表 8

十一酸睾丸素的鼠伤寒沙门氏菌诱变试验

十一酸睾丸素 (mg/ml)	每皿回变菌落数(均值)**							
	TA 100		TA 97		TA 98		TA 102	
	−S9	+S9	−S9	+S9	−S9	+S9	−S9	+S9
0	168	204	183	145	32	35	309	286
1	181	250	180	157	32	41	329	260
5	167	250	186	170	29	50	335	275
10	170	220	191	166	28	42	340	328
30	187	243	182	159	34	56	331	342
50***	217	227	192	160	35	60	335	409

** 重复 1—2 次，每次 3 皿。

*** 浓度至 50mg/ml 时，皿中有白色颗粒析出。

替换页(细则第 26 条)

结　　论

十一酸睾丸素5个不同剂量，50mg/ml，30mg/ml，10mg/ml，5mg/ml，1mg/ml，分别用TA100，TA97，TA98及TA102进行平板掺入试验，无论加或不加S9混合液，在上述实验条件下，均未测出该药品有致突变作用。

实施例4

十一酸睾丸素注射液临床验证总结

TU临床验证的主要目的为考察该药对男子性腺功能低下症（分为一般男子性功能障碍与不育症及克兰菲特综合征两类）与再生障碍性贫血的疗效以及用药过程的不良反应。

临床验证总结如下：

（1）男子性功能障碍与不育症。经六所医院临床验证，治疗组80例和安慰剂对照组35例，每月肌注1次十一酸睾丸素注射液2ml（含250mg），对照组肌注不含十一酸睾丸素的茶油2ml（安慰剂），连续4个月，对治疗阳萎有显著疗效，对少精症明显增加精子数，部分病人达到可生育的精子数水平。

试验采用双盲方法，按2:1比例随机划分为治疗与对照两组进行研究。时间从1983年4月起至1989年1月止，共有115例按规定要求完成了治疗。

结　　果

治疗效果

a. 少精不育症

治疗组30例，治疗前的精子均数及其95%可信限为2920±693万/ml，治疗后为5691±2104万/ml。治疗前后差别显著（$P<0.05$），属治疗"有效"13例，有效率为43.33%（其中5例的配偶分别于开始治疗后2.5—10个月怀孕，另8例精子数上升达正常）。治疗"无效"17例（包括10例精子数上升，但未达正常，1例无变化，6例减少）。

b. 勃起不坚

治疗组21例，其中原发性勃起不坚14例，继发性7例。经治

疗有效 20 例(其中显效 14 例),有效率为 95.2%,治疗无效 1 例。

对照组 9 例,其中原发性勃起不坚 5 例,继发性 4 例。治疗有效 6 例(其中显效 3 例),有效率为 66.67%,治疗无效 3 例。

两组有效率的差别显著(P<0.05),说明 TU 对勃起不坚有明显疗效。

c. 阳萎

治疗组 14 例,其中原发性阳萎 4 例,继发性阳萎 10 例。治疗有效 13 例(其中显效 9 例),有效率为 92.86%,无效 1 例。

对照组 12 例,其中原发性阳萎 4 例,继发性阳萎 8 例。治疗有效 5 例(其中显效 3 例),有效率 41.67%,无效 7 例。

两组治疗有效率的比较差别极显著(P<0.01),说明 TU 对阳萎有显著疗效。

(2) 克兰菲特综合征。经北京协和医院内分泌科以十一酸睾丸素注射液治疗克兰菲特综合征 13 例,每月肌注 1 次 250mg(2ml),连续 4 个月,患者血清睾酮水平明显升高,性功能均得到明显增强,已婚患者有接近正常性生活,睾丸体积显著增大,性毛的改变以阴毛最为明显。

此病为染色体异常的疾病,目前无病因治疗方法,患者需长期终身使用睾丸素制剂替代治疗。本发明注射液为长效制剂,疗效肯定,雄性激素活性持续时间长达 70 天左右,吸收良好,无显明副作用,比进口的庚酸睾丸素注射液和环戊丙酸睾丸素注射液作用时间更长,可减少注射次数,减轻病人痛苦,且价格也较进口注射液便宜,易被患者接受为终身替代药物。附临床疗效小结(提要)。

用十一酸睾丸素(TU)治疗克兰菲特综合征 疗效。13 例患者每月注射 TU250mg 共 4 个月后,患者的体力、第二性征及性功能均有改善,用药前血清睾酮(T)水平为 130.2±107.9(M±SD)ng/dl,在治疗第 4 月时血清 T 水平在注药第 10、20 及 30 日分别升高达 588.9±350.3,440.5±196.0 及 316.9±183.5ng/dl。治疗前及治疗 4 月时血 FSH、LH 及 E2 水平无明显改变,但血性激素结合球蛋白容量由 39.0±7.4 降至 30.2±5.8nmol/L,患者睾丸体积轻度增大。本结果表明国产十一酸睾丸素是男 性 性 功能低减替代治疗的

有效长效制剂，应每 3—4 周注射 250mg。

(3)再生障碍性贫血。经五所医院临床验证，以十一酸睾丸素注射液合并一叶 碱及左旋咪唑治疗“再障”60 例(称试验组)，同时以康力龙片合并一叶 碱及左旋咪唑治疗 32 例作为对照(称对照组)。试验组注射十一酸睾丸素每月 2 次，每次 500mg(4ml)；对照组口服康力龙片每日 3 次，每次 1 片 2mg，.所合并的一叶 碱 8mg，每日肌注 1 次，左旋咪唑 50mg，每日口服 3 次，每周连服 3 日同组相同。连续用药 4—6 个月，试验组总有效率为 55.6%，对照组总有效率为 53.3%；连续治疗 6 个月以上，试验组总有效率为 90%，对照组总有效率为 73.3。在治疗过程中，对照组有 31.2%病人谷丙转氨酶升高，试验组肝功能无明显影响。两组药物对重型“再障”均无显著效果，故十一酸睾丸素注射液适用于非重型慢性再生障碍性贫血。结果见表 9，表 10。所有的病例的诊断及分型的确定均符合 1981 年全国再障会议(廊坊)及 1987 年全国再障(宝鸡)会议所确定的标准，疗效标准按《指导原则》所规定的分为治愈，基本治愈，明显进步及无效四级，因本组病例治疗后的随访期不到一年，故疗效统计按基本治愈，明显进步及无效三级评定。

表 9

以十一酸睾丸素为主治疗组的疗效

型别	治疗持续时间	总例数	基本治愈	明显进步	无效	总有效率%
非重型	4—6个月	36	5	15	16	55.6
	6个月以上—11月	20	5	13	2	90.0
重　型	4—6个月	4	0	0	4	0
合计		60	10	28	22	63.3

表 10

以康力龙为主对照组的疗效

型别	治疗持续时间	总例数	基本治愈	明显进步	无效	有效率%
非重型	4—6个月	15	2	6	7	53.3
	6个月以上	15	3	8	4	73.3
重　型	4—6个月	2	0	0	2	0
合计		32	5	14	13	59.4

注：两组基本治愈病人中10例，其临床及骨髓象均符合治愈，因随访不到1年，或失访，故作为基本治愈计。

(4)男性避孕。浙江医科大学附属一院对14例育龄男性志愿者试验，以十一酸睾丸素注射液，每月肌注1次250mg，合并醋酸甲孕酮注射液，每月肌注1次200mg，连续4个月。在用药后1—4个月精子数均下降至400万/ml以下，随后再下降至零，大多数受试者在2个月内就可达节育效果，所有受试者在用药期间均获节育。停药后2—7个月精子数回升，并具生育力，9例甚至超过用药前的1—16.9倍，3例试验者的配偶后来怀孕。因此，其抗生育作用是可塑的。附临床研究小结。

小　　结

复方TU的抗生育作用是肯定的，多数用药者的性欲与性机能有所增强。每月肌注复方TU1剂，大多数在2个月内就可达节育效果。停用复方TU后2—7个月精子数回升，并具有生育力，因此，其抗生育作用是可逆的。为安全起见，在停药后2个月起就应采取避孕措施。本研究还表明，复方TU对正常人体是安全的，对重要脏器无明显影响。

(5)两种睾丸素注射液比较。德国Westfalischen Wilhelms大学生殖医学研究所主任E. Nieschlag教授，在其研究所对本发明的十一酸睾丸素注射液与庚酸睾丸素注射液比较，利用去势雄猴进行实验研究，结果表明：肌注1次庚酸睾丸素在第13周后，去势雄猴早已停止射精，血液中已测不到睾酮，而肌注1次十一酸睾丸素在13周后，去势雄猴仍可射精，血液中仍可测出睾酮。因此认为本发明注射液具有比国外现有的庚酸睾丸注射液更长的雄激素活性。

本发明内容，通过上述实施例，说明较已有注射用睾丸素酯类制剂，维持雄激素活性时间更持久(肌注1次，去势雄大鼠与雄鸡可持续药效70天以上，去势雄猴可持续药效13周以上)，不良反应少，对肝、肾等重要脏器无明显影响。与口服十一酸睾丸素胶囊(Organon药厂产品)比较，本发明肌注给药可避免首过消除，生物利用度高，其效价为口服胶囊的6倍。基于本发明的优点，适用于需雄激素作长程治疗或终生替代治疗的疾病，由于用量小，价格远低于同类产品，每月只需注射1次，减轻病人痛苦与药费负担，易为患

者所接受。本发明注射液配伍甲孕酮，通过对腺垂体的负反馈作用，可逆性抑制精子生成，可用于男性长效避孕。

权 利 要 求

1. 十一酸睾丸素注射液，其包括作为活性成份的十一酸睾丸素，注射用植物油，有或没有药用苯甲酸苄酯。

2. 权利要求 1 的注射液，其注射用植物油选自：茶油，麻油，花生油，橄榄油和豆油等。

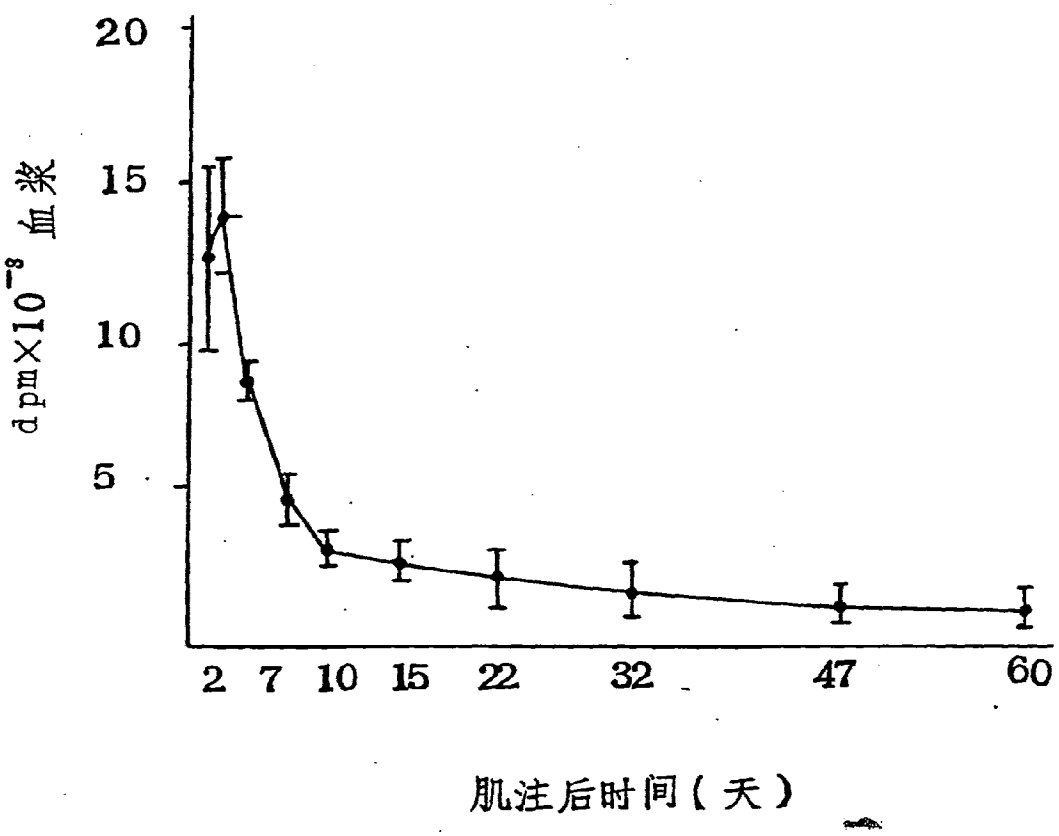
3. 权利要求 1 的十一酸睾丸素注射液用于治疗需雄激素治疗的疾病。

4. 权利要求 1 的十一酸睾丸素注射液用于治疗需雄激素类药作长程治疗或终生取代治疗的疾病。

5. 权利要求 1 的十一酸睾丸素注射液单用或与少量孕激素或雌激素联合用药，用于长效男性避孕。

Fig. 1

Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN 94/00084

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5] A61K 9/08, 31/565, 31/56

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[5] A61K 9/08, 31/565, 31/56

Documentation searched other than minimum documentation to the extent that such documents are included in t :lds searched

Chinese Patent

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CPRS, CIPIS

C. DOCUMENTENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Zhejiang Yike Daxue Xuebao, Volume 17, No. 2, 1988, Zheng, Jiang et al:"Absorption, distribution, and excretion of intramuscularly administered [^{3}H]testosterone undecanoate in rats", See P53	1—5
X	Chemical Abstract, Volume 86, 1977, (BV OSS. Neth.) Lakeman J. et al:"Study of the Biological availability of various oral dosage forms of testosterone undecanoate", abstract 111094d & Pharm. Weekbl. 1976,111(49),1233—8	1,2
Y	EP A 0001851(AKZO N. V.)16. 05. 1979 abstract, Claim 1	1,2

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15. December. 1994(15. 12. 1994)	29 DEC 1994 (29.12.94)
Name and mailing address of the ISA/ Chinese Patent Office, 6 Xitucheng Rd. Jimen Bridge, Haidian District, 100088 Beijing, China Facsimile No. (86—1)2019451	Authorized officer Sun Li Telephone No. (86—1)2093892

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN 94/00084

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstract, volume 104, 1986(Prague Czech.)Hampl, R. et al:"The use of andriol in treatment of androgen deficiency in transsexual women", abstract 219390b & J. Steroid Biochem. 1986,21(1),349—52	3,4
Y	Chemical Abstract, volume 109, 1988(Lyon Fr.)Guerin, J. F. et al:"Inhibition of spermatogenesis in men using various combinations of oral progestins and percutaneous or oral ardrogens", abstract 48600S & Int. J. Androl. 1988,11(3),187—99	5
Y	Chemical Abstract, volume 90, 1979(Muenster Ger.) Nieshlag, E. et al:"Chinical trial with testosterone undecanoate for male fertility control", abstract 133078m & Contraception 1978, 18(6), 607—14	5
A	Chemical Abstract, volume 105, 1989(BH Oss. Neth.) Neisingh, S. E. et al:"A dissolution method for hard and soft gelatin capsules containing testosterone undecanoate in oleic acid", abstract 11987q & Drug. Dev. Ind. Pharm. 1986,12(5) 651—63	1

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INTERNATIONAL SEARCH REPORT
Information patent family members

International application No.
PCT/CN 94/00084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP A 0001851	16. 05. 79	NZ A 188755	11. 02. 81
		AU B_2 523752	12. 08. 82
		FI B 67298	30. 11. 84

Form PCT/ISA/210(patent family annex)(July 1992)

国际检索报告

国际申请号
PCT/CN 94/00084

A. 主题的分类　　IPC[5] A61K 9/08, 31/565, 31/56

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IPC[5] A61K 9/08, 31/565, 31/56

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C. 相关文件

类　型*	引用文件,必要时,包括相关段落的说明	相关的权利要求编号
X	浙江医科大学学报,第17卷,第2期,1988,郑江等:"[^{3}H]十一酸睾丸素肌注后在大鼠的吸收、分布和排泄,"见第53页	1～6

☒ 其余文件在C栏的续页中列出.　　☒ 见同族专利附件.

