binding for the purposes of the present invention and can be for example a microfilm of approximately 0.2 – 0.3 micron.
30

Additionally the number of layers and the thickness of the single layer of the multilayer membrane 2 are also not binding for the purposes of the present invention: for example this membrane 2 can be made up of twenty layers of silicone, each one having a thickness of approximately 30 microns.
35

The multilayer membrane 2 in silicone which forms the body of the graft 1 in accordance

with the invention can be made according to a known technique, for example according to what is described in the international applications WO 2007/039159 and WO 2007/039160 in the name of the Applicant.

- 5 That is to say the multilayer membrane 2 of soft silicone, with a thickness of approximately 600 microns, is obtained from the raw material of silicone, by means of a procedure of processing known as dipping.

This technique of multilayer dipping consists of forming the first layer, making it
10 evaporate with cyclohexane for 10 minutes, superimposing the second layer, making it evaporate again with cyclohexane for 10 minutes, and so on as far as the final layer. At this point the layered membrane 2 of silicone is in a semifluid state, and is then placed in the oven for vulcanisation, at a temperature of approximately 150°C and for a time
15 varying from 30 min. to 1 h, on the basis of the size of the graft that is to be formed. After the cycle of vulcanisation the multilayer membrane 2 of silicone is in its consistency of optimal elasticity and softness, and no longer in the semifluid state.

The silicone used can be made up, for example, of copolymers of dimethyl and metavinyl siloxane, reinforced with silicon. A silicone for medical use is preferably used, such as
20 for example the soft elastomeric silicone with high tensile strength and high elongation known by the code MED 4735™ and marketed by the company Nusil Technology.

This silicone has an elongation which was found to be particularly suitable for the application in the construction of a graft to be applied after excision of the IPP plaque.

25 Subsequently a layer of pyrolytic turbostratic carbon or of amorphous diamond-like carbon 3 is applied according to a known technique, both on the lower surface and on the upper one of this membrane 2, preferably on all the surfaces of said membrane including the lateral edges.

30 Should a more rigid graft be needed, it is also possible to use a graft in silicone made up of the same coated membrane 2 described above yet which incorporates internally, in the thickness, a synthetic mesh 4 of reinforcement (Fig. 2a), in Dacron or another similar material, also suitable for facilitating its suturing.

35 Said mesh 4 is inserted by means of a known technique, for example, moulding, dipping

or similar techniques which allow said mesh to be incorporated in a layer of silicone. Subsequently the layer 3 of pyrolytic turbostratic carbon or amorphous diamond-like carbon is applied on the surface of the membrane according to a known technique.

5 The graft 1 in accordance with the invention is intended to be placed and implanted above the cavernous bodies 10 (Figs. 3a-3c, 4), and below the tunica albuginea, after having removed (excision) the IPP plaque 11 (Fig. 4) and being sutured in proximity of the tunica albuginea 12, after having performed an incision of the dermis 15 (Fig. 4) and of the Buck's fascia 14 (Fig. 4) according to the known techniques of surgery.

10

The function of said graft 1 is to encourage, from both the quality and quantity standpoint, the re-epithelialisation and the reconstruction of the cavernous bodies and of the albuginea, damaged following excision of the IPP plaque.

15 It should also be noted that this graft 1, thanks to the elasticity of the silicone and of the coating described above, allows the physiological movement of the male organ during and after this process of re-epithelialisation and reconstruction of the cavernous bodies and of the albuginea, that is to say also after reconstruction has occurred, without impacting on performances, so that once the graft has been implanted it no longer has to
20 be removed.

The advantages of the use of a graft in coated silicone as defined above are considerable, for example allowing completely revascularised tissue growth, without infections, without tissue fusion on its surface, showing at the same time high elasticity, greater than
25 the autologous grafts of saphenous vein.

