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(71) Applicant: JSF CONSULTANTS LTD. [US/US]; 50 East 79th Street, Suite 5C, New York, NY 10021 (US).

(72) Inventor: FREED, Jeffrey, S. ; 50 East 79th Street, Suite 5C, New York, NY 10021 (US).

(74) Agents: DOW, Karen, B. et al.; Townsend and Townsend Khourie and Crew, One Market Plaza, 20th Fl., Steuart Tower, San Francisco, CA 94105 (US).

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(54) Title: USE OF INJECTABLE BIOMATERIALS IN THE TREATMENT OF HEMORRHOIDS

(57) Abstract

This invention discloses methods of treating hemorrhoids and/or pruritis ani by administering an effective amount of an injectable biomaterial into the soft tissues of the anal verge. Preferred biomaterials to be used in this invention are collagen formulations.

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USE OF INJECTABLE BIOMATERIALS IN THE TREATMENT OF HEMORRHOIDS

Technical Field

This invention is in the field of medical implants and prostheses. Specifically, it concerns a nonsurgical technique for treating hemorrhoids and pruritis ani, a related condition, by injecting biomaterials into the soft tissue of the anal verge.

BACKGROUND OF THE INVENTION

The anatomy of the region known as the anal canal is complex and the etiology of the condition known as hemorrhoids has long been the subject of research and reexamination. The anal columns (folds of epithelia and muscle tissue) and anal sinuses (furrows separating the anal columns from each other) are found at the upper end of the anal canal. The anal sinuses end in valve-like folds, called the anal valves, and the anal canal is vascularized by veins derived from the superior and inferior rectal (hemorrhoidal) veins. The vascular tissues of the anal canal, known as the anal cushions, are found in the left lateral, right posterior, and right anterior positions of the anal canal, at or above the level of the anal valves. The anal cushions are submucosal and comprise blood vessels (mainly veins) supported by smooth muscle (Treitz's muscle) and connective tissue. The anal verge refers to the external or distal boundary of the anal canal; that is, the line where the anal walls contact during the normal state of apposition.

Hemorrhoids are believed to be caused by breakdown in the connective tissue and smooth muscle that support the anal cushions, causing displacement of the cushions into the lumen of the distal canal. This is especially likely to occur when there is a history of constipation or prolonged straining at stool, leading to stretching or disruption of Treitz's muscle together with venous engorgement. Once the cushions are displaced, the venous engorgement may be perpetuated by a tight internal anal sphincter.

Each hemorrhoid consists of an internal and external component. The internal component lies above the line of the anal valves, known as the dentate or pectinate line. The external component lies below this line. The internal and external component are clearly distinguished by a groove and by a differential epithelial covering. The internal component is usually covered with columnar epithelium, while the external is covered with skin and stratified squamous epithelium.

A number of predisposing factors for the development of hemorrhoids are known, such as heredity, pregnancy, and pelvic tumors. However, in the majority of patients, no explanation for the onset of hemorrhoids can be found. Hemorrhoids, rarely present before the third decade of life, are commonly associated with the aging process. In fact, aging weakens the connective tissue support of the anal cushions, resulting in increased venous dilatation. Although hemorrhoids occur in both sexes, they predominate in men, despite the predisposing factor of pregnancy.

Although not a life-threatening condition, the symptoms of hemorrhoids can cause the sufferer a great deal of discomfort and concern. Symptoms of hemorrhoids include anorectal bleeding during defecation; discomfort, pain, and/or itching in the perianal area (pruritis ani); prolapse of submucosal tissue into the anus during defecation; swelling at the anal margin due to the external component of the hemorrhoid becoming engorged with blood; and excessive mucus production and discharge due to inflammation.

Traditional classification of hemorrhoids is based only on the symptoms of bleeding and prolapse. First degree hemorrhoids are characterized by bleeding only. Second degree hemorrhoids involve prolapse of submucosal tissue at defecation (with or without bleeding) with spontaneous return of the tissue to the anal canal; whereas third degree hemorrhoids are defined by prolapse (with or without bleeding) requiring manual replacement of tissue into the anal canal. Fourth degree hemorrhoids protrude permanently and cannot be reduced or replaced manually.