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国际检索实际完成的日期	国际检索报告邮寄日期
15.12月.1994 (15.12.1994)	29·12月 1994 (29.12.94)
国际检索单位名称和通讯地址　　中国专利局 100088 中国北京市海淀区蓟门桥西土城路6号 传真号　(86-1) 2019451	受权官员　孙俐 电话号码　(86-1) 2093893

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C(续). 相关文件

类 型*	引用文件，必要时，包括相关段落的说明	相关的权利要求编号
X	Chemical Abstract, volume 86, 1977(BV Oss. Neth.) Lakeman J. et al: "Study of the Biological availability of various oral dosage forms of testosterone undecanoate", abstract 111094d & Pharm. Weekbl. 1976, 111(49), 1233-8	1, 2
Y	EP A 0001851(AKZO N.V.) 16.05月.1979(16.05.1979) 摘要，权利要求1	1, 2
Y	Chemical Abstract, volume 104, 1986(Prague Czech.) Hampl, R. et al: "The use of andriol in treatment of androgen deficiency in transsexual women", abstract 219390b & J. Steroid Biochem. 1986, 21(1), 349-52	3, 4
Y	Chemical Abstract, volume 109, 1988(Lyon Fr.)Guerin, J.F. et al: "Inhibition of spermatogenesis in men using various combinations of oral progestagens and percutaneous or oral androgens", abstract 48600s & Int. J. Androl. 1988, 11(3), 187-99	5
Y	Chemical Abstract, volume 90, 1979(Muenster Ger.) Nieshlag, E. et al: "Clinical trial with testosterone undecanoate for male fertility control", abstract 133078m & Contraception 1978, 18(6), 607-14	5
A	Chemical Abstract, volume 105, 1989(BH Oss.Neth.) Neisingh, S.E. et al: "A dissolution method for hard and soft gelatin capsules containing testosterone undecanoate in oleic acid", abstract 11987q & Drug. Dev. Ind. pharm. 1986, 12(5), 651-63	1

国际检索报告
同族专利成员的情报

国际申请号
PCT/CN 94/00084

检索报告中引用的专利文件	公布日期	同族专利成员	公布日期
EP, A, 0001851	16.05.79	NZ A 188755	11.02.81
		AU B_2 523752	12.08.82
		FI B 67298	30.11.84

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation [6] : **A61K 31/565 // (A61K 31/565, 31:565) (A61K 31/565, 31:135)**	**A1**	**(11) Internationale Veröffentlichungsnummer: WO 96/19997** **(43) Internationales Veröffentlichungsdatum:** 4. Juli 1996 (04.07.96)

(21) Internationales Aktenzeichen: PCT/EP95/05106

(22) Internationales Anmeldedatum: 23. December 1995 (23.12.95)

(30) Prioritätsdaten:
P 44 47 402.4 23. December 1994 (23.12.94) DE

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(81) Bestimmungsstaaten: AU, BG, BR, CA, CN, CZ, EE, FI, HU, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, UA, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: COMPOUNDS WITH PROGESTERONE-ANTAGONISTIC AND ANTI-OESTROGEN PROPERTIES INTENDED FOR COMBINED USE IN FEMALE CONTRACEPTION

(54) Bezeichnung: PROGESTERONANTAGONISTISCH- UND ANTIÖSTROGEN WIRKSAME VERBINDUNGEN ZUR GEMEINSAMEN VERWENDUNG FÜR DIE WEIBLICHE KONTRAZEPTION

(57) Abstract

The invention concerns the use of at least one compound with progesterone-antagonistic properties and at least one compound with anti-oestrogen properties, each in a dose which would not in itself inhibit ovulation, in a single dosing unit, in order to prepare medicaments for female contraception.

(57) Zusammenfassung

Die vorliegende Erfindung beschreibt die Verwendung mindestens einer Verbindung mit progesteronantagonistischer (PA) und mindestens einer Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption.

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Progesteronantagonistisch- und antiöstrogen wirksame Verbindungen zur gemeinsamen Verwendung für die weibliche Kontrazeption

Die vorliegende Erfindung betrifft die Verwendung mindestens einer Verbindung mit progesteronantagonistischer (PA) und mindestens einer Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption.

Die erfindungsgemäß hergestellten Arzneimittel entfalten ihre empfängnisverhütende Wirkung auf der Basis der Rezeptivitätshemmung, indem eine Einnistung einer befruchteten Eizelle in die Uterusschleimhaut verhindert wird, ohne daß die Ovulation bzw. der Zyklus gestört wird.

Bereits auf der ganzen Welt hat sich der Gebrauch von oralen Kontrazeptiva zu einem gesellschaftlichen Faktor entwickelt, der nicht mehr wegzudenken ist. Besonders unter dem Aspekt der sich nach wie vor rasant entwickelnden Weltbevölkerung ist eine Weiterentwicklung der bislang bewährten Methoden zur Fertilitätskontrolle unbedingt erforderlich.

Der Einsatz von kompetitiven Progesteronantagonisten in der weiblichen Fertilitätskontrolle wird sowohl bei diversen Tierspezies als auch am Menschen schon seit einigen Jahren diskutiert, wie den nachfolgend aufgeführten Publikationen entnommen werden kann, wobei insbesondere der Einsatz von RU 486 (11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on; EP-A-0057115) in diesem Zusammenhang aufgeführt wurde:

Collins et al., Blockade of the spontaneous mid-cycle gonadotropin surge in monkeys by RU 486; A progesterone antagonist or agonist. J. Cli. Metab., 63:1270-1276 (1986);

Croxatto, H.B., Salvatierra 1990 Cyclic use of antigestagens for fertility control. IIIrd International Symposium on Contraception, Heidelberg, June 19-23, 1990;

Danford et al., Contraceptive potential of RU 486 by ovulation inhibition. III. Preliminary observations on once weekly administration. Contraception 40: 195-200 (1989);

Kekkonen et al., Lähteoenmäki P 1990 Interference with ovulation by sequential treatment with the antiprogesterone RU 486 and synthetic progestin. Fertil Steril [Fertile Sterile] 53: 4747 (1990);

Puri et al., Gonadal and pituitary responses to progesterone antagonist ZK 98 299 during the follicular phase of the menstral cycle in bonnet monkeys. Contraception 39(2): 227-243 (1989);

Puri et al., Contraceptive potential of a progesterone antagonist ZK 98 734 ((*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estra-4,9-dien-3-on): Effect on folliculogenesis, ovulation and corpus luteum function in bonnet monkeys. In Moudgal et al., (eds) (1990).

Der kontrazeptive Effekt eines Progesteronantagonisten ist einerseits von der ovulationshemmenden Wirkung anderseits von direkten Effekten auf das Endometrium bedingt.

Hierbei ist zu erwähnen, daß diejeniege Dosierung eines kompetitiven Progesteronantagonisten, welche einen ovulationsinhibierenden Effekt hervorruft, sehr stark von dem jeweiligen kompetitiven Progesteronantagonisten abhängt:

Bei Progesteronantagonisten vom RU 486-Typ handelt sich um wenig-dissozierte Verbindungen mit einer stark ausgeprägten ovulationshemmenden Wirkung.

Bei Progesteronantagonisten vom Onapriston-Typ handelt sich um endometriumsspezifische (stark-dissozierte) Verbindungen, die die Ovulation erst bei hohen Dosierungen hemmen. Eine chronische Behandlung mit derartigen Progesteronantagonisten führt zur Wachstumsretardierung des Endometriums, wobei der ovarielle und menstruelle Zyklus nicht gestört wird. Im Endometrium kommt es zur Degeneration von endometrialen Drüsen und zur Verdichtung des Stromas, so daß die Implantation eines befruchteten Eies verhindert wird (Hemmung der Rezeptivität).

Die Klasse von 11β-Aryl- oder 11β,19-Arylen-substituierten Steroiden wird pharmakologisch nach ihrem stark progesteron- bzw. glukocortikoid-antagonistischen Effekt unterschieden. So kann RU 468 einerseits für einen therapeutisch induzierten Schwangerschaftsabbruch (die humane abortive Dosis in Kombination mit einem

Prostaglandin liegt bei 200-600 mg; EP-A 0 139 608), andererseits aber auch über seine antagonistische Wirkung am Glucocortikoid-Rezeptor zur Therapie des Cushing-Syndroms eingesetzt werden.

Eine andere Möglichkeit der Verwendung kompetitiver Progesteronantagonisten für die weibliche Fertilitätskontrolle, die sogenannte "LH+2"-Behandlung, wird von Swahn et al. [The effect of RU 486 administration during the early luteal phase on bleeding pattern, hormonal parameters and endometrium, Human Reproduction 5(4): 402-408 (1990)] vorgeschlagen, indem 2 Tage nach dem Anstieg des luteinisierenden Hormons (LH) im Menstruationszyklus der Frau (das ist im allg. am Tag 14, 15 oder 16) einmalig eine ovulationshemmende Dosiseinheit RU 486 verabreicht wird (luteale Kontrazeption). Eine Behandlung mit RU 486 in diesem Abschnitt des Menstruationszyklus führt nicht zur Störung des Zyklus. Applikation von RU 486 in anderen Phasen des Zyklus führt bei Dosierungen oberhalb von 1 mg/Tag entweder zur Amenorrhoe bzw. zu einer Abbruchblutung. Allerdings besitzt dieses Verfahren keine praktische Bedeutung, da die einfache und genaue zeitliche Bestimmung des LH-Peaks immer noch ein Problem darstellt.

Von Glasier et al. [Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception, The New England J. of Med. 327: 1041-1044 (1992)] wird auch die Verwendung von RU 486 für die postkoitale Kontrazeption (emergency postcoital contraception) beschrieben. Die Methode zeigt neben einer hohen Wirksamkeit ein geringes Ausmaß von Nebenwirkungen. Bei einem hohen Prozentsatz der Frauen dieser Studie trat eine Verlängerung des Zyklus auf. Dieser Effekt ist primär auf die antiovulatorische Wirkung von RU 486 zurückzuführen.

Des weiteren wird in WO 93/23020 beschrieben, daß kompetitive Progesteronantagonisten in einer Dosis, die sowohl unterhalb der abortiven als auch ovulationsinhibierenden Dosierung liegt, zur weiblichen Fertilitätskontrolle verwendet werden können. Es handelt sich hier um eine im allgemeinen wöchentliche, bzw. mehrfache und damit regelmäßige Applikation.

Ebenso beschreibt die EP-A 0 219 447, welche Effekte die tägliche Gabe eines Progesteronantagonisten während der follikulären, bzw. optional auch der lutealen Phase des weiblichen Zyklus in einem Zeitraum von bis zu 4 Tagen in einer Dosierung

von 10-200 mg bezüglich des endometrialen Differenzierungszustandes auslöst. Die hierbei resultierenden Veränderungen am Endometrium werden hinsichtlich des Nidationszeitpunktes für die in-vitro-Fertilisation genutzt.

Von Batista et al. [Daily administration of the progesterone antagonist RU 486 prevents implantation in the cycling guinea pig. Am. J. Obstet. Gynecol. 165: 82-86 (1991)] wird auch die Verwendung von RU 486 für die weibliche Fertilitätskontrolle beschrieben, welche durch tägliche Einnahme, präkoital und den gesamten weiteren Zyklus hindurch, in einer ovulationshemmenden Dosis die Nidation beim Meerschweinchen verhindert.

Von Kawano et al. [Effect of RU 486 on Glycogen Metabolism in Endometrium. Acta Obstetrica et Gynaecologica Japonica, 41: 1507-1511, (1989)] wird am Rattenmodell der Einfluß von RU 486 in einer Dosierung von 30 mg/kg Körpergewicht auf den endometrialen Glykogen-Metabolismus beschrieben, so daß eine erfolgreiche Eiimplantation gestört wird. Die Applikation erfolgt allerdings am Tag 2 oder 4 der Schwangerschaft.

Die hormonelle Steuerung der Implantation ist speziesabhängig. Bei allen bisher untersuchten Säugetieren ist die Anwesenheit des ovariellen Progesterons für eine erfolgreiche Implantation notwendig. Bei postkoital ovariektomierten Ratten und Mäusen, die mit Progestron substituiert werden, kommt es allerdings ohne Östrogengabe zu keiner Implantation (Finn CA, Porter DG [1975] Implantation of ova [Chapter 6] and The control of implantation and the decidual reaction [Chapter 8]; In Finn CA and Porter [eds] The Uterus, Elek Science, London, pp 57-73; 86-95). Wird bei diesen Tierspezies Östrogen injiziert, kommt es sofort zur Implantation der Blastocyste (delayed implantation model). Diese Beobachungen deuten darauf hin, daß das ovarielle Östrogen bei Anwesenheit des Progesterons die Implantation bei Nagetieren induziert. Es war bereits bekannt, daß beim Meerschweinchen und Primaten die ovariellen Östrogene für die Implantation nicht essentiel sind. Bei Meerschweinchen, die nach Anpaarung ovariektomiert wurden, findet die Implantation nur nach einer Progesteronsubstitution (ohne zusätzlicher Östrogenbehandlung) statt (Deansley R [1972] Retarded embryonic development and pregnancy termination in ovariectomized guinea pigs: progesterone deficiency and decidual collapse; J Reprod Fert [1972] 28:241-247).

