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ASUNTO	Radicación	10 025 602
	Trámite	011
	Evento	379
	Actuación	519
	Oficio	<u>3 1 5 9 2 0</u>
	Folios	10

Patente de Invención	☒	Patente de Modelo de Utilidad
Vía Nacional		
Vía PCT (Fase Nacional)	☒	Capítulo I ☐ Capítulo II ☒
No. Solicitud Internacional	PCT/MX2008/00011 9	
Fecha de Presentación Internacional	05/Septiembre/2008	

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 7 a 33	04/Marzo/2010
Reivindicaciones:	Folios 34 a 36	04/Marzo/2010
Prioridad:	MX/A/2007/011002	07/Septiembre/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Composición farmacéutica que contiene una combinación sinérgica de venotónicos y vasoprotectores" (modificado en el folio 74).

El problema planteado en esta solicitud consiste en proporcionar una composición farmacéutica que comprende la combinación sinérgica de tres agentes que manifiestan actividad farmacológica como venotónicos y vasoprotectores, para el control y tratamiento de la insuficiencia venosa.

Para resolver este problema técnico la solicitud en estudio proporciona una Expediente 10 025 602 1er Art 45

composición que comprende Diosmina en un rango de concentración desde 225.0 mg hasta 450.0 mg, Hesperidina en un rango de concentración desde 25.0 mg hasta 50.0 mg y Dobesilato de Calcio en un rango de concentración desde 250.0mg hasta 1.0 g y excipientes farmacéuticamente aceptables.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 31/7048.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 6 – 7 no es patentable, de acuerdo con el Art 14.

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La Reivindicación 7 no es clara porque indica el uso que puede darse a la composición reivindicada, el cual no es una característica técnica que defina a la invención. Se sugiere hacer la aclaración respectiva.

6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: Septiembre 07 de 2007, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	Artículo ¹	Drug treatment of haemorrhoids	2005
D2	Artículo ²	Calcium dobesilate versus purified flavonoid fraction of diosmin in the treatment of haemorrhoidal crises: a randomized,controlled study with an initial double-blind,double-dummy period	07/Julio/2001

D1 (ver folios 85-88), divulga (folio 85) medicamentos para el tratamiento de condiciones anorectales diversas, como hemorroides sintomáticas, tales medicamentos contienen la fracción flavonoide purificada micronizada en formulaciones para estas patologías y dobesilato de calcio para la insuficiencia venosa crónica.

D2 (ver folios 89 y 90), divulga (folio 89) dobesilato de calcio y la fracción flavonoide micronizada de diosmina en un estudio comparativo de determinación de mejoramiento de síntomas de episodios de hemorroides agudos.

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La Reivindicación 1 consiste en una composición farmacéutica caracterizada porque

¹ MISRA M.C. ET AL.: 'Drug treatment of haemorrhoids' DRUGS vol. 65, no. 11, 2005, pages 1481 – 1491.

² SARABIA M. ET AL.: 'Calcium dobesilate versus purified flavonoid fraction of diosmin in the treatment of haemorrhoidal crises: a randomized,controlled study with an initial double-blind,double-dummy period' CURRENT THERAPEUTIC RESEARCH vol. 62, no. 7, 2001, pages 424 – 529.
Expediente 10 025 602 1er Art 45

está compuesta por la combinación sinérgica de tres fármacos que actúan como agentes venotónicos y vasoprotectores, tal como son: la fracción flavonoide purificada micronizada de los principios activos Diosmina y Hesperidina y el principio activo Dobesilato de Calcio, además de excipientes farmacéuticamente aceptables; en donde dichos principios activos se encuentran presentes en la formulación en un rango de concentración desde 225.0mg hasta 450.0 mg para la Diosmina, desde 25.0 mg hasta 50.0 mg para la Hesperidina y desde 250.0 mg hasta 1.0 g para el Dobesilato de Calcio; mismos que se encuentran formulados en una sola unidad de dosificación para ser administrada por vía oral, la cual está indicada para el control y tratamiento de la insuficiencia venosa crónica.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
Composición farmacéutica	No menciona	Combinación de 2 agentes para insuficiencia venosa crónica (background, folio 89)
Diosmina 225.0mg hasta 450.0 mg	Fracción flavonoide que contiene el 90% de Diosmina (página 1482 y 1484, folios 86 y 87)	Fracción Flavonoide micronizada de Diosmina 2 tabletas (500mg) (folio 90)
Hesperidina 25.0 mg hasta 50.0 mg	Fracción flavonoide que contiene el 10% de Hesperidina (página 1482 y 1484, folios 86 y 87)	No menciona
Dobesilato de Calcio 250.0 mg hasta 1.0 g	Dobesilato de Calcio (folio 88)	Dobesilato de Calcio (500mg) (folio 90)

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la Reivindicación 1 porque divulgan medicamentos para el tratamiento de condiciones anorectales diversas, como hemorroides sintomáticas, tales medicamentos contienen la fracción flavonoide purificada micronizada en formulaciones para estas patologías y dobesilato de calcio para la insuficiencia venosa crónica (D1: folio 85) y la combinación de 2 agentes para insuficiencia venosa crónica (D2: background, folio 89).

