PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/275, 31/135, 31/22, 31/35, 31/645, 31/215, 31/19, 31/40, 9/00, 9/02

A1

(11) International Publication Number: **WO 98/11888**

(43) International Publication Date: 26 March 1998 (26.03.98)

(21) International Application Number: PCT/US97/16509

(22) International Filing Date: 17 September 1997 (17.09.97)

(30) Priority Data:
08/724,263 19 September 1996 (19.09.96) US

(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: GAST, Michael, Jay; 230 Country Lane, Phoenixville, PA 19460 (US). KOZIOL, Theodore, Richard; 241 McClenaghan Mill Road, Wynnewood, PA 19096 (US).

(74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD OF TREATING URINARY INCONTINENCE

(57) Abstract

This invention provides a method of treating urinary incontinence in a female mammal which comprises administering to said mammal an effective amount of an anti-incontinent agent intravaginally or rectally.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

METHOD OF TREATING URINARY INCONTINENCE

BACKGROUND OF THE INVENTION

Urinary incontinence is an involuntary leaking of urine which primarily affects women and older men. There are three major categories of urinary incontinence which are classified according to etiology; these are urinary stress incontenance (SI), urge incontinence (UI), and mixed incontinence. SI is the involuntary loss of urine as a result of increasing intra-abdominal pressure, typically occurring after coughing, straining, sneezing, lifting or any other activity which suddenly increases intra-abdominal pressure. In women, SI is the most common cause of involuntary loss of urine, and may be caused by the shortening of the urethra and loss of the normal urethrovesical angle resulting from pelvic relaxation that characteristically occurs with aging or multiparity.

UI is characterized by an urgent desire to void followed by the involuntary loss of urine. It is most often unassociated with any specific disease or disorder, but is increasingly common in older men and women. Among the causes of UI that are known, diabetes, multiple sclerosis, spinal cord injury, and other primarily neurologic disorders are among the most common. Anatomic and traumatic etiologies may also cause UI. Urge incontinence is also referred to as detrusor incontinence or instability, as it is associated with involuntary contractions of the detrusor muscle. Mixed incontinence is seen in patients having both SI and UI.

Although, SI is usually treated surgically, there are a number of drugs currently used use to treat UI and mixed incontinence. Since the urinary bladder is thought to contract primarily as a result of parasympathetic activity, drugs with anticholinergic properties have been the most common to be used to treat the unstable bladder. A number of other preparations have been used as well. Among these are antispasmodics, tricyclic antidepressants, calcium channel blockers, prostaglandin synthetase inhibitors, and other agents having an effect on smooth muscle contractility, such as potassium channel modulators. Agents typically used include oxybutynin, propantheline, imipramine, terodiline, dicyclomine, and flurbiprofen These drugs are usually administered orally and are associated with a number of side effects which limit their usefulness.

The most widely prescribed drug for the treatment of incontinence is oxybutynin. Currently it must be given orally two to four times per day. Although oxybutynin has shown to be effective in a number of clinical trials, side effects prevent more widespread usage. Reported side effects include dry mouth, blurred vision, nausea, and constipation. Alternatives to oral administration have been attempted with oxybutynin; it has been successfully instilled directly into the bladder showing therapeutic activity with reduced side effects [Weese, D.L., Urology 41:527-530, (1993); Prasad, K.V., Brit J Urology 72:719-722, (1993); Mizunaga, M., Paraplegia 32:25-29, (1994)].

DESCRIPTION OF THE INVENTION

This invention provides a method of treating urinary incontinence which comprises administering an anti-incontinent agent intravaginally or rectally. An anti-incontinent is defined an agent which is useful in treating urinary incontinence. Such agents have typically been administered orally or parenterally.