Sowohl Antiöstrogene als auch Östrogene in hoher Dosierung hemmen die Implantation bei Ratten und Mäusen (Martin L, Cox RJ, Emmens CW [1963] Further studies in the effects of estrogens and antiestrogens on early pregnancy in mice. J Reprod Fertil 5:239-247; Singh MM Kamboj VP [1992] Fetal resoption in rats treated with an antiestrogen in relation to luteal phase nidatory estrogen secretion. Acta endocrinol 126:444-50). Die implantationshemmende Wirkung von Antiöstrogenen mit östrogenen Partialwirkungen (Nafoxidine, Centchroman, Tamoxifen) wurde auch beim Meerschweinchen beschrieben (Wisel MS, Datta JK, Saxena RN [1994] Int J Fertil 39:156-163). Es ist unklar, ob die implantationshemmende Wirkung der oben genannten Antiöstrogene auf die antagonistische oder agonistische Wirkung zurückzuführen ist, da auch hochdosierte Östrogene die Implantation beim Meerschweinchen verhindern.

Die Verwendung von Östrogenantagonisten (Centchroman) zur Kontrazeption beim Menschen ist ebenfalls beschrieben (Nittyanand S, Kamboj VP [1992] Centchroman: contraceptive efficacy and safety profile. International Conference on Fertility Regulation, November 5-8, 1992 Bombay, India, Programme and abstracts). Allerdings treten bei wirksamen Dosierungen unerwünschte Nebenwirkungen vor, die auf die systemische Wirkung der Östrogenantagonisten zurückzuführen sind. Die Östrogendeprivation, die nach einer Langzeitbehandlung mit einem Antiöstrogen auftreten kann, limitiert zumindest deren regelmäßige Anwendung zur Kontrazeption.

Schließlich geht aus der DE-A 42 13 005 die Verwendung von Aromatasehemmern zur Empfängnisverhütung bei weiblichen Primaten im fortpflanzungsfähigen Alter in einer Dosierung, bei der der menstruelle Zyklus des weiblichen Primaten im wesentlichen unbeeinflußt bleibt, hervor. Aromatasehemmer blockieren die Biosynthese von Estrgenen aus deren metabolischen Vorstufen. Die Absoluthöhe der für die kontrazeptive Wirkung erforderlichen Tagesdosen hängt dabei ganz von der Art des verwendeten Aromatasehemmers ab. Für hochaktive Aromatasehemmer liegen die Tagesdosen in der Regel zwischen etwa 0,05 bis etwa 30 mg. Bei weniger aktiven Aromatasehemmern können die Tagesdosen auch höher liegen.

Der vorliegenden Erfindung liegt die Aufgabe zugrunde, ein Präparat für die endometriale Kontrazeption bereitzustellen (Hemmung der endometrialen Rezeptivität, postkoitale Anwendung, "Bedarfspille"), welches die oben genannte unerwünschte Nebenwirkung nicht zeigt und gleichzeitig eine höhere kontrazeptive

Sicherheit aufweist als die getrennte Applikation der entsprechenden Einzelkomponenten.

Unter "Bedarfspille" soll ein oral zu verabreichendes Arzneimittel verstanden werden, welches bei vorzugsweise einmaliger und praekoitaler bedarfsweiser Anwendung eine Konzeption verhindert. Ein derartiges Mittel, hergestellt unter ausschließlicher Verwendung eines kompetitiven Progesteronantagonisten, ist in der nicht veröffentlichten deutschen Patentanmeldung P 44 38 820.9 beschrieben.

Diese Aufgabe wird dadurch gelöst, daß mindestens eine Verbindung mit progesteronantagonistischer (PA) und mindestens eine Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, gemeinsam zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption verwendet werden.

Es wurde nunmehr gefunden, daß die Kombination eines Progesteronantagonisten und Antiöstrogens synergistisch die Endometriumsproliferation und -differenzierung hemmt, so daß der antifertile Effekt der Einzelkomponenten bei entsprechender Dosierung in der Kombination entweder verstärkt wird oder zur Erzielung eines mit den Einzelkomponenten bei deren separaten Anwendung vergleichbaren Effektes die Einzelkomponenten in der Kombination entsprechend niedriger dosiert werden können.

Mittel, enthaltend mindestens eine Verbindung mit antigestagener und mindestens eine Verbindung mit antiöstrogener Wirkung, insbesondere zur Geburtseinleitung und zum Schwangerschaftsabbruch sowie zur Behandlung gynäkologischer Störungen sowie die Verwendung mindestens einer Verbindung mit antigestagener und mindestens einer Verbindung mit antiöstrogener Wirkung zur Herstellung von Arzneimitteln für die angegebenen Indikationen, sind bereits Gegenstand der EP-A 0 310 541.

Pharmazeutische Zusammensetzungen zur postkoitalen Fertilitätskontrolle, die einen kompetitiven Progesteronantagonisten (Antigestagen) sowie einen Progesteron- und Östrogensyntheseblocker enthalten, sind bereits im US-Patent 4,670,426 beschrieben. Als typische Vertreter für den zu verwendenden kompetitiven Progesteronantagonisten sind Fluocinolonacetonid, Triamcinolonacetonid, Steroide mit einem zyklischen 16,17-Acetal mit Aceton und 11β-[4-(Dimethylamino)phenyl]-17β-

hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (RU 38 486) und äquivalente Derivate erwähnt. Der typische Gehalt liegt dabei zwischen 20 und 50 mg. Als Beispiele für den Progesteron- und Östrogensyntheseblocker sind Aminoglutethimid, 4β,17α-Dimethyl-17β-hydroxy-3-oxo-4α,5-epoxy-5α-androstan-2α-carbonitril, 20,25-Diazocholesterol und Verbindungen mit äquivalenter Aktivität angeführt und zwar in einer Dosis von 300 bis 1000 mg. Die Anwendung der Zusammensetzung hat gemäß US-Patent 4,670,426 möglichst früh innerhalb der ersten Woche nach dem Geschlechtsverkehr über einen Zeitraum von 3 Tagen zu erfolgen; am besten sollte die Behandlung 2 bis 6 Tage fortgesetzt werden. Die Verhinderung der Nidation und somit einer Schwangerschaft wird durch den synergistischen Effekt bei der gemeinsamen Anwendung der beiden Bestandteile der Zusammensetzung bewirkt, und zwar mit einer Erfolgsrate in der Größenordnung von 90% oder mehr.

Es wurde nunmehr gefunden, daß neben Antigestagenen (kompetitiven Progesteronantagonisten) auch reine Östrogenantagonisten, wie 7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol (ICI 182780), die Implantation beim Meerschweinchen hemmen. Dieser Befund deutet darauf hin, daß beim Meerschweinchen, anders als bisher angenommen, auch Östrogene eine wichtige Rolle bei der Implantation spielen.

Weiter wurde gefunden, daß beim Meerschweinchen überraschenderweise eine kombinierte Behandlung mit Progesteronantagonisten und Antiöstrogenen während der Periimplantationsphase (Tag 1-7 post coitum) eine synergistische Wirkung aufweisen. Diese Beobachtungen deuten darauf hin, daß bei dieser Spezies die Östrogene in der Blastozyste gebildet werden. Eine ähnliche Situation kann beim Menschen existieren.

Die wesentlichen Vorteile der vorliegenden Erfindung liegen nicht zuletzt in der niedrigen Dosierung der Wirkstoffe begründet, einerseits durch die mögliche Verringerung der bei einer Monotherapie erforderlichen wirksamen Mengen durch den synergistischen Effekt, andererseits durch die Verwendung niedrigerer, nicht-ovulationsinhibierender Dosierungen. So wird der weibliche Menstruationszyklus in keiner Weise in seiner Zyklizität beeinträchtigt (wie durch ovulationshemmende Substanzen wie RU 486 verursacht) und der Organismus nicht durch unnötig hohe Mengen des kompetitiven Progesteronantagonisten bzw. des Antiöstrogens belastet. Die Verwendung einer solchen Progesteronantagonisten/Antiöstrogen-Kombination

bietet eine sichere Empfängnisverhütung, d.h. die regelmäßige Einnahme eines derartigen Medikamentes (täglich, regelmäßig alle 3 bis 7 Tage) verhindert die Einnistung der Blastozyste ohne Beeinflußung des Zyklus. Ferner wird die kontrazeptive Sicherheit nach einer einmaligen, bedarfsorientierten präkoitalen Einahme unabhängig von dem Einnahmetag im Zyklus ("Bedarfspille") bzw. nach einer postkoitalen Behandlung erhöht.
Durch die Dosisreduktion des Antiöstrogens ist nicht mit einer Östrogendeprivation zu rechnen. Es kann so eine endometriumselektive Wirkung des Antiöstrogens erreicht und eine ungünstige Wirkung aufgrund einer Östrogendeprivation an anderen Organen, beispielsweise am Knochen, vermieden werden.

Das Gewichtsverhältnis beider Komponenten in dem neuen Arzneimittel kann dabei in weiten Grenzen variiert werden. So können sowohl gleiche Mengen PA und AÖ als auch ein Überschuß einer der beiden Komponenten eingesetzt werden. PA und AÖ werden gemeinsam, getrennt, gleichzeitig in einem Gewichtsverhältnis von im wesentlichen 50:1 bis 1:50, vorzugsweise 25:1 bis 1:25, und insbesondere 10:1 bis 1:10 verwendet. Die gleichzeitige Gabe ist bevorzugt. Vorzugsweise können PA und AÖ kombiniert in einer Dosiseinheit appliziert werden.

Die beiden Komponenten können einmal täglich oder intermittierend alle 3-6 Tage über den gesamten Zyklus appliziert werden. Sie können auch einmalig präkoital (nach Bedarf; "Bedarfs-Pille") unabhängig vom Zeitpunkt des Menstruationszyklus oder postkoital angewandt werden. Bei der präkoitalen Anwendung wird der Progesteronantagonist höher dosiert, allerdings unterhalb der ovulationshemmenden Dosierung.

Als kompetitive Progesteronantagonisten kommen alle Verbindungen in Frage, die die Wirkung des Progesterons am Gestagenrezeptor (Progesteronrezeptor) kompetitiv blockieren und dabei keine eigene gestagene Aktivität zeigen; die Blockade kann durch die verabreichte Substanz selbst oder durch deren Metaboliten bewirkt werden.

Bei den kompetitiven Progesteronantagonisten handelt sich gemäß vorliegender Erfindung vorzugsweise um endometriumsspezifische (dissozierte) Verbindungen die höchstenfalls eine schwache antiovulatorische Aktivität aufweisen. Es können auch nicht-dissozierte Progesteronantagonisten angewandt werden, wobei dann deren

Dosierung unterhalb der ovulationsinhibierenden Dosis liegt. Beispielsweise kommen folgende Steroide infrage:

11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (RU 38 486),
11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)-18a-homoestra-4,9-dien-3-on und
11β-[4-(Dimethylamino)phenyl]-17aβ-hydroxy-17aα-(1-propinyl)-17a-homoestra-4,9,16-trien-3-on (alle EP-A 0 057 115),
17α-Ethinyl-17β-hydroxy-11β-(4-methoxyphenyl)estra-4,9-dien-3-on (Steroids 37 (1981), 361-382),
11β-(4-Acetylphenyl)-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (EP-A 0 190 759),
4',5'-Dihydro-11β-[4-(dimethylamino)phenyl]-6β-methylspiro[estra-4,9-dien-17β,2'(3'*H*)-furan]-3-on
4',5'-Dihydro-11β-[4-(dimethylamino)phenyl]-7β-methylspiro[estra-4,9-dien-17β,2'(3'*H*)-furan]-3-on
11β-(4-Acetylphenyl)-19,24-dinor-17,23-epoxy-17α-chola-4,9,20-trien-3-on (alle US-A 4,386,085)
sowie
die in der EP-A 0 277 676 beschriebenen 11ß-Aryl-14ß-estradiene und -triene, die 19,11ß-überbrückten Steroide, die Gegenstand der EP-A-0 283 428 sind, die aus der EP-A-0 289 073 hervorgehenden 11ß-Aryl-6-alkyl (bzw. 6-Alkenyl oder 6-alkinyl)-estradiene und -pregnadiene und die aus der EP-A-0 321 010 bekannten 11ß-Aryl-7-methyl (bzw. 7-ethyl)-estradiene sowie die 10ß-H-Steroide der EP-A-0 404 283, beispielsweise (*Z*)-11β-[4-(Dimethylamino)phenyl]-17α-(3-hydroxy-1-propenyl)estr-4-en-17β-ol.

Weiterhin seien als typische Vertreter erfindungsgemäß zu verwendender, kompetitiver Progesteronantagonisten beispielsweise genannt:
11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on (EP-A-0 129 499);
(*Z*)-11β-(4-Acetylphenyl)-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estra-4,9-dien-3-on (EP-A-0 190 759);
(*Z*)-6'-(4-Cyanphenyl)-9,11α-dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on und

(*Z*)-9,11α-Dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-6'-(3-pyridinyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on
17α-Hydroxy-17β-(3-hydroxypropyl)-11β-[4-(1-methylethenyl)phenyl]-13α-estra-4,9-dien-3-on **(ZK 131 535)**
11β-[4-(3-Furanyl)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on **(ZK 135 695)**
(*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on
(*E*)-11β-[4-[[(Acetyloxy)imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on
(*E*)-11β-[4-[[[(Ethoxycarbonyl)oxy]imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on

Bei den letztgenannten PAs handelt es sich um solche vom dissoziierten Typ, bei denen bei einer bestimmten Schwellendosis Veränderungen des Endometriums beobachtet werden, während die Ovulation (zentrale Wirkung) nicht gehemmt wird. Der Quotient aus ovulationshemmender und abortiver Dosis (Dissoziationsfaktor) kann als ein Maß für die Dissoziation dienen. Dissoziierte PAs sind im Rahmen vorliegender Erfindung bevorzugt.

Die Aufzählung der PAs ist nicht abschließend; auch andere in den genannten Veröffentlichungen beschriebene kompetitive Progesteronantagonisten sowie solche aus hier nicht genannten Veröffentlichungen sind geeignet. Neuerdings sind auch nicht-steroidale, am Progesteronrezeptor als Antagonisten wirksame Verbindungen bekannt geworden (WO-A 93/21145), die für die Zwecke der vorliegenden Erfindung verwendet werden können.