La diferencia entre la invención, definida en la Reivindicación 1 y los compuestos de D1 consiste en la asociación en una composición farmacéutica de las fracciones flavonoide micronizadas de diosmina y hesperidina con el dobesilato de calcio.

La diferencia entre la invención, definida en la Reivindicación 1 y la combinación de D2 consiste en la fracción flavonoide que contiene hesperidina.

Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja a las composiciones reclamadas en esta solicitud, ya que no parecen presentar propiedades superiores en comparación con los compuestos del estado de la técnica cercano.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo combinar los compuestos de la fracción flavonoide que contiene diosmina y dobesilato de calcio conocidos en D2, junto con otro compuesto de fracción flavonoide como hesperidina en una composición farmacéutica útil para la insuficiencia venosa crónica".

Sin embargo, la utilización de hesperidina como un agente para la insuficiencia venosa crónica ya se encontraba sugerida en D1, que divulga medicamentos como la fracción flavonoide que contiene el 90% de Diosmina (página 1482 y 1484, folios 86 y 87), la fracción flavonoide que contiene el 10% de Hesperidina (página 1482 y 1484, folios 86 y 87) y dobesilato de calcio (folio 88), para el tratamiento de condiciones anorectales diversas, como hemorroides sintomáticas, tales medicamentos contienen la fracción flavonoide purificada micronizada en formulaciones para estas patologías y dobesilato de calcio para la insuficiencia venosa crónica.

En consecuencia, la persona del oficio normalmente versada en la materia, adicionaria el compuesto hesperidina como un agente adicional a los revelados en D2 en una combinación farmacéutica para llegar así al objeto de la Reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Conclusión:
La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 2 – 7 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	MISRA M.C. ET AL	1 – 7	Nivel Inventivo
D2	SARABIA M. ET AL	1 – 7	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifiquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
11 SET. 2012

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Drug Treatment of Haemorrhoids

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Abstract

Drug treatment for various anorectal conditions has been known since ancient times. Today, modern as well as traditional drugs are being increasingly used in all grades of symptomatic haemorrhoids. These drugs (oral and local) are used as a part of conservative management or as an adjuvant to invasive outpatient procedures. Flavonoids, in the new formulation of micronised purified flavonoid fraction (MPFF) or as part of the ancient traditional medicine derivative of the Ginkgo tree, are used for relief of acute symptoms (for control of bleeding and re-bleeding in all grades of haemorrhoids). MPFF has been recommended for control of acute bleeding in patients waiting for a definitive outpatient treatment. Similarly, better known drugs such as calcium dobesilate (used in diabetic retinopathy and chronic venous insufficiency), nitrates and nifedipine have also been effective and well tolerated in the medical treatment of haemorrhoids. However, drug treatment is not aimed at curing haemorrhoids. The prime objective of drug therapy is to control the acute phase (bleeding) so that definitive therapy (banding, injection sclerotherapy, infrared photocoagulation, cryotherapy or surgery) can be scheduled at a convenient time.

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Haemorrhoids, or varicose dilatation of the haemorrhoid plexus, have plagued mankind since the dawn of history and it is estimated that about 50% of the population has haemorrhoids by the age of 50 years. Treatment of anorectal disorders with suppositories, cautery and by excision was described by Hippocrates. After thousands of years the fundamentals of treating haemorrhoids remain more or less the same. Modern therapies for haemorrhoids include various medical (nonsurgical) and surgical options, with a trend towards outpatient procedures and day case surgery. In a British survey of general and subspecialist colorectal surgeons,^[1] the majority of the surgeons prescribed routine advice on fluid and diet. Among the patients seen by the general surgeons 75% were treated with banding, 56% with injection sclerotherapy, 47% with haemorrhoidectomy, 9% with submucosal diathermy and 2% with stapled anoplasty. Haemorrhoids can also be destroyed by freezing using cryotherapy with nitrous oxide or liquid nitrogen,^[2] or by heat using infrared photocoagulation.^[3,4] Recently, the development of certain drugs found to be effective in haemorrhoids has generated a lot of interest. This review describes the clinical trials published on the use of these drugs in patients with haemorrhoids.