In particular, this invention provides a method of treating urinary incontinence which comprises intravaginally or rectally administering an anticholinergic agent, antispasmodic agent, tricyclic antidepressant, calcium channel blocker, prostaglandin synthetase inhibitor, potassium channel modulator, estrogen agonist, tissue selective estrogen (selective estrogen receptor modulator), or α-agonist. Preferred anticholinergics include agents such as scopolamine, atropine, ipratropium bromide, poldine, glycopyrrolate, propantheline, isopropamide, trihexylphenidyl, benztropine, procyclidine, biperiden, ethopropazine, methancholine, emepronium, fentonium darifenacin, and tolterodine. Preferred antispasmodics include agents such as hyoscyamine, oxybutynin, flavoxate, and dicyclomine. Preferred tricyclic antidepressants include agents such as amitriptyline, nortriptyline, imipramine, desipramine, doxepin, trimipramine, clomipramine, and protriptyline. Preferred calcium blockers include agents such as diltiazem, nifedipine, nicardipine, nimodipine, isradipine, nitrendipine, felodipine, and terodiline. Preferred prostaglandin synthetase inhibitors include agents such as flurbiprofen, indomethacin, and mefanatnic acid. Preferred potassium channel modulators include agents such as (R)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile (see U.S. Patent 5,506,252, which is hereby incorporated by reference), 4-[(2-tert-butylamino-3,4-dioxo-cyclobut-1-enylamino)-methyl]-3-chloro-benzonitrile (see Example 5), and 3-(2,3-dichloro-6-methyl-benzylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione (see Example 6). Preferred estrogen agonists include 17β-estradiol and

estrogen. Preferred tissue selective estrogens include roloxafine and teremofine. Preferred α-agonists include phenyl propanolamine.

More preferred anti-incontinent agents include, but are not limited to, oxybutynin, propantheline, imipramine, terodiline, dicyclomine, flurbiprofen, darifenacin, tolterodine, (R)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile, 4-[(2-tert-butylamino-3,4-dioxo-cyclobut-1-enyl-amino)-methyl]-3-chloro-benzonitrile, and 3-(2,3-dichloro-6-methyl-benzylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione.

Treating covers treatment of an existing condition, inhibiting the progress or development of the condition, ameliorating the condition, and providing palliation of the condition. It is preferred that the anti-incontinent agents of this invention are employed in the treatment of urge or mixed incontinence.

Because of the proximity of the vagina and rectum to the bladder, the intravaginal or rectal administration of anti-incontinent agents provides several advantages over conventional treatments for urinary incontenance, which include all or some of the following (1) site specific delivery of the anti-incontinent agent very near the site of action, (2) locally high concentrations of the anti-incontenent agent in the bladder, (3) a reduction of side effects due to decreased serum concentration and/or reduced first pass metabolism, (4) a lower effective circulating concentration (systemic load) of the anti-incontenent agent, and (5) ability to control the rate of delivery of the agent with immediate release or longer duration of action based on controlled release from the vehicle. This invention, therefore, provides a useful and advantageous method of treating urinary incontinence.

When administered intravaginally or rectally, anti-incontenent agents can be formulated neat or using a variety of pharmaceutical carriers which are amenable for intravaginal or rectal administration including creams, gels, foams, tablets, suppositories, and pessaries containing a number of synthetic or natural materials including but not limited to silicone, silastic, polycarbophil, polyethylene glycol, and hydrogel. Such carriers may be non-therapeutic or therapeutic, in and of themselves. Therapeutic carriers with beneficial medicinal properties can be used, for example, to control vaginal pH, treat or inhibit sexually transmitted diseases, or provide vaginal hydration. When administered intravaginally or rectally, it is projected that the preferred dosage for oxybutynin would be 1-20 mg administered 1-4 times per day, the preferred dosage for propantheline would be 1-120 mg administered 1-4 times per day, the preferred dosage for imipramine would be 1-400 mg administered 1-4 times per

day, the preferred dosage for terodiline would be 1-100 mg administered 1-4 times per day, the preferred dosage for dicyclomine would be 1-40 mg administered 1-4 times per day, and the preferred dosage for flurbiprofen would be 1-100 mg administered 1-4 times per day.