Die kompetitiven Progesteronantagonisten können zum Beispiel lokal, topisch, enteral, transdermal oder parenteral appliziert werden. Für die bevorzugte orale Applikation kommen insbesondere Tabletten, Dragèes, Kapseln, Pillen, Suspensionen oder Lösungen in Frage, die in üblicher Weise mit den in der Galenik gebräuchlichen Zusätzen und Trägersubstanzen hergestellt werden können. Für die lokale oder topische Anwendung kommen beispielsweise Vaginalzäpfchen, Vaginalgels, Implantate, Vaginalringe, intrauterine Freisetzungssysteme (IUDs) oder transdermale Systeme wie Hautpflaster in Frage.

Eine Dosierungseinheit enthält etwa 0,25 bis 50 mg 11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on oder eine biologisch äquivalente Menge eines anderen kompetitiven Progesteronantagonisten.
Wirkäquivalente Mengen werden im Niditationshemmtest am Meerschweinchen (Behandlung Tag 1-7 post coitum) ermittelt.

Erfolgt die Applikation des erfindungsgemäß hergestellten pharmazeutischen Mittels durch ein Implantat, einen Vaginalring, ein IUD oder ein transdermales System, so müssen diese Applikationssysteme derart ausgebildet sein, daß die durch sie täglich freigesetzte Dosis des kompetitiven Progesteronantagonisten in diesem Bereich von 0,25 bis 50 mg liegt.

Die erfindungsgemäß zu applizierende Dosis eines kompetitiven Progesteronantagonisten kann im nicht-ovulationshemmenden sowie nicht-abortauslösenden Dosisbereich des betreffenden Progesteronantagonisten liegen.

Als antiöstrogen wirkende Verbindungen kommen erfindungsgemäß in erster Linie Östrogenantagonisten (kompetitive Antiöstrogene) infrage. Östrogenantagonisten gemäß vorliegender Erfindung können sowohl von Steroiden abgeleitet oder nicht-steroidale Verbindungen sein. Unter Östrogenantagonisten gemäß vorliegender Erfindung sollen nur solche Verbindungen verstanden werden, die möglichst selektiv wirken, d.h. die im wesentlichen nur die Wirkung von Östrogenen hemmen und/oder deren Konzentration senken.
Die Östrogenantagonisten wirken, indem sie Östrogen vom Rezeptor verdrängen.

Als Östrogenantagonisten kommen alle gebräuchlichen Verbindungen mit kompetitiver antiöstrogener Wirkung am Rezeptor in Betracht. Sie können etwa in gleichen Mengen eingesetzt werden wie die bereits im Handel befindlichen Östrogenantagonisten, das heißt die tägliche Dosis beträgt etwa 5-100 mg für Tamoxifen oder die biologisch äquivalente Menge eines anderen Östrogenantagonisten.

Als nicht-steroidale Östrogenantagonisten seien beispielsweise genannt:
(*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin (Tamoxifen),
1-[2-[4-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthalinyl)phenoxy]ethyl]pyrrolidin-hydrochlorid (Nafoxidin),

α-[4-[2-(Diethylamino)ethoxy]phenyl]-4-methoxy-α-phenylbenzenethanol (Mer-25), [6-Hydroxy-2-(4-hydroxyphenyl)-3-benzothienyl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanon-hydrochlorid (Raloxifen), (3*R-trans*)-3,4-Dihydro-2,2-dimethyl-7-methoxy-3-phenyl-4-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-2*H*-1-benzopyran (Centchroman),

weiter Verbindungen vom 1,1,2-Triphenylbut-1-en-Typ, insbesondere das 3,3'-(2-Phenyl-1-buten-1-yliden)bis[phenol]-diacetat [J. Cancer Res. Clin. Oncol., (1986), 112, S. 119-124];

ferner kommen als steroidale Östrogenantagonisten beispielsweise infrage:
17α-Ethinyl-11α-methylestra-1,3,5(10)-trien-3,17β-diol und 16β-Ethylestra-1,3,5(10)-trien-3,17β-diol,
N-Butyl-11-(3,17β-dihydroxyestra-1,3,5(10)-trien-7α-yl)-*N*-methylundecansäureamid und 7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol.

Erfindungsgemäß bevorzugt sind in jedem Fall solche Östrogenantagonisten, die besonders stark und möglichst selektiv am Endometrium wirken (beispielsweise Tamoxifen, Nafoxidin, 7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol).
Die Schwellendosis für endometriumselektive Wirkung wird an ovarektomierten, estradiolsubstituierten Ratten ermittelt. Als Parameter dient die mitotische Aktivität (Proliferationsmarker: PCNA). Als Schwellendosis gilt diejeniege Menge des Östrogenantagonisten, bei der nur ein Effekt am Uterus, nämlich eine Hemmung der estrogeninduzierten Proliferation des Endometriums, beobachtet wird.

Als Antiöstrogene gemäß vorliegender Erfindung können auch Aromatasehemmer in Verbindung mit Progesteronantagonisten verwendet werden. Aromatasehemmer unterdrücken die Synthese der Östrogene aus deren Vorstufen. Beispiele für Aromatasehemmer sind Atamestan = 1-Methylandrosta-1,4-dien-3,17-dion (DE-A 33 22 285), Pentrozol = 5-[Cyclopentyliden(1*H*-imidazol-1-yl)methyl]-2-thiophencarbonitril (EP-A 0 411 735) oder 4-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitril-monohydrochlorid (Cancer Res., 48, S. 834-838, 1988).
Die Verwendung von Östrogenantagonisten ist aber gegenüber derjenigen von Aromatasehemmern in jedem Fall bevorzugt, da die Östrogenantagonisten die Serum-

Östrogenkonzentration nicht beeinflussen und somit eine Beeinträchtigung des Zyklus vermieden wird.

Eine AÖ-Dosiseinheit enthält 0.01-100 mg Tamoxifen oder eine biologisch äquivalente Menge einer anderen antiöstrogen wirksamen Verbindung.
Ihre Formulierung kann analog wie die der Progesteronantagonisten erfolgen.

Progesteronantagonistisch- und antiöstrogen wirksame Verbindungen können z. B. lokal, topisch, enteral oder parenteral appliziert werden.

Vorzugsweise kommen der Progesteronantagonist und das Antiöstrogen in einer gemeinsamen Dosierungseinheit zur Anwendung.

Die nachfolgenden Beispiele dienen der näheren Erläuterung der vorliegenden Erfindung:

Beispiel 1

10,0 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
140,5 mg	Laktose
69,5 mg	Maisstärke
2,5 mg	Polyvinylpyrrolidon
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
225,0 mg	Gesamtgewicht der Tablette

Beispiel 2

20,0 mg	Tamoxifen (Antiestrogen mit agonistischer Partialwirkung)
50,0 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
105,0 mg	Laktose
40,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Beispiel 3

5,0 mg	7α-[9-(4,4,5,5,5-Pentafluorpentylsulfinyl)nonyl]estra-1,3,5(10)-trien-3,17β-diol (reines Antiestrogen)
50,0 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on

110,0 mg	Lactose
50,0 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Beispiel 4

0,5 mg	11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
0,2 mg	7α-[9-(4,4,5,5,5-Pentafluorpentylsulfinyl)-nonyl]-estra-1,3,5(10)-trien-3,17β-diol (reines Antiestrogen)
159,5 mg	Lactose
54,8 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
0,5 mg	Magnesiumstearat
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben ngegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Beispiel 5

Zusammensetzung einer öligen Lösung:

100,0 mg	Tamoxifen
343,4 mg	Rizinusöl
608,6 mg	Benzylbenzoat
1052,0 mg	= 1 ml
	Die Lösung wird in eine Ampulle gefüllt

Beispiel 6

5,0 mg	11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propinyl)estra-4,9-dien-3-on (RU-38486),
10,0 mg	(*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin, (Tamoxifen; Antiestrogen mit agonistischer Partialwirkung)
140,0 mg	Laktose
60,5 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
220,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird. Gegebenenfalls können auch die erfindungsgemäßen Wirkstoffe mit jeweils der Hälfte der oben angegebenen Zusätze getrennt zu einer Zweischichtentablette gepreßt werden.

Pharmakologische Beobachtungen

Versuch 1:

Die Versuche wurden an intakten Meerschweinchen mit normalem Zyklus durchgeführt. Die Behandlung wurde am Tag 1 post coitum angefangen. Die Tiere wurden über 6 Tage mit Vehikel (Benzylbenzoat/Rizinusöl), bzw. dem Tamoxifen in einer Dosis von 0,3, 1, 3 mg/Tag/Tier oder der progesteronantagonistisch wirksamen Verbindung Onapriston (0,3, 1,0, 3,0 mg/Tag/Tier), jeweils alleine, oder mit einer Kombination beider Verbindungen behandelt. Die Substanzen wurden subkutan appliziert. Als Parameter dient die Zahl der Implantationstellen am Tag 12 post coitum.

Die Kombination von Schwellendosen beider Komponenten (AG 0,3, 1 mg/ AÖ ca. 0,3, 1 mg) führt zu einer signifikanten Zunahme der Wirksamkeit (100%ige Implantationshemmung bei 1 mg AG + 1 mg AÖ und 1 mg AG + 0,3 mg AÖ) nach sechstägiger Behandlung (Abb. 1). Die synergistische Wirkung beider Komponenten ist nach einer Behandlung über 8 Tage noch stärker ausgeprägt.

Versuch 2

Die Versuche wurden an intakten Meerschweinchen mit normalem Zyklus durchgeführt. Die Behandlung wurde an Tag 1 p.c. angefangen. Die Tiere (n=6/Gruppe) wurden über 6 Tage mit Vehikel (Benzylbenzoat/Rizinusöl), bzw Tamoxifen/Antigestagen in einer Dosis von 0,3, 1, 3 mg/kg/Tier oder der progesteronantagonistisch wirksamen Verbindung (*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on jeweils alleine oder mit einer Kombination beider Verbindungen behandelt. Die Substanzen wurden s.c. appliziert. Als Parameter dient die Zahl der nichtgraviden Tiere an Tag 12.
Die Kombination von Schwellendosen (0,3 mg (*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on (ZK 137.316) + 0,3 mg AÖ) führt zu einer signifikanten Zunahme der Wirksamkeit (ca. 80% Rezeptivitätshemmung,
Abb. 2)

Versuch 3

Die Versuche wurden an intakten Meerschweinchen mit normalem Zyklus über einen Behandlungszeitraum von 2 Zyklen durchgeführt. Die Anpaarung fand im zweiten Zyklus statt.

Dosen von Onapriston: 0,1, 0,25, 0,5, 1,0 und 3,0 mg täglich s.c.

Dosen von Tamoxifen: 0,1, 0,25, 0,5, 1,0, 3,0 und 10,0 mg täglich s.c.

Die Kombination jeweils nur marginal wirksamer Einzeldosen (Onapriston 0,5 mg; Tamoxifen 0,5 mg) führt zu einer deutlichen Wirkungsverstärkung (Synergismus). Nur bei Verwendung einer Kombination im Sinne vorliegender Erfindung läßt sich eine vollständige Vermeidung von Schwangerschaften erzielen. In dem genannten Dosisbereich von Tamoxifen (0,1 - 10,0 mg/Tier) konnte keine vollständige Hemmung der Rezeptivität erreicht werden. Normale Schwangerschaften wurden bei 30% (10,0 mg) und 90% bis 100% (<1,0 mg) beobachtet. Auch nach der Behandlung mit hohen Onapriston-Dosen sind gelegentlich Schwangerschaften aufgetreten.

Nach einer Kombinationsbehandlung mit Onapriston und Tamoxifen (jeweils 1,0 mg) wird in allen Fällen eine vollständige Hemmung der Rezeptivität beobachtet. 100%ige Rezeptivitätshemmung bedeutet eine vollständige Vermeidung von Schwangerschaften.

Bei niedrigeren Dosen von Tamoxifen und Onapriston (<1,0 mg), die alleine keine bzw. eine marginale Wirkung aufweisen, lag die Rezeptivitätshemmrate bei 80% bis 100% aller Tiere.

Patentansprüche

1. Verwendung mindestens einer Verbindung mit progesteronantagonistischer (PA) und mindestens einer Verbindung mit antiöstrogener (AÖ) Wirkung, jeweils in nicht-ovulationshemmender Dosierung in einer einzelnen Dosiseinheit, zur Herstellung von Arzneimitteln zur weiblichen Kontrazeption.

2. Verwendung mindestens eines kompetitiven Progesteronantagonisten und eines Antiöstrogens nach Anspruch 1 zur Herstellung eines Arzneimittels zur postkoitaler weiblichen Fertilitätskontrolle in einer einmalig zu verabreichenden Dosiseinheit.

3. Verwendung mindestens eines kompetitiven Progesteronantagonisten und eines Antiöstrogens nach Anspruch 1 zur Herstellung eines Arzneimittels zur bedarfsorientierten weiblichen Fertilitätskontrolle, welches unabhängig vom Zeitpunkt des Menstruationszyklus angewandt werden kann, in einer einmalig zu verabreichenden Dosiseinheit.