Haemorrhoids are classified according to the location and degree of prolapse.^[5] Internal haemorrhoids arise proximal to the dentate line and are covered by mucosa, while external haemorrhoids arise below the dentate line and have squamous epithelium. Mixed (interno-external) haemorrhoids arise both above and below the dentate line. Haemorrhoids are further graded according to the degree of prolapse, that is, protrusion below the pectinate line (table I).

Table I. Classification of haemorrhoids

Grade	Description
1	Bleed but do not prolapse
2	Prolapse during defecation but return spontaneously
3	Prolapse during defecation but require manual reduction
4	Permanently prolapsed

1. Drug Treatment of Haemorrhoids

1.1 Flavonoids

Tables II and III provide summaries of clinical trials published on the use of flavonoids in patients with haemorrhoids.

1.1.1 Micronised Purified Flavonoid Fraction

Micronised purified flavonoid fraction (MPFF)^[26] is an oral phlebotropic drug made up of 90% micronised diosmin and 10% flavonoids expressed as hesperidin. It is believed to improve venous tone and lymphatic drainage, and reduce capillary hyperpermeability by protecting the microcirculation from inflammatory processes.

Three placebo-controlled trials have investigated the efficacy of MPFF in the management of acute internal haemorrhoids and/or, in the longer-term, reducing the risk of relapse of acute haemorrhoidal symptoms. Cospite^[6] randomised 100 patients with acute haemorrhoidal attack to receive MPFF or placebo in parallel under double-blind conditions. Overall improvement of anal discomfort, pain and anal discharge was greater in the MPFF group than in the placebo group, from day 2 through to day 7. Inflammation, congestion, oedema and prolapse were also more markedly improved in the MPFF group, along with a major reduction in the duration and severity of the current haemorrhoidal episode, and in the use of analgesics and topical medications.

In a 90-day (7 days acute phase then 83 days maintenance phase) randomised, double-blind study by Misra and Parshad,^[7] treatment with MPFF (six tablets for 4 days followed by four tablets daily for 3 days) was compared with placebo in 100 outpatients

Table III. Clinical trials of nonmicronised oral flavonoids for the treatment of haemorrhoids

Study (year)	No. of patients	Grade of haemorrhoid	Drug(s)	Endpoint/results
Diana et al. ^[14] (2000)	66	All	Diosmin	Reduction of pain = 79%, bleeding = 67% in first week and in second week = 98% and 86%, respectively
Basile et al. ^[15] (2001)	30	Post-haemorrhoidectomy	Troloxerutin + carbazochrome vs placebo	Visual analogue scale on days 3 and 4 = difference of $p = 0.007$ and $p = 0.001$
Annoni et al. ^[16] (1986)	40	2, 3, 4	O-(β -hydroxyethyl)-rutosides vs placebo	Significant reduction of pain and bleeding
Wijayanegara et al. ^[17] (1992)	97	1, 2, 3	O-(β -hydroxyethyl)-rutosides vs placebo	Significant improvement in signs and symptoms Safely used in pregnancy
Benzi et al. ^[18] (1992)	42	All	O-(β -hydroxyethyl)-rutosides	Clinical efficacy = positive in 95% Clinical improvements of $p < 0.01$
Tilapant et al. ^[19] (2001)	53	1, 2	Trihydroxyethylrutosides vs placebo	Improvement in symptoms only at 2 weeks and also in signs at 4 weeks

affect pregnancy, fetal development, birth weight, infant growth and/or feeding. Meyer^[13] reported the safety of MPFF clinical trials of >2850 patients treated with MPFF 500mg at the dosage of two tablets per day for 6 weeks to 1 year. Only 10% of those treated developed adverse effects, essentially of a gastrointestinal or autonomic nature (causing 1.1% trial withdrawals) compared with 13.9% of patients on placebo. MPFF was found to be equally acceptable in the short term as well as in long-term treatment. Haemodynamic and laboratory parameters (haematology, liver and renal function) were not affected even by prolonged treatment for 1 year at the dosage of two tablets per day. A review article by Lyseng-Williamson and Perry^[26] evaluated placebo-controlled trials of MPFF in patients with both acute and chronic haemorrhoids, and found that overall MPFF had a tolerability profile similar to that of placebo; the most frequently reported adverse events were gastrointestinal and autonomic in nature.