The following provides representative example of intravaginal or rectal formulations and their preparation.

EXAMPLE 1

Propantheline Bromide Vaginal or Rectal Suppository

	Amount per 5g Suppository
Propantheline bromide	0.03 g
Glycerin	3.5 g
Gelatin (Type A)	1.0 g
Purified Water	0.47 g

Propantheline bromide is dissolved in the Purified Water; gelatin is added and the mixture is heated nearly to boiling. Glycerin is heated to nearly 100°C and added to the gelatin-water mixture. The resulting mixture is heated in a water bath until the gelatin is dissolved. Water is slowly added to achieve the correct weight and stirred until uniform. The mass is poured into molds, allowed to solidify and packaged.

EXAMPLE 2

Oxybutynin Hydrochloride Vaginal Cream

	Amount per 5g dose
Oxybutynin Hydrochloride	0.05 g
Polyethylene Glycol 1000 Monocetyl Ether	0.09 g
Cetostearyl Alcohol	0.3 g
Mineral Oil	0.3 g
White Petrolatum	0.75 g
Propyl paraben	0.004 g
Methyl paraben	0.0075 g
Benzyl Alcohol	0.075 g
Purified Water, freshly boiled and cooled	3.4085 g

Oxybutynin hydrochloride, methyl and propyl paraben and benzyl alcohol are dissolved in the water with the aid of gentle heat. On a hot water bath, the polyethylene glycol 1000 monocetyl ether, cetostearyl alcohol, mineral oil and white petrolatum are melted together. The aqueous solution is added to the molten oils and stirred until cold. The cream is packed into tubes and dispensed with a vaginal applicator to provide a 5 g dose.

EXAMPLE 3

Dicyclomine Hydrochloride Vaginal Gel

	Amount per 5g dose
Dicyclomine Hydrochloride	0.01 g
Carbopol 934	0.038 g
Triethanolamine	0.056 g
Propyl paraben	0.004 g
Methyl paraben	0.0075 g
Purified Water, freshly boiled and cooled	4.885 g

Dicyclomine hydrochloride, methyl and propyl paraben are dissolved in the water with the aid of gentle heat. The solution is cooled and carbopol 934 is dispersed in the solution with gentle agitation. Triethanolamine is added gently to avoid air entrapment until the gel is formed. The gel is packed into tubes and dispensed with a vaginal applicator to provide a 5g dose.

EXAMPLE 4

Imipramine Hydrochloride Slow Release Vaginal Tablets

	Amount per 1g tablet
Imipramine hydrochloride	0.05 g
Polycarbophil	0.5 g
Lactose	0.4425 g
Polyvinylpyrrolidone	0.005 g
Magnesium Stearate	0.0025 g

Polyvinylpyrrolidone and imipramine hydrochloride are dissolved in a suitable quantity of purified water and used to make a wet granule mass of the polycarbophil.

The wet mass is screened through a suitable mesh screen and the resulting granules dried. Lactose is blended with the polycarbophil granules. Magnesium stearate is added and blended just sufficiently to disperse the lubricant. The mixture is compressed into diamond shaped tablets, packed in foil strips and dispense with a vaginal applicator.

The following provide preparations of (R)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile, 4-[(2-tert-butylamino-3,4-dioxo-cyclobut-1-enylamino)-methyl]-3-chloro-benzonitrile, and 3-(2,3-dichloro-6-methyl-benzylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione.