Hemorrhoids are treated in response to a patient's complaints of symptoms. Dietary modification, specifically increasing the consumption of dietary fiber, has been shown to have moderate success in the treatment of minor bleeding. Topical ointments, pharmaceutical preparations, and related application devices have long been described in the art for the treatment of mild symptoms.

Various mechanical, electrical, and thermal (both heat and cold) devices for treating more severe degrees of hemorrhoids have been described in the art. U.S. Patent 3,826,242 describes a tubular member that is inserted into the anal canal, engaging the walls of the canal and the area around the rectal opening, which maintains pressure on the hemorrhoidal veins of the anal canal, lower rectum, and anal area during defecation to prevent swelling and distention of the hemorrhoidal veins and extrusion of the internal hemorrhoidal veins out of the anal canal during defecation. A device that is inserted into the rectum to treat hemorrhoids by application of gentle pressure against the dilated veins is disclosed in U.S. Patent 4,583,542. U.S. Patent 4,906,239 describes a cone-shaped hemorrhoid treatment rod to dilate the anus. U.S. Patent 4,932,397 discloses a therapeutic, horseshoe-shaped rectal device, comprising a malleable core element surrounded by a resilient covering, for alleviating hemorrhoids by protecting the irritated anorectal area from pressure and friction.

U.S. Patent 4,898,169 describes an instrument for direct current electrical therapy of hemorrhoids. U.S. Patents 4,142,529 and 4,227,535 disclose a suppository appliance that intimately contacts the anal canal wall and hemorrhoids. The appliance contains an internal electrical resistor for generating heat in response to the application of electrical energy, which maintains the temperature of the appliance above body temperature and below 45°C, thereby facilitating the opening of the vascular channels and allowing shrinkage of the hemorrhoids. A chemical-containing device for insertion into the anal canal that raises the temperature of the wall surface to approximately 45°C is described in U.S. Patent 4,696,302.

U.S. Patent 4,331,151 describes a hemorrhoid bandage or cold pack that is positioned within the anal canal to continuously supply a cool fluid to provide a controlled temperature within the rectal area for extended periods of time in connection with the treatment of hemorrhoids. U.S. Patent 4,563,182 discloses the use of a cylindrical insert comprising a water-expandable polymer which has been previously frozen that is inserted into the rectum to treat hemorrhoids. A cryogenic proctologic insert for treating hemorrhoids by lowering the surface temperature of the affected portion of the rectal canal is disclosed in U.S. Patent 4,841,970.

Any electrical, mechanical, or thermal device that is inserted into the body is unfortunately subject to complications resulting from the malfunction, breakage, or displacement of the device. Any such device is also inherently not "natural" to the body. Therefore, other methods are used to treat hemorrhoids. For example, traditional nonsurgical therapies for hemorrhoids include sclerotherapy, rubber band ligation, anal dilatation, cryotherapy, and photocoagulation. These procedures all have comparable success rates in the treatment of first and second degree hemorrhoids. However, all have side effects and result in tissue destruction. Complications range from flatulence to death as a result of infection or excessive bleeding.

Sclerotherapy involves the injection of solutions containing carbolic acid into the submucosa proximal to the hemorrhoidal mass to induce fibrosis of the hemorrhoid. This procedure is seldom used in the treatment of hemorrhoids due to unpredictable results and because the procedure is very subject to physical error. Complications of this therapy may include ulceration, pain, abscess and oleogranuloma (if oil-containing solutions are used), bleeding, and bacteremia.

Although less subject to physician error, rubber band ligation is generally more uncomfortable than sclerotherapy. This treatment involves applying a rubber band to the non-innervated portion of mucosa above the hemorrhoidal mass to induce necrosis of the hemorrhoid. Though rare, complications may be potentially serious or life-threatening. Delayed

hemorrhage due to localized infection and ulceration occurs in about one percent (%) of patients and may result in massive bleeding requiring hospitalization.

The technique of anal dilatation is believed to lower intra-anal pressures and relieve hemorrhoidal congestion through traumatic disruption of anal fibrotic bands. However, because many surgeons find such uncontrolled trauma to the sphincter mechanism offensive, this procedure has not received widespread acceptance in the United States. Also, the complication rate is relatively high (approaching 10%), with the most frequent complications being splitting of the anal canal, mucosal prolapse, and anal incontinence.