In particular said graft combines a high elasticity, understood as high elongation and/or expansion, in general equal to two-three times its dimensions at rest, with a high biocompatibility, understood as the capacity to minimise the formation of granulomas, keloids, hypertrophic tissues and infections, leading to a better quality of the tissue
30 reconstruction, in particular of the cavernous albuginous sheath, substantially similar to the original pre-excision tissue, and with low tendency towards retraction.

These features mean that the membrane in coated silicone in accordance with the present
35 invention can be used in a permanent and definitive manner in the excision of the IPP plaque, without any need for removal.

The graft 1 is prepared in a controlled environment that is to say with controlled contamination, in a white room. Once processing has finished, the graft 1 is placed in a double blister closed with sheet of Tyvek to avoid contaminations and sent to a cycle of sterilisation with base of ETO (ethylene oxide).

5

At this point the graft 1 is ready to be used in an operation.

Numerous detail variations and changes can be made to the present embodiment of the invention, within the reach of a person skilled in the art and in any case coming within
10 the scope of the invention expressed by the annexed claims.

CLAIMS

1. Use as graft (1) for permanent implant after excision of the IPP (induratio penis plastica) plaque, due to Peyronie's disease, of an elastic and soft membrane (2), in
5 vulcanised silicone, having at least both the upper and lower surfaces coated by a layer (3) of pyrolytic turbostratic carbon or amorphous diamond-like carbon, preferably pyrolytic turbostratic carbon.
2. Use according to claim 1 wherein the surface of said coating layer (3) of said
10 membrane (2) is smooth.
3. Use according to claim 1 or 2 wherein the thickness of the membrane (2) is approximately 600 microns.
- 15 4. Use according to any one of the previous claims wherein said membrane (2) is formed by twenty layers of silicone.
5. Use according to any one of the previous claims wherein the thickness of the layer (3) of pyrolytic turbostratic carbon or of amorphous diamond-like carbon is comprised
20 between approximately 0.2 – 0.3 micron.
6. Use according to any one of the previous claims wherein the silicone consists of copolymers of dimethyl and metavinyl siloxane, reinforced with silicon, preferably silicone for medical use, more preferably soft elastomeric silicone with high tensile
25 strength and high elongation such as MED 4735™.
7. Use according to any one of the previous claims wherein the silicone membrane (2) internally incorporates, within its thickness, a synthetic mesh (4) in Dacron or another similar material.
30
8. Use according to any one of the previous claims wherein the shape is planar, rectangular or square, preferably rectangular with dimensions of 5 cm x 10 cm.
9. Use according to any one of the previous claims wherein its suture to the incision is
35 performed by means of suture yarn with diameter of 3/0 or 4/0, in absorbable material, for example PGA, or a non-absorbable one.

10. Graft (1) as defined in any one of previous claims 1 to 9.

AMENDED CLAIMS + STATEMENT

received by the International Bureau on 14 May 2012 (14.05.2012)

1. **Graft (1)** for **use in** permanent implant after excision of the IPP (induratio penis plastica) plaque, due to Peyronie's disease, **said graft (1) being made** of an elastic and soft membrane (2), in vulcanised silicone, having at least both the upper and lower surfaces coated by a layer (3) of pyrolytic turbostratic carbon or amorphous diamond-like carbon, preferably pyrolytic turbostratic carbon.
2. **Graft for use** according to claim 1 wherein the surface of said coating layer (3) of said membrane (2) is smooth.
3. **Graft for use** according to claim 1 or 2 wherein the thickness of the membrane (2) is approximately 600 microns.
4. **Graft for use** according to any one of the previous claims wherein said membrane (2) is formed by twenty layers of silicone.
5. **Graft for use** according to any one of the previous claims wherein the thickness of the layer (3) of pyrolytic turbostratic carbon or of amorphous diamond-like carbon is comprised between approximately 0.2 – 0.3 micron.
6. **Graft for use** according to any one of the previous claims wherein the silicone consists of copolymers of dimethyl and metavinyl siloxane, reinforced with silicon, preferably silicone for medical use, more preferably soft elastomeric silicone with high tensile strength and high elongation such as MED 4735™.
7. **Graft for use** according to any one of the previous claims wherein the silicone membrane (2) internally incorporates, within its thickness, a synthetic mesh (4) in Dacron or another similar material.
8. **Graft for use** according to any one of the previous claims wherein the shape is planar, rectangular or square, preferably rectangular with dimensions of 5 cm x 10 cm.
9. **Graft for use** according to any one of the previous claims wherein its suture to the incision is performed by means of suture yarn with diameter of 3/0 or 4/0, in absorbable material, for example PGA, or a non-absorbable one.