EXAMPLE 5

4-[(2-tert-Butylamino-3,4-dioxo-cyclobut-1-enylamino)-methyl]-3-chloro-benzonitrile

A. 2-Chloro-4-cyanobenzyl bromide

A mixture of 3-chloro-4-methylbenzonitrile (22.74 g, 150 mmol), N-bromosuccinimide (32.04 g, 180 mmol) and 2,2'-azobis-2-methylpropionitrile (2.46 g, 15 mmol) in carbon tetrachloride (120 mL) was carefully warmed to reflux temperature whereupon a moderate exotherm occurred and refluxing proceeded for approximately 10 minutes without external heating. Heating was then resumed and refluxing continued for 26 hours. The hot reaction mixture was suction filtered and the insolubles were rinsed with carbon tetrachloride (3 x 25 mL). The combined carbon tetrachloride fractions were washed with water and dried (anhydrous Na_2SO_4). Removal of solvent gave a yellow mush which was crystallized from hexane (charcoal). The product again was recrystallized from hexane to yield 20.44 g (59%) of the white bromide: mp 80.5 - 83.5°C (softens 71.5°C) (lit. mp 85-85.5°C (B. Gogolimska, Acta Pol. Pharm., 25 (4), 391 (1968) [C.A., 70, 87493e (1969)].)); ^{1}H NMR (DMSO-d_6) δ 8.10 (d, 1H), 7.82 (m, 2H), 4.69 (s, 2H) ppm. IR (KBr): 2220 cm^{-1}.

B. N-(2-chloro-4-cyanobenzyl)phthalimide

A mixture of product from Example 5, Step A (20.29 g, 88.0 mmol) and potassium phthalimide (17.92 g, 96.8 mmol) in N,N-dimethylformamide (200 mL)

was stirred as the reaction temperature rose to approximately 36°C during approximately 5 minutes with formation of a tan suspension. The temperature then receded and stirring was continued for 2 hours. After removal of solvent, the residue was triturated thoroughly with water and dried.

The buff solid product was treated with approximately 500 mL boiling ethyl acetate, gravity filtered to remove a small amount of white insoluble material, heated to boiling, treated with charcoal and filtered. Concentration and cooling of the filtrate afforded (after drying) 20.26 g (78%) of the title compound phthalimide as a white solid: mp 172.5 - 173.0°C (softens 170.5°C); ^{1}H NMR (DMSO-d_6) δ 8.10 (d, 1H), 7.90 (m, 4H), 7.75 (dd, 1H), 7.52 (d, 1H), 4.88 (s, 2H) ppm. IR (KBr): 2220, 1770, 1715 cm^{-1}.

C. 2-chloro-4-cyanobenzylamine

A mechanically stirred suspension of product from Example 5, Step B (18.99 g, 64 mmol) in absolute ethanol (150 mL) was treated with hydrazine hydrate (6.41 g, 128 mmol) and the mixture was stirred and refluxed for 1 hour and then was allowed to stand at room temperature for approximately 16.5 hours. With stirring 2N HCl (90 mL) was added slowly, and after 10 minutes of further stirring the mixture was filtered. The insolubles were triturated thoroughly with ethanol and then with water. The combined filtrate and triturates were freed of solvent and the residue in approximately 250 mL ice-H_2O was basified with 2.5 N NaOH (90 mL). The mass was extracted thoroughly with chloroform and the extracts were washed with water, with brine and dried (anhydrous Na_2SO_4). Removal of solvent gave a cream-colored solid which was recrystallized from hexane to provide 6.85 g (64%) of a white amine: mp 85.0 - 87.0°C (soften 82.5°C); ^{1}H NMR (DMSO-d_6) δ 7.96 (d, 1H), 7.82 (dd, 1H), 7.77 (m, 1H), 3.82 (s, 2H), 2.12 (br m, 2H) ppm. IR (KBr): 3380, 3320, 2230 cm^{-1}.