Cryotherapy relies on the thermal destruction of hemorrhoidal cells. Complications include discomfort, swelling and edema associated with excessive drainage, and prolonged drainage and recovery time when compared with the other nonsurgical techniques. Photocoagulation involves the use of infrared rays to coagulate the hemorrhoidal mass, resulting in tissue necrosis. Complications include discomfort and minor bleeding.

Surgical hemorrhoidectomy remains the standard against which the success of alternative treatments is judged. However, even "minor surgery" involves inherent risks. Therefore, surgical hemorrhoidectomy is avoided by physicians whenever possible and is used only as a "last resort" in the most advanced cases: incarcerated hemorrhoids, necrotic hemorrhoids, or hemorrhoids with a significant external component.

A condition often related to hemorrhoids is pruritis ani. The prolapsing or inflamed hemorrhoids can cause excessive moisture and itching in the perianal region. The appearance of the perianal skin varies from patient to patient depending upon the severity of the condition. In mild cases, the skin may appear completely normal. If the condition is acute, the skin may be erythematous and weeping, with numerous excoriations. In chronic cases, the skin is thickened, leathery, and white. For mild conditions, dietary

modifications, such as increasing fiber, or topical treatments are sufficient to alleviate the burning and itching.

SUMMARY OF THE INVENTION

As with most diseases, the least invasive and/or destructive treatment that is effective should be offered to the patient. As hemorrhoids are normal anatomical structures, they preferably should not be removed or destroyed except in very advanced disease cases. Therefore, an ideal treatment for hemorrhoids and/or pruritis ani would comprise an effective nonsurgical procedure that is easy to administer, with little likelihood of physician error, a low rate of complications, no serious side effects, little tissue destruction, and a low risk for infection. An ideal hemorrhoid treatment would also be "natural" to the body and would not comprise any device that could potentially malfunction, break, or be displaced from its intended position.

The present invention meets all of the above criteria. As described herein, the invention teaches a method for treating hemorrhoids and/or pruritis ani by perianally administering an effective amount of an injectable biomaterial(s) into the soft tissues of the anal verge, thereby preventing the displacement of submucosal tissue into the anal canal.

DETAILED DESCRIPTION OF THE INVENTION

The invention is a nonsurgical method for treating hemorrhoids and/or pruritis ani by perianally administering an effective amount of an injectable biomaterial into the soft tissues of the anal verge to prevent the displacement of the submucosal tissue into the anal canal. The term "effective amount" as used herein, means the quantity of biomaterial needed to achieve significant improvement in the symptoms of hemorrhoids or pruritis ani or the quantity of wound healing agents needed to achieve improved healing. The effective amount of biomaterial administered may vary depending on the patient's own ability to absorb or break down the biomaterial, the consistency and concentration of the material, and the site

and condition being treated. Furthermore, the biomaterial may be administered over a number of treatment sessions in order to effect the improvement of hemorrhoid and related pruritis ani symptoms.

The biomaterial used in the invention may be selected from a number of sources; however, it must be injectable, biocompatible, essentially non-immunogenic, and persist at the site of placement for at least three months. Alternatively, the biomaterial may be an aqueous suspension of a biopolymer with a biocompatible fluid lubricant to improve the intrusion of the biopolymer into the tissue. See U.S. Patent 4,803,075, which is incorporated herein by reference. Commercially available suspensions of a biopolymer and fluid lubricant may be obtained from Bioplasty, Inc. (Minneapolis, Minnesota) under the tradename Bioplastique Micro-Implants. Fluid lubricants may include: hyaluronic acid, dextran sulfate, dextran, succinylated non-crosslinked collagen, methylated non-crosslinked collagen, glycogen, glycerol, dextrose, maltose, triglycerides of fatty acids, egg yolk phospholipids, heparin, and the like. Biopolymers may include: atelopeptide fibrillar, crosslinked or non-crosslinked collagen, gelatin beads, polytetrafluoroethylene beads, silicone rubber beads, hydrogel beads, silicon carbide beads, glass beads, and the like.