1.1.2 Diosmin

Diana et al.^[14] gave purified (nonmicronised) diosmin, at a dose of two 450mg tablets twice daily for the first 7 days then one tablet twice daily for up to 2 months, to a group of 66 patients with haemorrhoids of grade 1–4. Their results showed the efficacy of diosmin in decreasing both pain and bleeding in the

first (79% and 67%, respectively) and second (98% and 86%, respectively) treatment week.

Topical diosmin ointment was used in 50 patients with grade 1, 2, 3 or 4 haemorrhoids with strangulation and thrombosis, and without any previous treatment. The drug was most effective on oedema and erythema, producing 75% and 73% improvements as assessed in three consecutive weekly visits.^[27]

1.1.3 Troloxerutin

In a double-blind, placebo-controlled study by Basile et al.,^[15] 30 patients were randomised to receive one of two treatments: troloxerutin (a flavonoid) 150mg plus carbazochrome 1.5mg, or intramuscular placebo (3mL twice daily for 5 days, starting from the day of surgery). Analysis of scores based on pain, discharge, bleeding, inflammation and pruritus, analgesic intake, time to restore a physiological defecation, oedema and blood coagulation tests between the treatment groups revealed a significant difference at day 3 and day 4 in favour of the active combination treatment. No adverse events were reported. Neither the active combination nor placebo affected blood coagulation tests.

1.1.4 Hydroxyethylrutosides

Hydroxyethylrutosides (rutosides) are a standardised mixture of semisynthetic flavonoids, mainly mono-, di-, tri- and tetrahydroxyethylrutosides, which act primarily on the microvascular en-

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so induced the remission of skin rash and itching (table IV).

1.4 Calcium Dobesilate

Calcium dobesilate is used in the treatment of diabetic retinopathy, chronic venous insufficiency, haemorrhoids and other ill-defined vascular conditions. Cases of agranulocytosis in patients on calcium dobesilate have been reported.^[29] Marsicano et al.^[30] compared calcium dobesilate, dexamethasone plus lidocaine with prednisolone plus dibucaine in the treatment of grade 1 and 2 haemorrhoids. They observed that both combinations were equally effective in relieving symptoms, though it was faster with the calcium dobesilate combination. In a randomised double-blind study by Mendes et al.,^[20] 29 patients with grade 1 and 2 internal haemorrhoids were treated with calcium dobesilate and a high-fibre diet for 2 weeks, while 16 patients received only a high-fibre diet. A success rate of 86.2% with cessation of bleeding at 2 weeks was achieved with calcium dobesilate. Significantly better symptom and anoscopic inflammation scores were also observed with the calcium dobesilate treatment (table IV).

1.5 Local Application to the Anal Canal

Table V provides a summary of clinical trials of topical antihaemorrhoidal drugs.

1.5.1 Nitrates

Anal sphincter spasm is believed to play an important role in pain with thrombosed external haemorrhoids and in post-haemorrhoidectomy patients. Sphincterotomy and anal dilatation has been found to decrease pain after haemorrhoidectomy and in other painful anal conditions. Studies show that nitric oxide is one of the most important inhibitory neurotransmitter in the internal sphincter. Nitric oxide (like nitroglycerin [glyceryl trinitrate]) may cause 'chemical sphincterotomy' without the risk of permanent incontinence.^[43] Cundall et al.^[44] found that there was a progressive relaxation of anal tone with increasing doses of locally applied nitroglycerin ointment without any serious adverse effects. Loder et al.^[43] reported that the internal anal pressure decreased by a mean of 27% after administration of the drug. However, nitrates, even when applied topically, do cause headaches and many patients find this intolerable.^[43]

The most commonly studied nitrate in patients with haemorrhoids is nitroglycerin (glyceryl trinitrate). Five patients with thrombosed external

Table IV. Clinical trials primarily investigating nonflavanoid oral agents for the treatment of haemorrhoids

Study (year)	No. of patients	Grade of haemorrhoid	Drug(s)	Endpoint/results
Mendes et al. ^[20] (2001)	45	1, 2	Calcium dobesilate + high-fibre diet vs high-fibre diet only	Cessation of bleeding at 2 weeks = 86.2% (with better symptom and anoscopic score at 2 weeks)
De Cecco ^[21] (1992)	40	2, 3	Heparan sulfate vs O-(β -hydroxyethyl)-rutosides (oxerutin)	Persistent pain in 45% (vs 55%)
Soullard and Contou ^[22] (1978)	37	All	Ginkor-fort®	Satisfactory results in 12 patients (incomplete = 13, moderate = 3, no effect = 9)
Hep et al. ^[23] (2000)	45	NA	Ginkor-fort®	Benefit seen
Reddy et al. ^[24] (1984)	82 (+ 26 with fissure)	All	Pilex® tablets and ointment	Very good response in 15% of grade 1 and 7% of grade 2 haemorrhoids, good in 50% and 41%, respectively
Tripathy ^[25] (2000)	30	1, 2, 3	Pilex® tablets and ointment vs tablets MPFF	90% complete relief in grade 1 and 2 haemorrhoids with Pilex® Pilex® better in reducing pain, inflammation and size

MPFF = micronised purified flavanoid fraction; NA = not available.