D. 4-[(2-tert-Butylamino-3,4-dioxo-cyclobut-1-enylamino)-methyl]-3-chloro-benzonitrile

Tetrahydrofuran (50 mL), 3-butoxy-4-tert-butylamino-cyclobut-3-ene-1,2-dione (6.76 g, 30 mmol, Example 1) and the product of Example 2, Step 3 (5.00 g, 30 mmol) were refluxed for 6 hours and allowed to stand at room temperature for 16 hours. Following removal of solvent from the reaction mixture, the residue was triturated thoroughly with diethyl ether and dried to give a buff solid. This material in approximately 1.4 L of boiling acetone, was filtered to remove a small amount of white

solid. The hot filtrate was treated with charcoal, filtered, concentrated and cooled to afford 6.521 g of a cream-colored solid. Two additional recrystallizations of this material from acetone gave 4.779 g (50%) of the title compound as a white solid: mp 243.5-245.°C (softens 241.0°C); ^{1}H NMR (DMSO-d_6) δ 8.10 (d, 1H), 7.88 (dd, 1H), 7.82 (m, 1H), 7.66 (s, br, 1H), 7.61 (d, 1H), 4.88 (d, 2H), 1.34 (s, 9H) ppm. IR (KBr): 3320, 3230, 2240, 1780, 1665 cm^{-1}; MS (m/z) 317/319 (M^+). HPLC indicates a major component (99.6%).

Elemental analysis for $C_{16}H_{16}ClN_3O_2$

Calc'd: C, 60.48; N, 5.08; N, 13.22; Cl, 11.16.

Found: C, 60.08; H, 4.97; N, 13.06; Cl, 10.82, 10.71.

EXAMPLE 6

3-(2,4-Dichloro-6-methyl-benzylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione

A. 3-Butoxy-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione

A solution of 3,4-dibutoxy-3-cyclobutene-1,2-dione (4.53 g, 20 mmol) and 1,1-dimethylpropylamine (1.74 g, 20 mmol) in tetrahydrofuran (20 mL) was stirred at room temperature for approximately 19.5 hours. The solvent was removed and the residue was chromatographed (gravity, chloroform/hexane) on neutral, activity III silica (150 g). The white solid isolated from the appropriate eluates was recrystallized from hexane to give 4.105 g (86%) of a white product: mp 56.5-57.5°C (softens 55.5°C).

One gram of this material was recrystallized twice from hexane to provide 0.794 g of the title compound as a white solid: mp 56-57°C (softens 55°C); ^{1}H NMR (DMSO-d_6): δ 8.63 and 8.48 (two br s, 1H, rotamers), 4.67 (m, br, 2H), 1.67 (m, br, 4H), 1.39 (m, 2H), 1.26 (m, br, 6H), 0.91 (t, 3H), 0.78 (t, 3H) ppm. IR (KBr): 3170, 1790, 1700 cm^{-1}; MS (m/z): 239 (M^+).

Elemental Analysis for $C_{13}H_{21}NO_3$

Calcd: C, 65.24; H, 8.85; N, 5.85

Found: C, 65.12; H, 8.90; N, 5.77

B. 3-(2,4-Dichloro-6-methyl-benzylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione

A solution of 3-ethoxy-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione (16.67 g, 79.0 mmol) and 2,4-dichloro-6-methylbenzylamine (15.02 g, 79.0 mmol) in absolute ethanol (395 mL) were allowed to stand for 4 days at room temperature. The title compound formed as a white solid, which was filtered, washed with diethyl ether/hexane and dried in vacuo. This yielded 25.7 g (92%) of the title compound as a white solid: mp 247.1-248.3°C; ^{1}H NMR (DMSO-d_6) δ 7.54 (d, 1H), 7.44 (br t, 1H), 7.39 (d, 1H), 7.31 (s, 1H), 4.90 (d, 2H), 2.40 (s, 3H), 1.66 (q, 2H), 1.28 (s, 6H), 0.80 (t, 3H) ppm. IR (KBr): 3200, 2980, 1800, 1650 cm $^{-1}$; MS (m/z) 354/356/358 (M^+). Analytical HPLC indicates a major component (99.9%).

Elemental analysis for $C_{17}H_{20}Cl_2N_2O_2$

Calc'd: C, 57.47; H, 5.67; N, 7.89.