4. Verwendung nach einem der Anspruche 1-3, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist aus der Gruppe der folgenden Verbindungen ausgewählt ist:
11β-[4-(Dimethylamino)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on,
(*Z*)-11β-(4-Acetylphenyl)-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estra-4,9-dien-3-on,
(*Z*)-6'-(4-Cyanphenyl)-9,11α-dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on,
(*Z*)-9,11α-Dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)-6'-(3-pyridinyl)-4'*H*-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-on,
17α-Hydroxy-17β-(3-hydroxypropyl)-11β-[4-(1-methylethenyl)phenyl]-13α-estra-4,9-dien-3-on,
11β-[4-(3-Furanyl)phenyl]-17α-hydroxy-17β-(3-hydroxypropyl)-13α-estra-4,9-dien-3-on
(*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on,
(*E*)-11β-[4-[[(Acetyloxy)imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on,

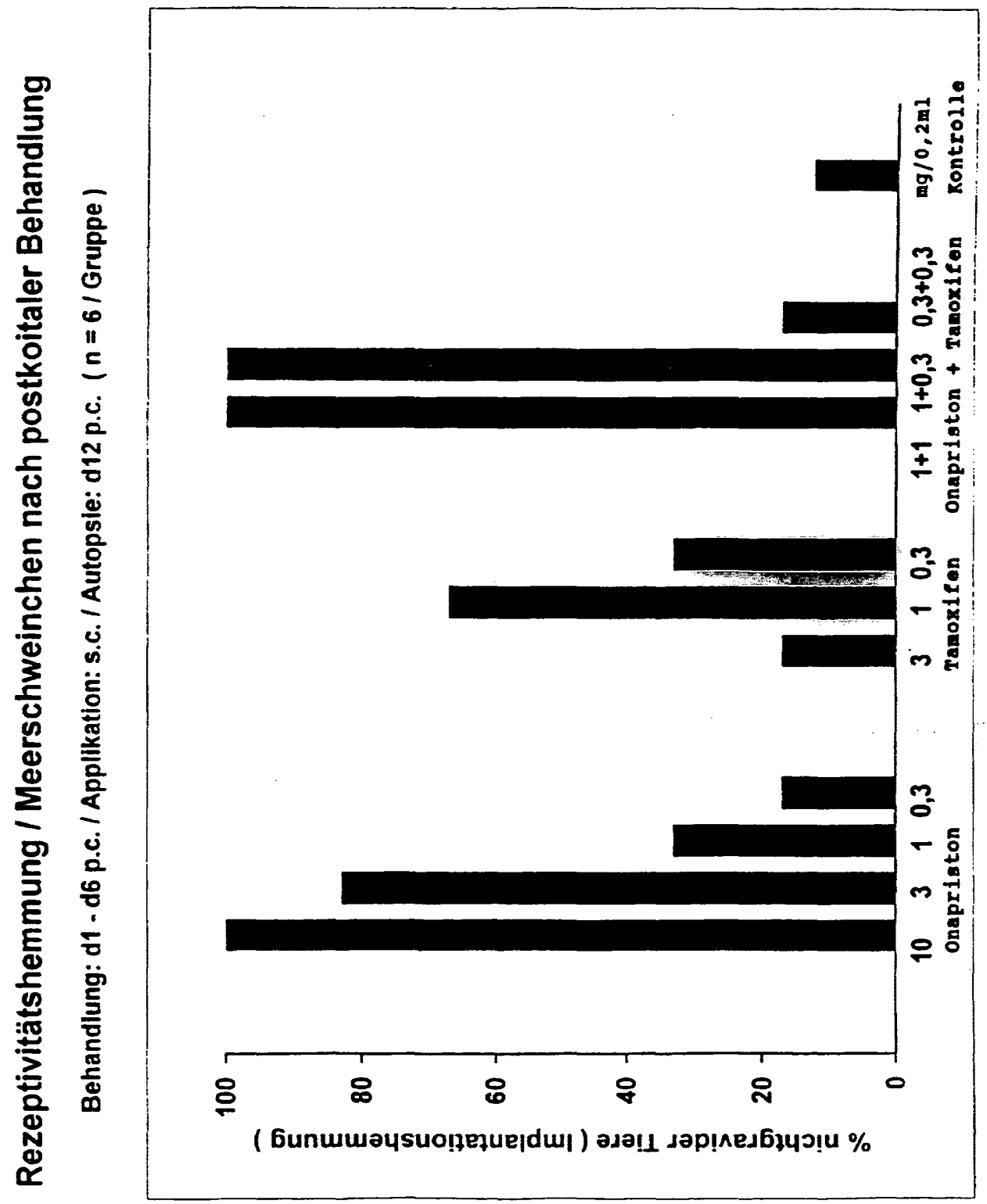
(*E*)-11β-[4-[[[(Ethoxycarbonyl)oxy]imino]methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-on,

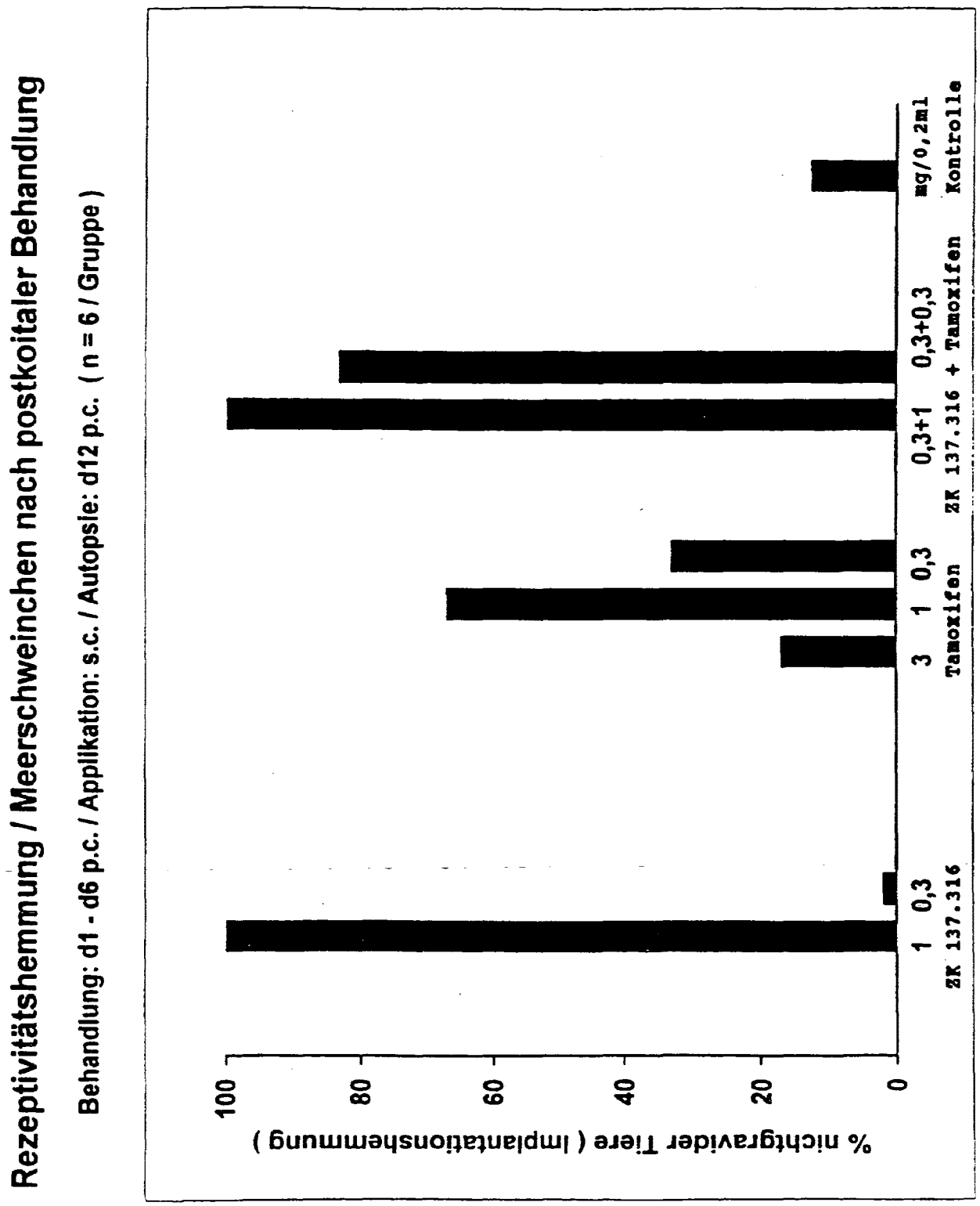
5. Verwendung nach einem der Ansprüche 1-4, dadurch gekennzeichnet, daß die Verbindung mit antiöstrogener Wirkung ein Östrogenantagonist ist.

6. Verwendung nach Anspruch 5, dadurch gekennzeichnet, daß der Östrogenantagonist aus der Gruppe der folgenden Verbindungen ausgewählt ist:
(*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin,
1-[2-[4-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthalinyl)phenoxy]ethyl]pyrrolidin-hydrochlorid,
[6-Hydroxy-2-(4-hydroxyphenyl)-3-benzothienyl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanon-hydrochlorid (Raloxifen),
N-Butyl-11-(3,17β-dihydroxyestra-1,3,5(10)-trien-7α-yl)-*N*-methylundecansäureamid,
7α-[9-[(4,4,5,5,5-Pentafluorpentyl)sulfinyl]nonyl]estra-1,3,5(10)-trien-3,17β-diol.

7. Verwendung von (*Z*)-11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propenyl)estr-4-en-3-on als PA und (*Z*)-*N*,*N*-Dimethyl-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]ethanamin als AÖ nach einem der Ansprüche 1-3.

8. Verwendung nach einem der Ansprüche 1-3, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist und das Antiöstrogen in dem Arzneimittel zur Applikation in lokaler, topischer, enteraler oder parenteraler Weise hergerichtet ist.





INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 95/05106

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 //(A61K31/565,31:565),(A61K31/565,31:135)

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.
A	EP,A,0 310 541 (SCHERING AG) 5 April 1989 see claims ---	1-8
A	EP,A,0 310 542 (SCHERING AG) 5 April 1989 see abstract -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1996	29. 05. 96

Name and mailing address of the ISA	Authorized officer
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	Leherte, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 95/05106

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-B-	2332188	20-04-89
		AU-B-	2332288	08-06-89
		CA-A-	1330039	07-06-94
		CA-A-	1329126	03-05-94
		DE-D-	3850026	06-07-95
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		JP-A-	1106823	24-04-89
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		US-A-	4888331	19-12-89

INTERNATIONALER RECHERCHENBERICHT

Internales Aktenzeichen
PCT/EP 95/05106

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K31/565 //(A61K31/565,31:565),(A61K31/565,31:135)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
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C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP,A,0 310 541 (SCHERING AG) 5.April 1989 siehe Ansprüche ---	1-8
A	EP,A,0 310 542 (SCHERING AG) 5.April 1989 siehe Zusammenfassung -----	1-8

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Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Leherte, C

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Angaben zu Veröffentlich. _n, die zur selben Patentfamilie gehören

Inter vales Aktenzeichen
PCT/EP 95/05106

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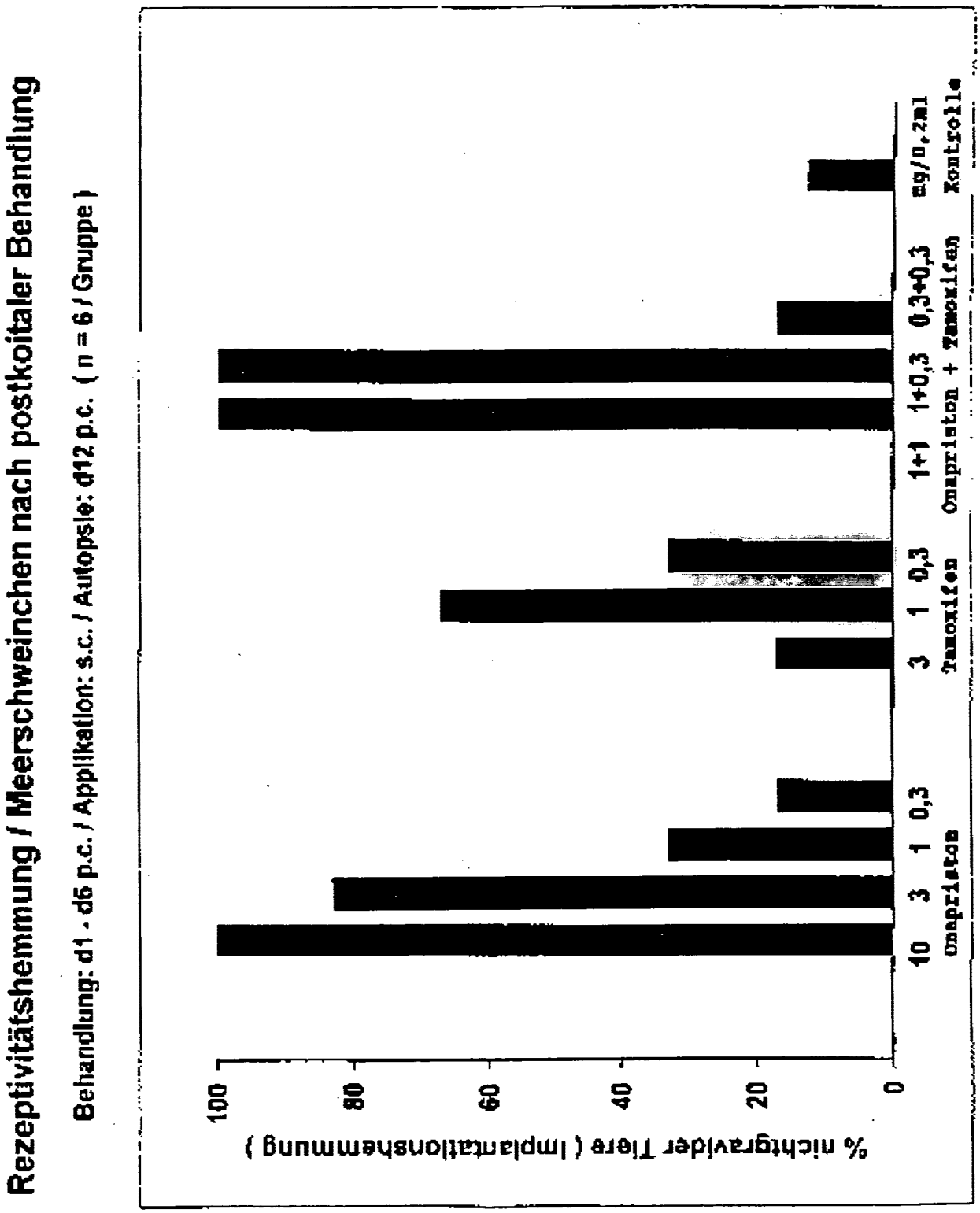