A preferred biomaterial comprises a collagen formulation. Most preferred are those collagen formulations wherein the collagen is atelopeptide fibrillar, crosslinked, or non-crosslinked collagen, or collagen mixed with a mineral material. Collagen is a major protein component of bone, cartilage, skin, and connective tissue in animals. Collagen in its native form is typically a rigid, rod-shaped molecule approximately 300 nanometers (nm) long and 1.5 nm in diameter. It is composed of three collagen polypeptides which form a tight triple helix. The collagen polypeptides are characterized by a long midsection having the repeating sequence -Gly-X-Y-, where X and Y are often proline or hydroxyproline, bounded at each end by the "telopeptide" regions, which constitute less than about 5% of the molecule.

The telopeptide region of the collagen chains are typically responsible for the crosslinking between chains and for the immunogenicity of the protein. Collagen occurs in types, of varying physical properties; the most abundant are Types I-III.

The collagen used in the invention may be collected from any number of mammalian sources, such as bovine or porcine corium and human placenta. The preparation of purified substantially nonantigenic collagen in solution from the skin is basically a three-step process involving solubilization, enzyme treatment, and purification. See U.S. Patents 4,140,537; and 4,488,911; which are incorporated herein by reference. The term "collagen" or "collagen material" as used herein refers to all forms of collagen, including those which have been processed or otherwise modified.

Preferred collagens are treated to remove the immunogenic telopeptide regions ("atelopeptide collagen"), are soluble, and will have been reconstituted into the fibrillar form ("atelopeptide fibrillar"). The reconstituted fibrillar collagen may optionally be crosslinked using methods generally known in the art, such as by heat, radiation, or chemical crosslinking agents. Commercially reconstituted collagens are available under the tradenames Zyderm Collagen Implant and Zyplast Collagen Implant (Collagen Corporation, Palo Alto, California). See U.S. Patents 4,582,640 and 3,949,073; which are incorporated herein by reference.

U.S. Patent 4,424,208; incorporated herein by reference, discloses an improved collagen formulation suitable for use in soft tissue augmentation. The formulation comprises reconstituted fibrillar atelopeptide collagen in combination with particulate, crosslinked atelopeptide collagen dispersed in an aqueous medium. The addition of particulate crosslinked collagen improves the biomaterial's persistence, or ability to resist shrinkage following injection.

U.S. Patent 4,557,764; incorporated herein by reference, discloses a "second nucleation" collagen precipitate which exhibits a desirable malleability and putty-like consistency. Collagen is provided in solution [e.g., at 2-4 milligrams per milliliter (mg/ml)], and a "first nucleation

product" is precipitated by rapid titration and centrifugation. The remaining supernatant (containing the bulk of the original collagen) is then decanted and allowed to stand overnight. The precipitated second nucleation product is collected by centrifugation.

Copending U.S. Patent Application Serial No. 07/433,441, incorporated herein by reference, discloses an improved injectable collagen formulation which is conjugated to a chemically activated polymer, such as polyethylene glycol. The conjugated collagen has improved persistence at the implantation site. Also disclosed in the pending application is a method for crosslinking the collagen material with a bifunctional activated polymer in situ, such as polyethylene glycol. This improved process method allows the collagen implant to be crosslinked to the host tissue by the activated polymer.

Another embodiment of the biomaterial to be used in the invention includes a high collagen concentration formulation, which is disclosed in copending U.S. Patent Application Serial No. 07/843,770, filed 28 February 1992. (Attorney Number 05921-13) incorporated herein by reference. Briefly, collagen in solution (Vitrogen 100 Collagen, Celtrix Laboratories, Palo Alto, California) is reconstituted to fibril form by neutralizing the solution with the addition of a phosphate buffer at ambient temperatures. The resultant fibrillar collagen may be optionally crosslinked using standard techniques known in the art prior to concentration. The high concentration collagen materials disclosed herein are passed through a homogenizer (HC5000, Microfluidics Corporation, Newton, Massachusetts) to improve the extrudability of the material through a fine gauge needle. High concentrations of non-crosslinked and crosslinked fibrillar collagen are expected to have improved persistence compared to commercially available forms.

Another particularly useful biomaterial to be used in the disclosed invention is described in copending U.S. Patent Application Serial No. 07/843,646, filed 28 February 1992; (Attorney Number 05921-11) incorporated herein by reference,

which describes an injectable collagen/ceramic formulation. Briefly, porous and/or non-porous ceramic particles are prepared to have a uniform particle size distribution in the range of about 50-250 microns. The preferred ceramic particles are admixed with fibrillar collagen to produce an injectable ceramic/collagen formulation. The addition of the ceramic particles improves the persistence of the injectable collagen formulation.