Found: C, 57.31; H, 5.50; N, 7.80.

WHAT IS CLAIMED IS:

1. A method of treating urinary incontinence in a mammal which comprises administering to said mammal an effective amount of an anti-incontinent agent intravaginally or rectally.

2. The method according to claim 1 wherein the anti-incontinent agent is an anticholinergic agent, antispasmodic agent, tricyclic antidepressant, calcium channel blocker, prostaglandin synthetase inhibitor, potassium channel modulator, tissue selective estrogen, estrogen agonist, or α-agonist.

3. The method according to claim 1 wherein the anti-incontinent agent is selected from the group consisting of oxybutynin, propantheline, imipramine, terodiline, dicyclomine, flurbiprofen, darifenacin, tolterodine, (R)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile, 4-[(2-tert-butyl-amino-3,4-dioxo-cyclobut-1-enylamino)-methyl]-3-chloro-benzonitrile, and 3-(2,3-dichloro-6-methyl-benzylamino)-4-(1,1-dimethyl-propylamino)-cyclobut-3-ene-1,2-dione.

4. An intravaginal or rectal composition which comprises an anti-incontinent agent and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Internat' l Application No
PCT/US 97/16509

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/275 A61K31/135 A61K31/22 A61K31/35 A61K31/645
A61K31/215 A61K31/19 A61K31/40 A61K9/00 A61K9/02

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 6 A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 23492 A (SEPRACOR) 8 August 1996 see abstract see page 5, line 16 - line 19 see page 10, line 4 - line 11 ---	1-4
X	GB 2 278 054 A (ZENECA LTD) 23 November 1994 see abstract see page 9, paragraph 2 - paragraph 3 ---	1,2,4
P,X	WO 97 09980 A (PFIZER RESEARCH AND DEVELOPMENT COMPANY) 20 March 1997 see abstract see page 1, line 6 - line 9 see page 2, line 10 see page 5, line 21 - line 29 --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] 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.

"&" document member of the same patent family

1

Date of the actual completion of the international search
19 December 1997

Date of mailing of the international search report
21. 01. 98

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 97/16509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROUSSEAU: "Urinary incontinence in the aged, Part 2: management strategies" GERIATRICS, vol. 47, no. 6, 1992, pages 37-48, XP002050834 see the whole document	1,2,4
A	---	3
X	SCHONBERGER: "Adrenerg oder cholinerg gegen "nasse Nächte" ?" KRANKENHAUS ARTZ, vol. 68, no. 1-2, 1995, pages 12-17, XP002050835 see pages 12-14,16,17, especially page 13	1,2,4

X	ANONYM: "ACOG technical bulletin : Urinary incontinence" INT. J. GYNECOL. OBSTET., vol. 52, no. 1, January 1996, pages 75-86, XP002050836 see page 82 see page 83, left-hand column, paragraph 1	1,2,4

X	WALTERS: "The evaluation and treatment of urinary incontinence in women : a primary care approach" J. AM. BOARD PRACT., vol. 5, no. 3, 1992, pages 289-301, XP002050837 see the whole document	1,2,4
A	---	3
X	WO 93 08800 A (THE NEW YORK UNIVERSITY) 13 May 1993 see abstract see page 14, line 13 - line 23	1,2,4

X	EP 0 445 749 A (FUJISAWA PHARMACEUTICALS) 11 September 1991 see page 2, line 5 see page 14, lines 40 and 43	1,2,4

X	EP 0 617 010 A (ZENECA LTD) 28 September 1994 see abstract see page 8, line 51 - line 56 see page 9, line 4 - line 5	1,2,4

X	US 5 441 950 A (J. T. COLLINS) 15 August 1995 see column 8, lines 3, 10, 20-23, 33	1,4
1 A		2