10. Use of an elastic and soft planar membrane (2), in vulcanised silicone, having at least both the upper and lower surfaces coated by a layer (3) of pyrolytic turbostratic carbon or amorphous diamond-like carbon, preferably pyrolytic turbostratic carbon, for the preparation of a graft (1) for permanent implant after
5 excision of the IPP (induratio penis plastica) plaque, due to Peyronie's disease.

11. Use according to claim 10 wherein the thickness of the membrane (2) is approximately 600 microns, said membrane (2) being optionally formed by twenty
10 layers of silicone.

13. Use according to any one of the previous claims wherein the thickness of the layer (3) of pyrolytic turbostratic carbon or of amorphous diamond-like carbon is comprised between approximately 0.2 – 0.3 micron.

15 14. Use according to any one of the previous claims 10-13 wherein the silicone consists of copolymers of dimethyl and metavinyl siloxane, reinforced with silicon, preferably silicone for medical use, more preferably soft elastomeric silicone with high tensile strength and high elongation such as MED 4735™.

20 15. Use according to any one of the previous claims 10-14 wherein the silicone membrane (2) internally incorporates, within its thickness, a synthetic mesh (4) in Dacron or another similar material.

25

Statement under Article 19(1) PCT

Original claims 1-9 are deleted.

Original claim 10 is changed by rewording as "graft for use in..." and by dividing it into new claims 1 to 9.

New claims 10-15 are added.