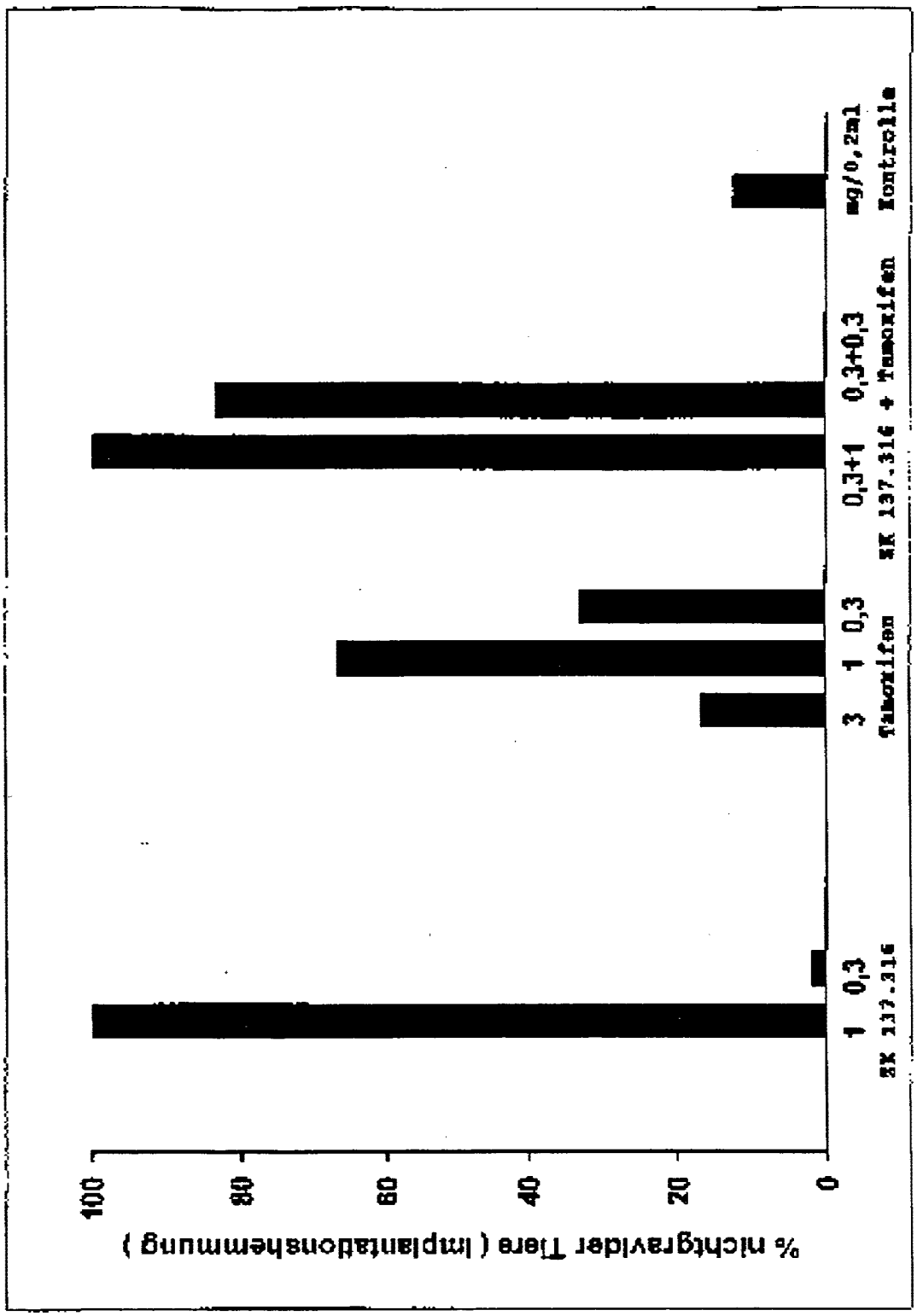

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/565, 9/08, 47/44

A1

(11) International Publication Number: WO 97/21440

(43) International Publication Date: 19 June 1997 (19.06.97)

(21) International Application Number: PCT/GB96/03022

(22) International Filing Date: 9 December 1996 (09.12.96)

(30) Priority Data:
9525194.8 12 December 1995 (12.12.95) GB

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(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, HU, 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, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), 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.

(54) Title: A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

(57) Abstract

The invention concerns a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises ICI 182,780, a pharmaceutically-acceptable oil, a pharmaceutically-acceptable lipophilic surfactant, a pharmaceutically-acceptable hydrophilic surfactant, and a pharmaceutically-acceptable water-miscible solvent, and the use of the composition on oral administration to a warm-blooded animal to produce an antioestrogenic effect.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
PCT/GB 96/03022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Form PCT ISA 210 (patent family annex) (July 1992)

A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

The invention relates to a novel pharmaceutical composition, particularly to a pharmaceutical composition adapted for oral administration containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, and more particularly to a solution formulation containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. The invention also relates to the use of the pharmaceutical composition of the invention for oral administration to a warm blooded animal to produce an antioestrogenic effect and to a method of producing an antioestrogenic effect by the oral administration of an effective amount of the pharmaceutical composition of the invention.

It is disclosed in European Patent Application No. 0 138 504 that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives of that invention. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration. For oral administration it is stated that a tablet or capsule containing the steroid derivative of the invention is particularly convenient. It is further stated therein that the tablet formulation can contain diluents, for example mannitol or maize starch, disintegrating agents, for example alginic acid, binding agents, for example methyl-cellulose, and lubricating agents, for example magnesium stearate. No pharmaceutically-acceptable diluent or carrier for a capsule formulation is specifically disclosed therein.

Subsequently the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol has been identified by the code number ICI 182,780 and that number shall be utilised for the compound hereinafter.

It is further disclosed in Cancer Research, 1991, 51, 3867-3873 and J. Endocrinology, 1992, 135. 239-247 that the antioestrogenic effect of ICI 182,780 in immature rats, mature rats or monkeys can be assessed by the administration of a suspension of the compound in arachis oil. This formulation was dosed either orally or by subcutaneous injection. The studies in rats demonstrated that the potency of the compound when dosed in arachis oil suspension was at least ten fold poorer when administration was by the oral route than when administration was by the subcutaneous route suggesting that the oral bioavailability of the compound from that formulation was low. A prolonged antioestrogenic effect was demonstrated when a dispersion of the compound in arachis oil was administered subcutaneously.

It is further disclosed in, for example, Laboratory Animal Science, 1993, 43, 247-251 that ICI 182,780 may be formulated for administration by intramuscular injection in a castor oil-based depot formulation. That formulation when given to laboratory animals at a dose of 4 milligrams per kilogram was found to inhibit the effects of endogenous oestrogen for three to four weeks.

Furthermore it is disclosed in J. Endocrinology, 1992, 135, 239-247, J. Endocrinology, 1993, 138, 203-209 and Cancer Research, 1994, 54, 408 that ICI 182,780 may be provided for administration by daily intramuscular injection in a 'short-acting' liquid formulation comprising ICI 182,780 in a propylene glycol-based solution.

It is an object of the present invention to provide a solution formulation containing the hydrophobic drug ICI 182,780 which does not exhibit, or which exhibits to a lesser degree, the problem of low oral bioavailability.

Many pharmaceutical compositions have been disclosed which are stated to be suitable for the dosing of hydrophobic drugs. Many of these formulations contain an oil such as arachis oil in which the hydrophobic drug is dissolved or dispersed. However the lack of miscibility of the oil with the aqueous environment of the gastrointestinal tract can lead to variable rates of absorption of the drug. To try to overcome the problem, it is common practice for a surfactant to be added to the pharmaceutical composition, particularly a hydrophilic surfactant such as a surfactant with a hydrophilic-lipophilic balance (HLB) of greater than about 8 and less than about 30. Such a surfactant may

produce an emulsion which, if the particle size is small, may lead to more complete absorption of the hydrophobic drug. However the use of hydrophilic surfactants may give a formulation of poor homogeneity as the surfactant may not be sufficiently miscible with the oil in which the hydrophobic drug is dissolved or dispersed. In a further refinement of such hydrophilic surfactant formulations, it is known that a lipophilic surfactant may be added to try to obtain the desired balance of hydrophilic and hydrophobic components to provide a stable emulsion when the formulation is added to an aqueous environment. The problem with this approach is that for each hydrophobic drug more than routine skill and knowledge is required to identify the exquisite balance of lipophilic and hydrophobic components which will provide a pharmaceutical composition of that hydrophobic drug which can be dosed orally to provide a reasonable oral bioavailability.

The many and various pharmaceutical compositions of the hydrophobic drug cyclosporin illustrate the complexities in this field of pharmaceutical research.

Thus, for example, it is disclosed in UK Patent Application No. 2 222 770 that cyclosporin may be formulated in a mixture of an oil such as a medium chain fatty acid triglyceride, a hydrophilic phase such as a mono- or di-alkyl ether of a polyoxyalkanediol, and a surfactant such as a hydrophilic or lipophilic surfactant or mixtures thereof.

Further it is disclosed in UK Patent Application No. 2 257 359 that cyclosporin may be formulated in a mixture of an oil such as a mixture of mono-, di- and tri-glycerides, a hydrophilic surfactant such as a surfactant having a HLB of at least 10, and the hydrophilic solvent 1,2-propylene glycol.

In addition it is disclosed in UK Patent Application No. 2 228 198 that cyclosporin may be formulated in a mixture of an oil such as a fatty acid triglyceride, a lipophilic surfactant such as a glycerol fatty acid partial ester, and a hydrophilic surfactant having a HLB of at least 10.

It has also been disclosed in PCT Patent Application WO 95/24893 that a hydrophobic drug may, for example, be formulated in a mixture of an oil such as a complete or partial ester of a medium chain or long chain fatty acid with a low molecular weight mono-, di- or polyhydric alcohol (for example a vegetable oil), a lipophilic surfactant such as a fatty acid or a mono- or di-glyceride of a fatty acid, and a hydrophilic surfactant having a HLB of greater than 10.

While this prior art shows some promising results, it should be recognised that ICI 182,780 is not a cyclic peptide like cyclosporin. ICI 182,780 is also a compound of higher molecular weight (Mol. Wt. = 603) and lipophilicity (estimated log P = 8 approx.) than the many drugs listed in PCT Patent Application WO 95/24893. Accordingly a pharmaceutical composition of ICI 182,780 is not disclosed in this prior art, nor can such a formulation be directly or unambiguously identified from consideration of this prior art.

We have investigated the factors which influence the solubilisation of ICI 182,780 and the maintenance of the compound in an absorbable form when it is dosed orally. We have developed solvents and mixtures of solvents which effectively solubilise the compound and we have also identified those oils and surfactants which facilitate the presentation of the compound in a suitable emulsion form to allow the enhanced absorption of the compound. We have discovered that surprisingly the selection and combination of particular classes of ingredients from within the formulations of known hydrophobic drugs provides the desired increase in oral bioavailability.

According to the invention there is provided a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

Suitable pharmaceutically-acceptable oils include, for example, medium or long chain (C6 to C22, preferably C12 to C20, more preferably C6 to C12) fatty acids and mono-, di- or tri-glycerides of such fatty acids and mixtures of said fatty acids and mono-, di- and tri-glycerides. Preferably the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid. Examples of preferred pharmaceutically-acceptable oils include vegetable oils such as soyabean oil, olive oil, arachis oil and coconut oil, fractionated vegetable oils such as fractionated coconut oil, and animal oils such as fish liver oil. Of these oils, fractionated coconut oil is more preferred.

Suitable fractionated coconut oils include, for example, those made available commercially under the trade name "Miglyol" from Huls (UK) Ltd., Milton Keynes, UK such as:-

Miglyol 810 which comprises a mixture of caprylic and capric acid triglycerides having an approximate fatty acid composition of C6 : 2%; C8 : 68%; C10 : 28% and C12 : 2%;

Miglyol 812 which comprises a mixture of caprylic and capric acid triglycerides having an approximate fatty acid composition of C6 : 3%; C8 : 56%; C10 : 36% and C12 : 5%; and

Miglyol 818 which comprises a mixture of caprylic, capric and linoleic acid triglycerides having an approximate fatty acid composition of C6 : 3%; C8 : 53%; C10 : 33%; C12 : 4% and C18 : 5%.

Of these fractionated coconut oils, Miglyol 812 is preferred.

Suitable pharmaceutically-acceptable lipophilic surfactants include, for example, surfactants with a hydrophilic-lipophilic balance (HLB) of less than about 10, for example fatty acids such as capric, caprylic, oleic and linoleic acid, and mono- or di-glycerides (or mixtures of mono- and di-glycerides) of fatty acids such as capric, caprylic and oleic acid, for example the lipophilic surfactants made available under the trade name "Imwitor" from Huls (UK) Ltd. such as Imwitor 988, Imwitor 742 and Imwitor 308 and those made available under the trade name "Capmul" from Karlshamns, Karlshamn, Sweden such as Capmul MCM.

Of these lipophilic surfactants, mixtures of the mono- and/or di-glycerides of capric and caprylic acids such as Imwitor 988 and Imwitor 742, especially Imwitor 988, are preferred.

Suitable pharmaceutically-acceptable hydrophilic surfactants include, for example, surfactants with a HLB of greater than about 10, for example the condensation products of an alkylene oxide such as ethylene oxide with castor oil or with hydrogenated castor oil, for example the hydrophilic surfactants made available under the trade name "Cremophor" from BASF, Cheadle Hulme, Cheshire, England such as Cremophor RH40, those made available under the trade name "Etocas" from Croda Chemicals, North

Humberside, England such as Etocas 40, and those made available under the trade name "Nikkol" from Nikko Chemicals Co. Ltd., Tokyo, Japan such as Nikkol HCO-60.

Of these hydrophilic surfactants, Cremophor RH40 is preferred.

Suitable pharmaceutically-acceptable water-miscible solvents include, for example, a (1-4C)alcohol such as ethanol and propanol, a poly-alcohol, for example, a monomeric poly-alcohol such as a (1-4C)alkylenepolyol, for example glycerol (propane-1,2,3-triol), or a (1-12C)glycol, for example ethylene glycol (ethane-1,2-diol), propylene glycol (propane-1,2-diol), diethylene glycol (3-oxapentane-1,5-diol), triethylene glycol (3,6-dioxaoctane-1,8-diol) and tetraethylene glycol (3,6,9-trioxaundecane-1,11-diol). Alternatively a suitable pharmaceutically-acceptable water-miscible solvent is, for example, a polymeric poly-alcohol such as polyethylene glycol (PEG), for example a PEG having an average molecular weight in the range 150 to 800 such as PEG 200, PEG 300, PEG 400 and PEG 600. Alternatively a suitable pharmaceutically-acceptable water-miscible solvent is, for example, an ether derivative of a pharmaceutically-acceptable poly-alcohol as defined hereinbefore, for example a mono-(1-4C)alkyl ether derivative such as a mono-methyl ether derivative or, for example a mono-cyclic ether derivative such as a furfurylmethyl, tetrahydrofurfurylmethyl or tetrahydropyranylmethyl ether derivative. Examples of such suitable etherified poly-alcohols include glycerol mono-methyl ether, ethylene glycol mono-methyl ether, propylene glycol mono-methyl ether, ethylene glycol mono-tetrahydrofurfurylmethyl ether, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether (ethyl digol), diethylene glycol mono-tetrahydrofurfurylmethyl ether (glycofurol), diethylene glycol mono-tetrahydropyranylmethyl ether, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-tetrahydrofurfurylmethyl ether, tetraethylene glycol mono-methyl ether and tetraethylene glycol mono-tetrahydrofurfurylmethyl ether. A suitable pharmaceutically-acceptable water-miscible solvent includes a mixture of two or more of the above-mentioned suitable water-miscible solvents. Preferred pharmaceutically-acceptable water-miscible solvents include propylene glycol and ethyl digol. Preferably ethanol or propylene glycol, or a mixture of ethanol and propylene glycol is used.