Other commercially available biomaterials useful in the described invention are a polytetrafluoride (Teflon) paste, known as Polytef Paste, and a porcine collagen particulate suspended in saline, known as Fibrel Gelatin Matrix Implant (both available from Mentor Corporation, Santa Barbara, California). Further biomaterials include fluid suspensions containing: gelatin beads, glass beads, hydrogel beads, silicone rubber or carbide beads, polytetrafluoride beads, and the like.

An effective amount of wound healing agents may be added to the biomaterial used in the invention. These agents include protein growth factors such as fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), connective tissue activated peptides (CTAPs), transforming growth factors (TFGs), and the like. These biologically active agents are known to facilitate regrowth of connective tissue cells and accumulation of fibroblasts, endothelial cells, and wound healing regulatory cells to speed wound healing. One or more of these agents in combination can be used in the invention. The amount of wound healing agent(s) to be included with the biomaterial may vary, depending upon the biomaterial used, the patient (age, sex, medical history) and the site being treated. Typically the weight ratio of wound healing agent(s) to the biomaterial would be in the range of about 1:5,000 to 1:50,000.

The wound healing agents may be isolated from native or natural sources, such as from mammalian cells, or may be prepared synthetically, such as by recombinant DNA or by chemical processes. In addition, analogs, fragments, or derivatives of these agents may be used provided they exhibit

some of the biological activity or wound healing properties of the native molecule. For example, analogs can be prepared by expression of genes altered by site-specific mutagenesis or other genetic engineering techniques.

These agents may be added to the biomaterial during preparation or just prior to treatment. It is preferred that the wound healing agents be incorporated into the biomaterial such that the agents are released through a sustained delivery. In this way, the agents can be released over an extended period of time into the hemorrhoid sites and surrounding areas, promoting wound healing. It is most preferred that these agents will be included in the treatment of patients with hemorrhoids associated with inflammatory bowel disease, whose wounds may heal poorly, worsening symptoms.

Optionally, antimicrobial additives and/or antibodies may be added to these biomaterials to reduce the potential for infection at the treatment site. In addition, local anesthetics may be used at the injection site. Any appropriate additive may be utilized as long as it is compatible with the biomaterial used and the patient.

A preferred method of the invention is performed in an outpatient setting under aseptic conditions with the patient in the lithotomy position. A retractor is used to clearly visualize the anal orifice, and the biomaterial is typically supplied in a sterile 3.0 cubic centimeters (cc) syringe fitted with a 25 gauge needle.

A complete anorectal examination should be conducted prior to treatment. The exam includes inspection, palpation, sigmoidoscopy, and proctoscopy. Inspection will provide the physician with a great deal of information regarding the severity and degree of a patient's hemorrhoids. Palpation will help the physician to estimate the tone of the anal sphincter. Any thrombosed area will feel indurated, but it should be emphasized that uncomplicated hemorrhoids are not palpable. As the symptoms of hemorrhoids may resemble those of serious colorectal disease, namely cancer and inflammatory bowel disease, sigmoidoscopy is performed to rule out other problems. The concurrent presence of inflammatory bowel disease will

modify the physician's approach to treating hemorrhoids, and tumors must be excluded. The exam concludes with proctoscopy to give the physician a more accurate assessment of the hemorrhoids.

Anal manometric evaluation is also sometimes performed prior to hemorrhoid treatment, as increased sphincter activity and anal canal pressure have been shown to be associated with hemorrhoids. However, no correlation has been found between sphincter activity and anal canal pressure with respect to predominant symptoms, duration and severity of symptoms, size of hemorrhoids, or length of symptom history. It has been suggested that increased sphincter activity is an effect of the presence of hemorrhoids, rather than their cause. In fact, the passage of a standard proctoscope has been shown to produce a decrease in anal canal pressure equivalent to that measured after successful hemorrhoid treatment. Therefore, anal manometry may be of little value in the treatment of the individual patient.