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Calcium Dobesilate Versus Purified Flavonoid Fraction of Diosmin in the Treatment of Hemorrhoidal Crises: A Randomized, Controlled Study with an Initial Double-Blind, Double-Dummy Period

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ABSTRACT

Background: Calcium dobesilate and purified, micronized flavonoid fraction of diosmin, 2 products used in the treatment of chronic venous insufficiency in the lower limbs, have been shown in open-label, placebo-controlled studies to improve symptoms of acute hemorrhoidal episodes.

Objective: This study was performed to compare the efficacy and tolerability of calcium dobesilate and purified, micronized flavonoid fraction of diosmin in the treatment of hemorrhoidal crisis.

Methods: Patients with a diagnosis of hemorrhoidal crisis were randomized to receive 1 of 2 treatments: calcium dobesilate one 500-mg capsule TID for ≥ 4 weeks or purified, micronized flavonoid fraction of diosmin two 500-mg capsules TID for ≥ 4 weeks. For the first 10 days, patients in both groups were given dummy capsules or tablets to maintain the double-blind provision. Patients underwent physical examination at baseline and after 2 days, 8 days, and 4 weeks of treatment. The following symptoms were assessed using a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe): pain, discharge, bleeding, edema, inflammation, pruritus, and anal pressure.

Results: A total of 51 patients were treated; 25 received calcium dobesilate and 26 received micronized flavonoid fraction of diosmin. In both treatment groups, significant improvement was observed in 6 of 7 evaluated symptoms after 2 days of treatment ($P < 0.05$) and in all symptoms after 4 weeks. After 4 weeks of treatment, 19 of 25 patients (76%) in the calcium dobesilate group and

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PATIENTS AND METHODS

Patients

Male and female patients aged 18 to 75 years who came to the participating hospitals during an acute hemorrhoidal episode were eligible for enrollment. Patients had to have a diagnosis of hemorrhoidal crisis defined as symptoms of rapid onset, including pain, bleeding, discharge, edema, inflammation, or thrombosis, which when evaluated by physical examination, including rectoscopy, showed the presence of hemorrhoids and were considered responsible for the patients' symptoms. Patients with previous rectal surgery, indication for surgery, chronic or serious disease, altered hepatic or renal function, pelvic tumor, or portal hypertension were excluded.

All patients were informed about the study and gave written consent. The protocol was approved by the ethics committee of each participating institution. Patients were not allowed to take any local or systemic treatment for their hemorrhoidal condition for more than 24 hours within 5 days of study initiation.

Study Design

Patients were randomized to receive 1 of 2 treatments: calcium dobesilate 1 capsule (500 mg) TID for ≥ 4 weeks or purified, micronized flavonoid fraction of diosmin two 500-mg tablets TID for ≥ 4 weeks. For the first 10 days, patients in both groups were given dummy capsules or tablets to maintain the double-blind provision. Thus, each patient received 6 tablets and 3 capsules per day. Because of the large number of pills required to maintain the double-blind provision, and because open-label studies indicated that most patients were asymptomatic within 10 days of treatment, we discontinued the double-blind provision after 10 days. We did not include a placebo group in the study design because a previous study⁴ showed that treatment with micronized flavonoid fraction of diosmin plus nonpharmacologic interventions such as Sitz baths, stool softeners, and increased fluid intake was more effective than nonpharmacologic interventions alone.

Physical examination was performed at baseline and after 2 days, 8 days, and 4 weeks of treatment. If for any reason patients could not be assessed on a Friday, the double blind was maintained until Monday. The following acute hemorrhoidal symptoms were assessed based on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe): pain, discharge, bleeding, edema, inflammation, pruritus, and anal pressure. Use of pain medication, new acute episodes, patient perception of efficacy (good, moderate, or poor), incidence of adverse events, and compliance were also assessed through direct patient interviews.

Statistical Analysis

Age, body weight, and height in the 2 groups were compared using the Student *t* test. Sex distribution, medical history, stool consistency, number of previous