In a further advantage of the invention, it has been determined that, surprisingly, the combination of the above-mentioned ingredients of the pharmaceutical composition of the invention in the correct ratios improves the desired increase in oral bioavailability. In the table below, the advantageous relative ratios (as percentages of the weight of the formulation) are disclosed:-

Component	Generally	Preferred	More Preferred	Further Preferred
ICI 182,780	1-20%	2-18%	5-15%	8-12%
oil	1-20%	2-18%	5-15%	5-15%
hydrophilic surfactant	5-45%	10-40%	20-30%	20-30%
lipophilic surfactant	15-70%	25-60%	35-50%	35-50%
water-miscible solvent	1-30%	2-28%	5-25%	8-16%

The solution formulation of the invention may be presented in a form suitable for oral administration, for example a unit dosage form may be metered onto a spoon of suitable size and administered by mouth. Alternatively the solution formulation may be encapsulated by methods well known to those skilled in the arts of pharmaceutical science, for example by encapsulation within a shell comprising a gelatin or starch capsule such as a hard gelatin or starch capsule or a soft gelatin capsule [which may be formed from gelatin. an appropriate plasticiser (such as glycerin and sorbitol) and water].

The compositions of the invention may be obtained using conventional pharmaceutically-acceptable diluents well known in the art such as colouring, sweetening, flavouring and/or preservative agents. In the case of a soft gelatin capsule said diluents may be present in the liquid solution formulation encapsulated within the gelatin capsule or alternatively they may be present within the gelatin shell of the capsule. Capsule forms of the invention may be coated or uncoated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

The amount of active ingredient i.e. ICI 182,780, which is employed in a single dosage unit will necessarily vary depending on the host treated and the particular dosage

form employed. For example a solution formulation which is administered on a spoon will generally have a volume in the range, for example, 0.5 ml to 10 ml and will contain the active ingredient at a concentration in the range, for example, 5 mg/ml to 150 mg/ml, preferably in the range, for example, 20 mg/ml to 100 mg/ml. Alternatively a soft gelatin capsule having an internal volume of, for example, 0.5 ml, 1 ml, 2 ml, 3 ml or 5 ml may be employed and will contain the active ingredient at a concentration in the range, for example, 5 mg/ml to 150 mg/ml, preferably in the range, for example, 15 mg/ml to 120 mg/ml, more preferably 100 mg/ml.

The size of the dose of ICI 182,780 will naturally vary according to the nature and severity of the disease state being treated, and the age of the animal or patient being treated. In general ICI 182,780 will be administered so that a daily dose in the range, for example, 0.1 to 10 mg/kg body weight is received given, if required, in divided doses. Preferably a daily dose in the range, for example, 0.1 to 2 mg/kg body weight will be administered.

As stated previously it was disclosed in J. Endocrinology, 1992, 135, 239-247 and 1993, 138, 203-209 that ICI 182,780 may be formulated for administration by intramuscular injection as a solution formulation comprising ICI 182,780 in a propylene glycol-based solution. There was no disclosure therein of the dosing of that solution formulation by the oral route. The only specific disclosures of the administration of ICI 182,780 by the oral route were made in the first of the above-mentioned papers in J. Endocrinology and in Cancer Research, 1991, 51, 3867-3873 wherein the formulation comprised a suspension of the compound in arachis oil.

Thus according to this aspect of the invention there is provided the use of a solution formulation comprising:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent;

in the manufacture of a medicament for oral administration to a warm-blooded animal to produce an antioestrogenic effect.

This aspect of the invention also includes a method of producing an antioestrogenic effect by the oral administration to a warm-blooded animal in need of such an effect of an effective amount of a solution formulation comprising:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

In these aspects of the invention the weight ratios of the ingredients of the solution formulation are as defined hereinbefore. In addition the single dosage unit of the liquid solution formulation and the daily dosage rate are as defined hereinbefore.

The invention will now be illustrated in the following Examples which involve tests of the aqueous dispersion profiles and oral bioavailabilities of ICI 182,780 contained within various pharmaceutical formulations. In general the test procedures used were those described below:-

Test of Aqueous Dispersion Profiles

The aqueous dispersion profiles of the solution formulations of the invention were assessed using the following conventional procedure which was conducted at ambient temperature. An aliquot (0.2 ml of the formulations containing 2 g of ICI 182,780 per 100 ml and 0.04 ml of the formulation containing 10 g of ICI 182,780 per 100 ml) of each test formulation was added to an aqueous sodium chloride solution (0.154 M, 10 ml) in a vial. The vial was sealed with a cap and the contents were mixed by the repeated inversion of the vial. The dispersion of the formulation and/or the precipitation of the active ingredient of the formulation was assessed visually.

Test of Oral Bioavailability

The oral bioavailability of ICI 182,780 in the dog from various formulations of the compound was determined using the following method. Each test formulation was dosed to a group of five male beagle dogs, each weighing approximately 18 kg. Unless

otherwise stated the studies were carried out with the animals in a 'fasted' state, that is the animals were not fed later than 18 hours prior to the dosing of a test formulation and they were not fed until 5 or 6 hours after dosing. The formulation of Example 1 was dosed orally by gavage. Each of the other formulations was contained in a hard gelatin capsule (size 00) and dosed orally. In each case, water (approximately 150 ml) was dosed immediately thereafter by way of gavage. Blood samples were taken from an external jugular vein at various times up to 8 hours after dosing. The level of ICI 182,780 in each blood sample was determined using a conventional radioimmunoassay using an analogous procedure to that described in Cancer Research, 1994, 54, 408 {antibodies were obtained on administration to a group of sheep of a conjugate obtained by a mixed anhydride based coupling of 17β-(3-carboxypropionyloxy)-7α-[9-(4,4,5,5,5-pentafluoropentylthio)nonyl]-oestra-1,3,5(10)-triene-3-ol [obtained from 7α-[9-(4,4,5,5,5-pentafluoropentylthio)nonyl]oestra-1,3,5(10)-triene-3,17β-diol (Example 35 of European Patent Application No. 0 138 504) and succinic acid] and thyroglobulin}.

Using this methodology, the oral bioavailability of ICI 182,780 obtainable from each test formulation was assessed using the conventional parameters of maximum drug concentration [Cp (max)], the area under the graph of drug concentration versus time [AUC (0-8h)] and a percentage figure for the oral bioavailablity based on a comparison of the AUC results obtained for the test formulation and for a formulation which was dosed intramuscularly (IM) comprising:-

IM Formulation	% Weight in grams per ml
ICI 182,780	2.0
Ethanol	10.0
Water (Ph. Eur.)	8.0
poloxamer 407	1.0
propylene glycol (Ph. Eur.)	to 100%

The following calculation was carried out to determine the oral bioavailability:-

$$\% \text{ Oral Bioavailability} = \frac{\text{AUC (oral)} \times \text{Dose (IM)}}{\text{AUC (IM)} \times \text{Dose (oral)}} \times 100$$

Comparative Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a precipitate which was noted to aggregate over a period of about 10 minutes.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	2.0	Dose	50 mg
ethanol	10.0	Cp (max)	13.3 ± 2.7 ng ml^{-1}
water	8.0	AUC (0 to 8 hours)	34.9 ± 6.3 ng h ml^{-1}
propylene glycol	to 100%	Bioavailability	1.1 %

Comparative Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a crude emulsion.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
ethanol	13.5	Cp (max)	14 ± 2 ng ml^{-1}
Imwitor 988	76.5	AUC (0 to 8 hours)	28 ± 5 ng h ml^{-1}
		Bioavailability	0.8 %

Comparative Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
propylene glycol	10.0	Cp (max)	20 ± 4 ng ml^{-1}
Imwitor 988	80.0	AUC (0 to 8 hours)	51 ± 10 ng h ml^{-1}
		Bioavailability	1.5 %

Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	40.0		
Cremophor RH40	26.8	Cp (max)	83 ± 19 ng ml^{-1}
Miglyol 812	13.2	AUC (0 to 8 hours)	194 ± 34 ng h ml^{-1}
ethanol	10.0	Bioavailability	5.5 %

Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	45.9		
Cremophor RH40	22.95	Cp (max)	78 ± 17 ng ml^{-1}
Miglyol 812	7.65	AUC (0 to 8 hours)	193 ± 35 ng h ml^{-1}
propylene glycol	13.5	Bioavailability	5.4 %

Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 742	40.0		
Cremophor RH40	26.8	Cp (max)	80 ± 14 ng ml^{-1}
Miglyol 812	13.2	AUC (0 to 8 hours)	195 ± 26 ng h ml^{-1}
ethanol	10.0	Bioavailability	5.6 %

Example 4

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182.780	10.0	Dose	50 mg
Imwitor 988	37.4		
Cremophor RH40	22.95	Cp (max)	83 ± 11 ng ml^{-1}
Miglyol 812	7.65	AUC (0 to 8 hours)	194 ± 24 ng h ml^{-1}
ethanol	7.0	Bioavailability	5.6 %
propylene glycol	15.0		

CLAIMS

1. A pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

2. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid.

3. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is fractionated coconut oil.

4. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable lipophilic surfactant is a mixture of mono- and di-glycerides of capric and caprylic acids.

5. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable hydrophilic surfactant is the condensation product of ethylene oxide with castor oil or with hydrogenated castor oil.

6. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable water-miscible solvent is ethanol, propylene glycol, diethylene glycol mono-ethyl ether or diethylene glycol mono-tetrahydrofurfurylmethyl ether, or a mixture thereof.

7. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	2-18%
oil	2-18%
hydrophilic surfactant	10-40%
lipophilic surfactant	25-60%
water-miscible solvent	2-28%

8. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	5-15%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	5-25%

9. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	8-12%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	8-16%

10. The use of a pharmaceutical composition as claimed in any one of claims 1 to 9 in the manufacture of a medicament for oral administration to a warm-blooded animal to produce an antioestrogenic effect.

11. A method of producing an antioestrogenic effect by the oral administration to a warm-blooded animal in need of such an effect of an effective amount of a solution formulation as claimed in any one of claims 1 to 9.

5

INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/GB 96/03022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K9/08 A61K47/44

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 95 24893 A (SCHERER LTD R P ;LACY JONATHAN ERNEST (GB); EMBLETON JONATHAN KENN) 21 September 1995 cited in the application * p.14,; p.17, l.24-p.19, l.4; p.24, l.13-18; p.28, l.9; claims 1-9 *	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
6 March 1997	26. 03. 97

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 :		(11) Internationale Veröffentlichungsnummer:
A61K 31/35, 47/44	A1	WO 97/37653
		(43) Internationales Veröffentlichungsdatum: 16. Oktober 1997 (16.10.97)

(21) Internationales Aktenzeichen: PCT/EP97/01569

(22) Internationales Anmeldedatum: 27. März 1997 (27.03.97)

(30) Prioritätsdaten:
196 13 972.4 9. April 1996 (09.04.96) DE

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(81) Bestimmungsstaaten: AU, BB, BG, BR, BY, CA, CN, CZ, HU, IL, JP, KR, KZ, LK, MX, NO, NZ, PL, RO, RU, SK, TR, UA, US, europäisches 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).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: INJECTION FORMULATIONS OF AVERMECTINS AND MILBEMYCINS BASED ON CASTOR OIL

(54) Bezeichnung: INJEKTIONSFORMULIERUNGEN VON AVERMECTINEN UND MILBEMYCINEN AUF BASIS VON RIZINUSÖL

(57) Abstract

Injection formulations of avermectins and milbemycins based on castor oil are disclosed.

(57) Zusammenfassung

Gegenstand der vorliegenden Erfindung sind Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis von Rizinusöl.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis von Rizinusöl

Die Erfindung betrifft neue Injektionsformulierungen von Avermectinen und Milbemycinen in Tiere auf Basis von Rizinusöl.

Injektionsformulierungen von Ivermectin sind bekannt aus EP-A 146 414. Die Formulierungen enthalten ein Lösemittelgemisch aus Propylenglykol und Glycerinformal im Verhältnis 60:40 V/V. Von Propylenglykol ist bekannt, daß es in bestimmten Konzentrationen lokale Unverträglichkeiten hervorrufen kann (siehe Review: B. Kruss, Acta Pharm. Technol. 35(4) (1989) 187-196). Auch kann es zur Ausfällung des wasserunlöslichen Wirkstoffs Ivermectin im Gewebe um die Applikationsstelle kommen. So wurden bei der Anwendung entsprechender Formulierungen deutliche Schwellungen und Gewebeunverträglichkeiten an den Injektionsstellen beobachtet, die sich zum Teil erst nach mehreren Wochen zurückbildeten.

Injektionsformulierungen bestimmter Avermectine sind bekannt aus EP-A 393 890. Es handelt sich um ölige Formulierungen auf Basis von Sesamöl und Ethyloleat im Verhältnis 90:10 V/V. Diese Formulierungen sind verträglich, haben aber den Nachteil, daß bei Lagerung im Kühlschrank bei 4°C bereits nach einigen Tagen ein wolkiger Niederschlag entsteht.

Weitere Injektionsformulierungen von Avermectinen sind bekannt aus EP-A 45 655. Die dort beschriebenen Formulierungen enthalten verhältnismäßig hohe Anteile an Emulgatoren und sind zum Teil wenig verträglich.

Injektionsformulierungen von Avermectinen, die Triacetin (Glycerintriacetat) enthalten, sind in EP-A 413 538 beschrieben. In EP-A 535 734 werden Injektionsformulierungen von Avermectinen auf Basis von Triacetin und hydriertem Rizinusöl beschrieben.

Weitere Formulierungen zur Injektion von Milbemycinen und Avermectinen sind in EP-A 525 307 beschrieben. Die Herstellung der Formulierungen erfolgt, indem Glycerintristearat mit dem Wirkstoff geschmolzen und mit einem öligen neutralen Triglycerid vermischt und unter Verwendung von z.B. Methylcellulose und Salzen

emulgiert wird. Die durchschnittliche Partikelgröße in der so erhaltenen Mikroemulsion soll zwischen 25 und 300 µm liegen.

Gegenstand der vorliegenden Erfindung sind Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis von Rizinusöl.