When treating hemorrhoids, the biomaterial is injected perianally into the soft tissues and/or skin of the anal verge until the treated area is completely filled with biomaterial. A preferred amount of biomaterial to be used is approximately 1-10 cc, most preferably 5 cc. The amount of material necessary to restore the tissue to its original position will, of course, vary from person to person. The exact amount of material used is therefore left to the discretion of the administering physician.

As treatment is performed in response to a patient's complaints of symptoms, treatment success is defined by a patient's report of an improvement in symptoms. Improvement is expected to last approximately 3 to 12 months as a result of treatment. The injections may optionally be repeated on a regular basis to maintain patient comfort level. Subsequent injections will likely require the use of less material than the initial treatment.

Thus, methods for treating hemorrhoids and/or pruritis ani may be conducted by perianally administering an injectable biomaterial, with or without wound healing agents,

into the soft tissues of the anal verge. These methods provide nonsurgical approaches to relieve the symptoms of hemorrhoids and related conditions. The invention has been described above in some detail for the purposes of clarity and understanding. It will be apparent, however, that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method of treating hemorrhoids and/or pruritis ani comprising perianally administering an effective amount of an injectable biomaterial into the soft tissues of the anal verge.

2. The method of claim 1 wherein said injectable biomaterial is atelopeptide fibrillar, crosslinked or non-crosslinked collagen.

3. The method of claim 1 wherein said injectable biomaterial is an aqueous suspension of a biopolymer with a biocompatible fluid lubricant.

4. The method of claim 3 wherein said biopolymer is selected from the group consisting of: atelopeptide fibrillar, crosslinked or non-crosslinked collagen, gelatin beads, polytetrafluoroethylene beads, silicone rubber beads, hydrogel beads, silicon carbide beads, and glass beads.

5. The method of claim 3 wherein said biocompatible fluid lubricant is selected from the group consisting of: hyaluronic acid, dextran sulfate, dextran, succinylated non-crosslinked collagen, methylated non-crosslinked collagen, glycogen, glycerol, dextrose, maltose, triglycerides of fatty acids, egg yolk phospholipids, and heparin.

6. The method of claim 1 wherein said injectable biomaterial is a second nucleation collagen.

7. The method of claim 2 wherein said collagen is conjugated to a chemically activated polymer.

8. The method of claim 7 wherein said chemically activated polymer is polyethylene glycol.

9. The method of claim 2 wherein said collagen is crosslinked with a bifunctional activated polymer.

10. The method of claim 9 wherein said collagen and said bifunctional activated polymer crosslink in situ.

11. The method of claim 9 wherein said bifunctional activated polymer is polyethylene glycol.

12. The method of claim 2 wherein said biomaterial further comprises a ceramic and/or mineral material.

13. The method of claim 12 wherein said ceramic material comprises ceramic particles in the size range of about 50-250 microns.

14. The method of claim 1 wherein said biomaterial further comprises one or more wound healing agents.

15. The method of claim 14 wherein said wound healing agent is selected from the group consisting of: fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), connective tissue activating peptides (CTAPs), transforming growth factor (TGFs), and biologically active analogs, derivatives or fragments thereof.

16. The method of claim 1 wherein said composition further comprises an antimicrobial additive and/or antibiotic.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01391

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/00, 37/12, 9/14; C07K 3/12; C08G 63/48
US CL :514/21; 530/356; 424/484; 435/273; 525/54.1
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)

U.S. : 514/21; 530/356; 424/484; 435/273; 525/54.1

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 practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,424,208 (Wallace et al) 03 January 1984, entire document.	1-16
Y	US, A, 4,803,075 (Wallace et al) 07 February 1989, entire document.	1-16
Y	US, A, 4,557,764 (Chu) 10 December 1985, entire document.	1-16
A,P	US, A, 5,162,430 (Rhee et al) 10 November 1992, abstract.	2-13
A,P	US, A, 5,128,136 (Bentley et al) 07 July 1992, abstract.	2-16

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 31 MARCH 1993	Date of mailing of the international search report 07 APR 1993
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01391

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US, A, 5,110,604 (Chu et al) 05 May 1992, abstract.	2-16

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

CAS ONLINE, REGISTRY, MEDLINE, EMBASE, BIOSIS, APS,
Search Terms: Hemorrhoid or pruritis, atelopeptide, collagen, biopolymer, lubricant, polyethylene glycol or PEG, ceramic, crosslink.