	-/--	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/US 97/16509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 546 547 A (HOECHST JAPAN LTD) 16 June 1993 see abstract see page 5, lines 16 and 20 ---	1,4
X	EP 0 534 756 A (ELI LILLY AND COMPANY) 31 March 1993 see page 2, line 42 see page 5, line 7 ---	1,4
X	WO 96 05817 A (MEDINNOVA SF) 29 February 1996 see abstract see page 9, paragraph 1 see page 10, paragraph 2 -----	1,4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr. nal application No.
PCT/US 97/16509

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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

International Application No. PCT/US 97/16509

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1,2,4

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:

In view of the large number of coumpounds which are defined by the general pharmacological concepts of claims 1 and 2, the search had to be restricted for economic reasons. The search was limited to the compounds specifically mentioned in claim 3 AND to the general pharmacological classes of compounds mentioned in claim 2 without any particular preference for any specific compound, taking the general idea underlying the present invention (rectal or veaginal administration of an anti-incontinence agent) into account.
(see PCT Guidelines Chapter III,
paragraph 2.3).

Remark : Although claims 1-3
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/16509

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9623492 A	08-08-96	US 5532278 A	02-07-96
		US 5677346 A	14-10-97
		AU 4966496 A	21-08-96
		EP 0806948 A	19-11-97
		FI 973163 A	30-09-97
		NO 973516 A	07-08-97
GB 2278054 A	23-11-94	NONE	
WO 9709980 A	20-03-97	AU 6927596 A	01-04-97
WO 9308800 A	13-05-93	US 5234947 A	10-08-93
		AU 2896292 A	07-06-93
		CA 2124856 A	13-05-93
		EP 0663824 A	26-07-95
		JP 7500836 T	26-01-95
EP 445749 A	11-09-91	AT 140213 T	15-07-96
		AU 645062 B	06-01-94
		AU 7266291 A	12-09-91
		CA 2037721 A	09-09-91
		CN 1054586 A	18-09-91
		DE 69120699 D	14-08-96
		DE 69120699 T	09-01-97
		HU 9500345 A	28-09-95
		JP 2099462 C	22-10-96
		JP 4234832 A	24-08-92
		JP 8019058 B	28-02-96
		NO 175679 B	08-08-94
		US 5256824 A	26-10-93
EP 617010 A	28-09-94	CA 2118821 A	16-09-94
		JP 6321879 A	22-11-94
		US 5482969 A	09-01-96
US 5441950 A	15-08-95	AU 2694195 A	04-01-96
		WO 9533734 A	14-12-95
		US 5504077 A	02-04-96
EP 546547 A	16-06-93	JP 2549480 B	30-10-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internation oplication No
PCT/US 97/16509

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 546547 A		JP 5155773 A	22-06-93
		AT 110569 T	15-09-94
		AU 656443 B	02-02-95
		AU 2998592 A	17-06-93
		CA 2084962 A	11-06-93
		CN 1073861 A	07-07-93
		DE 69200365 D	06-10-94
		DE 69200365 T	16-02-95
		ES 2062860 T	16-12-94
		IL 104026 A	27-11-95
		MX 9207123 A	30-07-93
		US 5496823 A	05-03-96
		ZA 9209529 A	15-06-93
EP 534756 A	31-03-93	US 5281624 A	25-01-94
		AT 124934 T	15-07-95
		AU 655075 B	01-12-94
		AU 2537092 A	01-04-93
		CA 2079161 A	28-03-93
		CA 2079162 A	28-03-93
		CN 1071416 A,B	28-04-93
		CZ 281817 B	12-02-97
		DE 69203424 D	17-08-95
		DE 69203424 T	11-01-96
		EP 0537915 A	21-04-93
		HU 65375 A	02-05-94
		JP 5201961 A	10-08-93
		JP 5238996 A	17-09-93
		MX 9205433 A	01-03-93
		NO 178109 B	16-10-95
		NZ 244460 A	26-10-94
		RU 2057120 C	27-03-96
		ZA 9207240 A	22-03-94
WO 9605817 A	29-02-96	AU 3263795 A	14-03-96