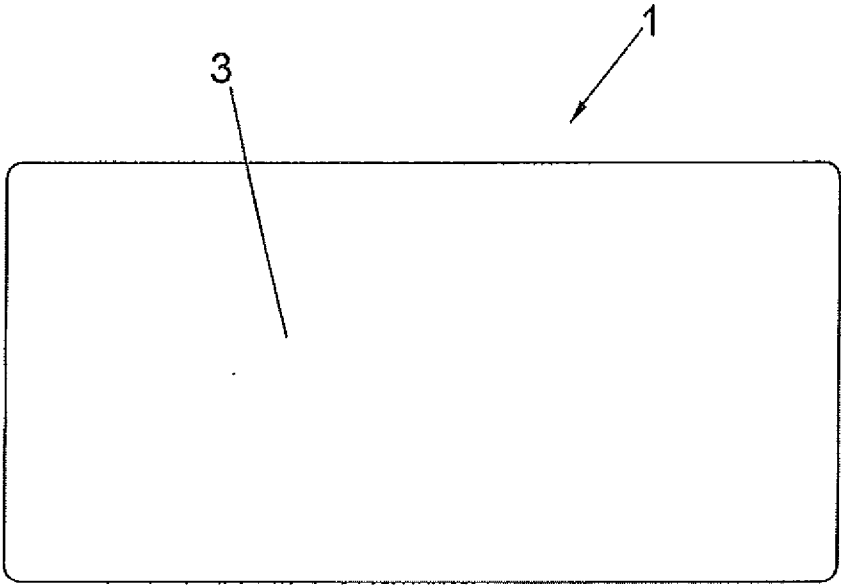


FIG. 1a

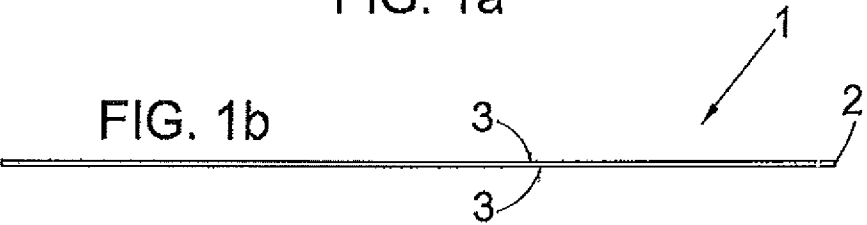


FIG. 1b

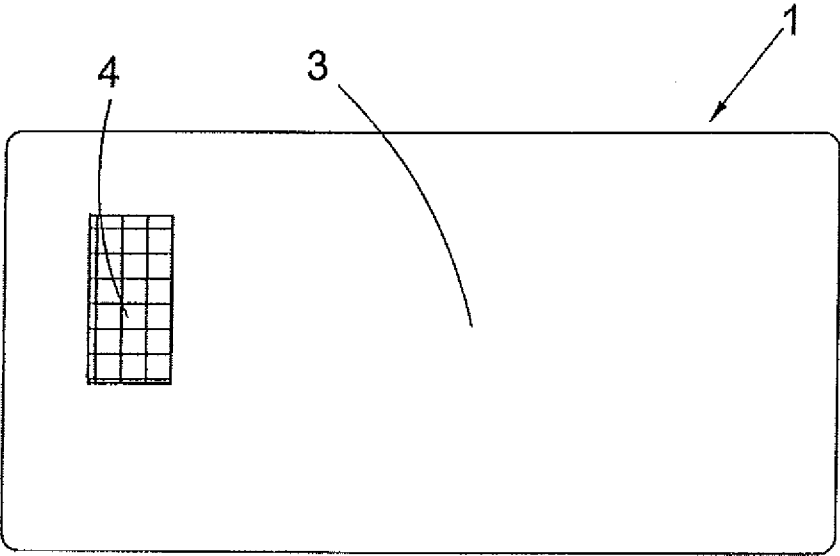


FIG. 2a

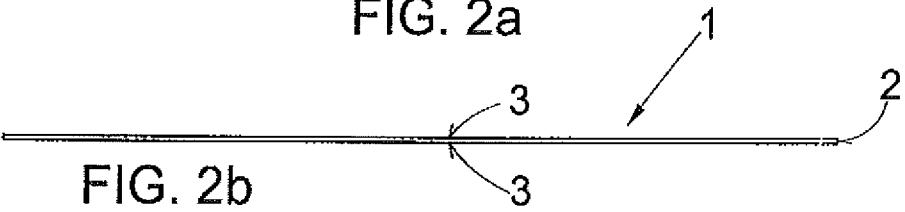


FIG. 2b

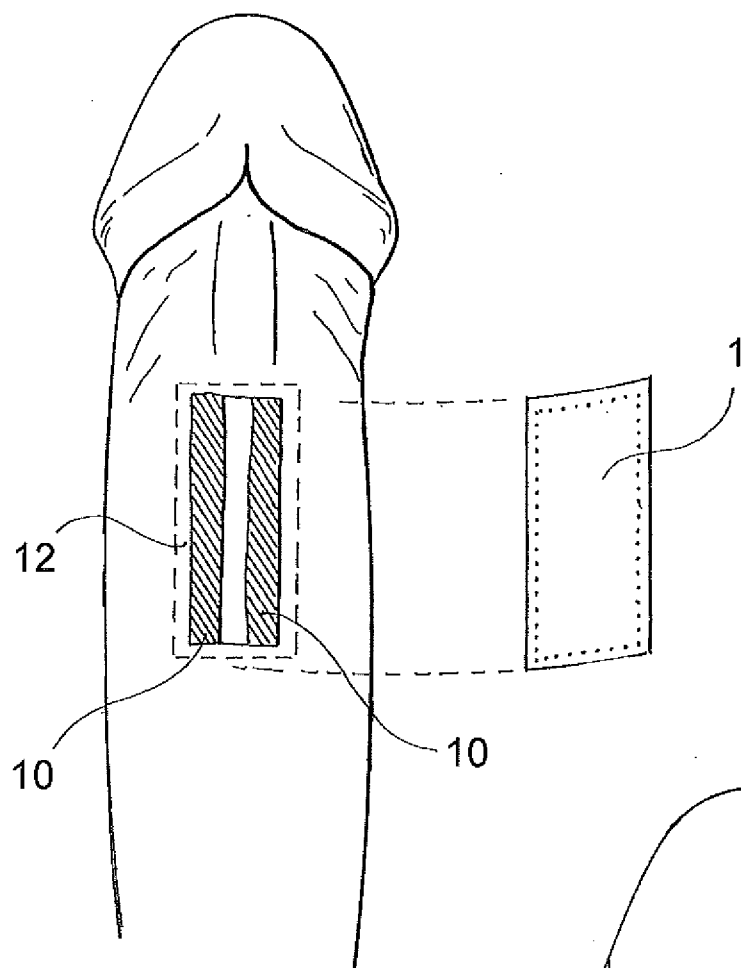


FIG. 3a

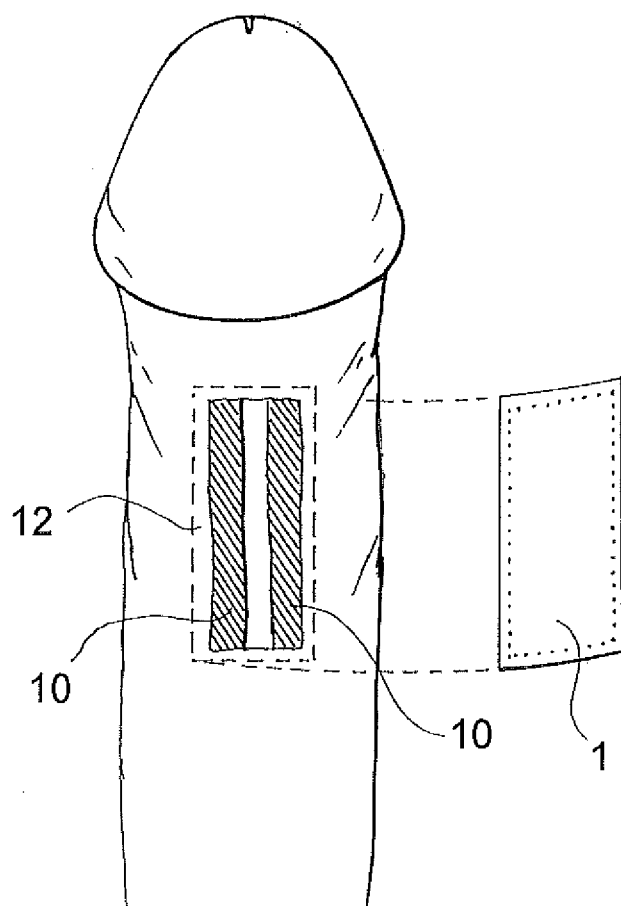


FIG. 3b

FIG. 4

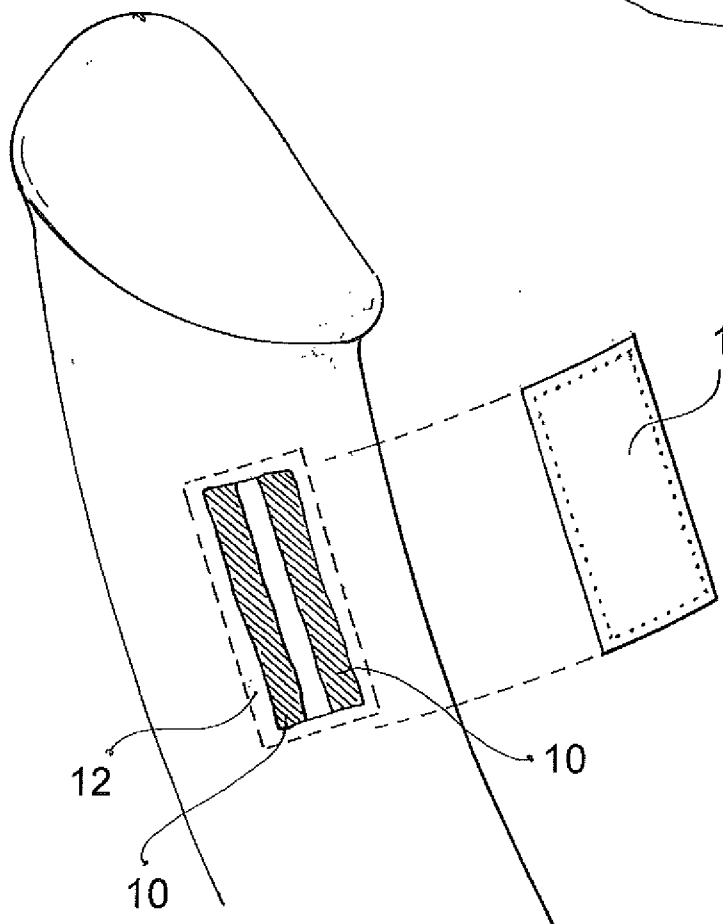
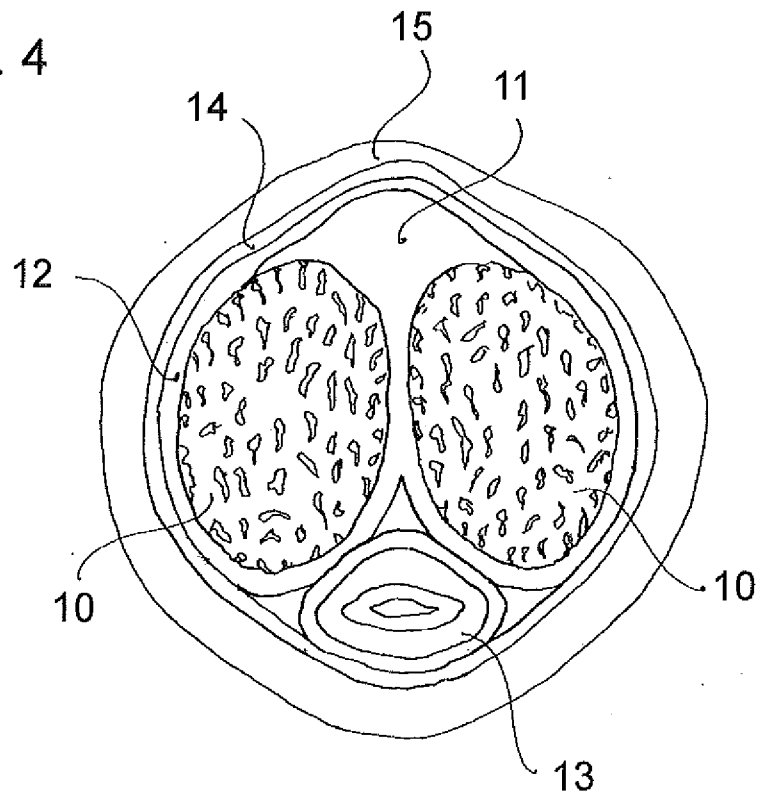


FIG. 3c

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/051775

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 1-9
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/051775

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61F2/00 A61F2/26
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/039160 A1 (SAMBUSSETI ANTONIO [IT]) 12 April 2007 (2007-04-12) page 2, line 35 - page 3, line 33 page 4, line 27 - line 29 page 5, line 31 - line 36 -----	10
A	WO 2009/131682 A1 (MARDIL INC [US]; RAMAN JAISHANKAR [US]; LEINSING KARL R [US]) 29 October 2009 (2009-10-29) paragraph [0026] - paragraph [0028] paragraph [0036] - paragraph [0037] -----	10
X	WO 2009/033528 A1 (SAMBUSSETI ANTONIO [IT]) 19 March 2009 (2009-03-19) page 3, line 9 - page 4, line 10 ----- -/-	10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 March 2012

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