Die Formulierungen enthalten bevorzugt

1. Wirkstoff 0,1 bis 10 Gew.-%

2. Rizinusöl 15 bis 50 Gew.-%

3. Ein oder mehrere Co-Lösungsmittel aus der Reihe pflanzlicher oder synthetischer Fettsäureester ein- oder mehrwertiger Alkohole, aliphatischer oder aromatischer Alkohole, cyclischer Carbonate in Konzentrationen von 30 bis 85 Gew.-%

4. gegebenenfalls weitere Hilfsstoffe.

Die erfindungsgemäßen Formulierungen weisen eine hervorragende Löslichkeit für die Wirkstoffe auf.

Die hohe Viskosität von Rizinusöl kann durch Zusatz von mittelkettigen Triglyceriden oder Propylenglykol-octanoat/decanoat oder Ethyloleat auf ein gewünschtes niedrigeres Maß eingestellt werden. Zusätzlich kann durch Addition von kleineren Volumina hydrophiler Lösemittel wie Benzylalkohol, Propylenglykol oder Propylencarbonat unter Beibehaltung eines einphasigen Systems die Löslichkeit des Wirkstoffs verbessert, die Viskosität weiter herabgesetzt und die Bioverfügbarkeit des Wirkstoffs verbessert werden. Die neuen Formulierungen sind außerordentlich gut verträglich und zeigen eine hohe Bioverfügbarkeit.

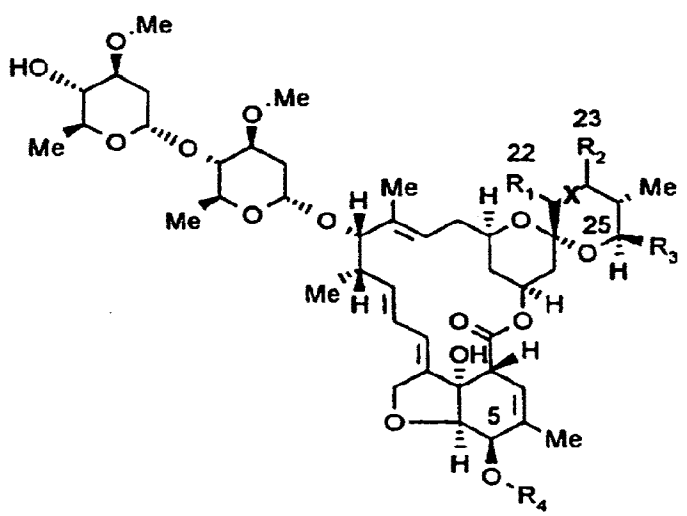
Die in den erfindungsgemäßen Formulierungen eingesetzten Wirkstoffe sind bekannt.

Avermectine wurden aus dem Mikroorganismus Streptomyces avermitilis als mikrobielle Metabolite isoliert (US-Pat. 4 310 519) und können im wesentlichen als Gemisch, bestehend aus den acht Komponenten A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b},

B_{2a} und B_{2b}, auftreten (I. Putter et al. Experentia 37 (1981) S. 963, Birkhäuser Verlag (Schweiz)). Daneben besitzen auch die synthetischen Derivate, insbesondere das 22,23 Dihydroavermectin B_1 (Ivermectin), Interesse (US-Pat. 4 199 569). Milbemycin B-41 D wurde fermentativ aus Streptomyces hygroscopicus isoliert werden (vgl. "Milbemycin: Discovery and Development" I. Junya et al. Annu. Rep. Sankyo Res. Lab. 45 (1993), S. 1-98; JP-Pat. 8 378 549; GB 1 390 336).

Die Verwendung der Avermectine, z.B. 22,23 Dihydroavermectinen B_1 (Ivermectin) und Milbemycine als Endoparasitizide ist bekannt und Gegenstand zahlreicher Patentanmeldungen sowie Übersichtsartikel (z.B. Biologische Wirkungen in: "Ivermectin and Abamectin" W. C. Campbell, Ed., Springer Verlag, New York, N. Y., 1989; "Avermectins and Milbemycins Part II" H. G. Davies et al. Chem. Soc. Rev. 20 (1991) S. 271-339; Chemische Modifikationen in: G. Lukacs et al. (Eds.), Springer-Verlag, New York, (1990), Chapter 3; Cydectin® [Moxidectin und Derivate]: G. T. Carter et al. J. Chem. Soc. Chem. Com-mun. (1987), S. 402-404); EP 423 445-A1) "Doramectin - a potent novel endectozide" A. C. Goudie et al. Vet. Parasitol. 49 (1993), S. 5-15).

Besonders hervorgehoben seien Avermectine und deren Derivate der allgemeinen Formel (I)



(I)

in welcher

die Reste R^1 bis R^4 die in der nachfolgenden Tabelle 1 angegebene Bedeutung haben und X für eine Einfach- oder Doppelbindung zwischen der C_{22}- und C_{23}-Position ($-C_{22}R^1-X-C_{23}R^2-$) stehen kann.

Im Falle einer Doppelbindung befinden sich keine Substituenten (R^1, R^2) an der C_{22}- und C_{23}-Position.

Tabelle 1

Makrocyclisches Lacton	$-C_{22}R^1-X-C_{23}R^2-$	R^3	R^4
Avermectin A_{1a}	-CH=CH-	-sec-Bu	-Me
Avermectin A_{1b}	-CH=CH-	-iso-Pr	-Me
Avermectin A_{2a}	$-CH_2$-CHOH-	-sec-Bu	-Me
Avermectin A_{2b}	$-CH_2$-CHOH-	-iso-Pr	-Me
Avermectin B_{1a}	-CH=CH-	-sec-Bu	-H
Avermectin B_{1b}	-CH=CH-	-iso-Pr	-H
Avermectin B_{2a}	$-CH_2$-CHOH-	-sec-Bu	-H
Avermectin B_{2b}	$-CH_2$-CHOH-	-iso-Pr	-H
22,23-Dihydroavermectin B_{1a}	$-CH_2-CH_2-$	-sec-Bu	-H
22,23-Dihydroavermectin B_{1b}	$-CH_2-CH_2-$	-iso-Pr	-H
Doramectin	-CH=CH-	-Chx	-H

22,23-Dihydroavermectin B_1 steht für Ivermectin;
sec-Bu = sekundär Butyl; iso-Pr = Isopropyl; Chx = Cyclohexyl; -Me = Methyl

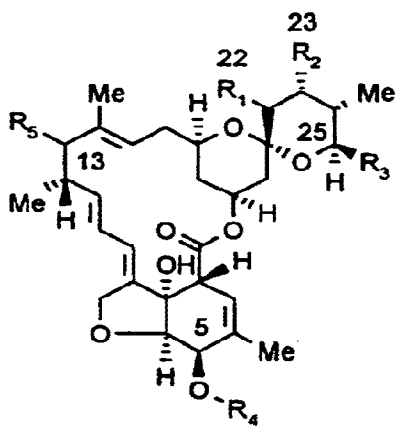
Die Avermectine und 22,23-Dihydroavermectine B_1 (Ivermectin) der allgemeinen Formel (I) werden in der Regel als Gemische eingesetzt. Von besonderem Interesse ist hierbei das Produkt Abamectin, das im wesentlichen die Avermectine B_1 enthält, und deren Hydrierungsprodukte, die 22,23-Dihydroavermectine B_1 (Ivermectin).

Die mit "b" bezeichneten Verbindungen der makrocyclischen Lactone, die in der C_{25}-Position einen iso-Propylrest besitzen, müssen nicht notwendigerweise von den "a" Verbindungen, welche eine sec-Butylgruppe in der C_{25}-Position haben, ge-

trennt werden. Es wird generell das Gemisch beider Substanzen, bestehend aus > 80 % sec-Butylderivat (B_{1a}) und < 20 % iso-Propylderivat (B_{1b}) isoliert, und kann erfindungsgemäß verwendet werden. Zudem können bei den Stereoisomeren die Substituenten in der C_{13}- und C_{23}-Position sowohl α- als auch ß-ständig am Ringsystem angeordnet sein, d. h. sich oberhalb oder unterhalb der Molekülebene befinden. In jedem Fall werden alle Stereoisomeren erfindungsgemäß berücksichtigt.

Besonders genannt seien die Milbemycine. Die Milbemycine haben die gleiche makrolide Ringstruktur wie die Avermectine oder 22,23-Dihydroavermectine B_1 (Ivermectin), tragen aber keinen Substituenten (d.h. fehlendes Oleandrose-Disaccharidfragment) in Position 13 (R^5 = Wasserstoff).

Beispielhaft seien als Milbemycine aus der Klasse der macrocyclischen Lactone die Verbindungen mit der allgemeinen Formel (II) genannt

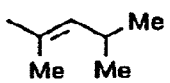
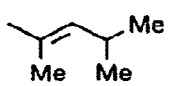


(II)

in welcher

die Reste R^1 bis R^5 die in der nachfolgenden Tabelle 2 angegebene Bedeutung haben:

Tabelle 2

Makrocyclisches Lacton	R^1	R^2	R^3	R^4	R^5
Milbemycin B41 D	-H	-H	-iso-Pr	-H	-H
Nemadectin	-H	-OH		-H	-H
Moxidectin	-H	=N-O-Me		-H	-H

iso-Pr = Isopropyl

Ganz besonders hervorgehoben seien die Wirkstoffe

Avermectin B_{1a}/B_{1b} (Ivermectin),
22,23-Dihydroavermectin B_{1a}/B_{1b} (Ivermectin),
Doramectin,
Moxidectin.

Die Wirkstoffe liegen in den erfindungsgemäßen Formulierungen in Konzentrationen von 0,1 bis 10 Gew.-%, bevorzugt von 0,5-5 Gew.-%, besonders bevorzugt von 1-2 Gew.-% vor.

Das in den erfindungsgemäßen Formulierungen eingesetzte Rizinusöl ist bekannt. Es wird hier in Konzentrationen von 15 bis 50 Gew.-% verwendet.

Die in den erfindungsgemäßen Formulierungen eingesetzten Colösungsmittel sind bekannt.

Geeignete pflanzliche oder synthetische Fettsäureester mehrwertiger Alkohole (Öle) sind Fettsäuretriglyceride, vorzugsweise Fettsäuretriglyceride mit mittlerer Kettenlänge. Besonders eignen sich neutrale Öle, wie neutrale Pflanzenöle, und

insbesondere fraktionierte Kokosnußöle, wie sie beispielsweise unter der Warenbezeichnung Miglyol bekannt und im Handel erhältlich sind, wozu erneut auf Lexikon der Hilfsstoffe, 3. Auflage, Seiten 808 bis 809, (1989) von Fiedler hingewiesen wird. Hierzu gehören beispielsweise: Miglyol 810: Hierbei handelt es sich um ein fraktioniertes Kokosnußöl, das Triglyceride von Caprylsäure und Caprinsäure enthält und ein Molekulargewicht von etwa 520 hat. Es weist eine Fettsäurezusammensetzung mit C_6 maximal 2 %, C_8 etwa 65 bis 75 %, C_{10} etwa 25 bis 35 % und C_{12} maximal 2 % auf, hat eine Säurezahl von etwa 0,1, verfügt über eine Verseifungszahl von etwa 340 bis 360 und verfügt über eine Iodzahl von maximal 1. Miglyol 812: Hierbei handelt es sich um ein fraktioniertes Kokosnußöl, das Triglyceride von Caprylsäure und Caprinsäure enthält und ein Molekulargewicht von etwa 520 hat. Es weist eine Fettsäurezusammensetzung mit C_6 maximal 3 %, C_8 etwa 50 bis 65 %, C_{10} etwa 30 bis 45 % und C_{12} maximal 5 % auf, hat eine Säurezahl von etwa 0,1, verfügt über eine Verseifungszahl von etwa 330 bis 345 und verfügt über eine Iodzahl von maximal 1. Miglyol 818: Triglyceride von Caprylsäure, Caprinsäure und Linolensäure mit einem Molekulargewicht von etwa 510. Es weist eine Fettsäurezusammensetzung mit C_6 maximal 3 %, C_8 etwa 45 bis 60 %, C_{10} etwa 25 bis 40 %, C_{12} etwa 2 bis 5 % und $C_{18:1}$ etwa 4 bis 6 auf, hat eine Säurezahl von etwa 0,2, verfügt über eine Verseifungszahl von etwa 315 bis 335 und verfügt über eine Iodzahl von maximal 10. Captex 355[(1)]: Triglycerid von Caprylsäure und Caprinsäure. Dieses Triglycerid weist einen Fettsäuregehalt an Capronsäure von etwa 2 %, an Caprylsäure von etwa 55 % und an Caprinsäure von etwa 42 % auf. Es hat eine Säurezahl von maximal 0,1, weist eine Verseifungszahl von maximal etwa 325 bis 340 auf und verfügt über eine Iodzahl von maximal 0,5. Ferner sind auch Triglyceride von Caprylsäure und Caprinsäure geeignet, wie die unter der Warenbezeichnung Myritol bekannten und im Handel erhältlichen Produkte, wozu beispielsweise auf Lexikon der Hilfsstoffe, 3. Auflage, Seite 834 (1989) von Fiedler hingewiesen wird. Das hierzu gehörende Produkt Myritol 813 hat eine Säurezahl von maximal 1, weist eine Verseifungszahl von etwa 340 bis 350 auf und verfügt über eine Iodzahl von etwa 0,5.

Weiter geeignet sind: Monoglyceride, Diglyceride und Mono/Di-Glyceride, insbesondere Veresterungsprodukte von Caprylsäure oder Caprinsäure mit Glycerin. Bevorzugte Produkte dieser Klasse sind beispielsweise die Produkte, welche Monoglycerid und Diglyceride von Caprylsäure/Caprinsäure enthalten oder daraus im wesentlichen oder praktisch bestehen, und solche Produkte sind im Handel unter

der Warenbezeichnung Imwitor erhältlich, wozu auf Lexikon der Hilfsstoffe, 3. Auflage, Seite 645 (1989) von Fiedler verwiesen wird. Ein besonders geeignetes Produkt aus dieser Klasse für die Anwendung in den erfindungsgemäßen Zusammensetzungen ist das Produkt Imwitor 742, bei dem es sich um ein Veresterungsprodukt aus einem Gemisch von etwa 60 Gewichtsteilen (ppw) Caprylsäure und etwa 40 Gewichtsteilen (ppw) Caprinsäure mit Glycerin handelt. Imwitor 742 ist gewöhnlich eine gelbliche kristalline Masse, die bei etwa 26°C flüssig ist. Es weist eine Säurezahl von maximal 2 auf, hat eine Iodzahl von maximal 1, verfügt über eine Verseifungszahl von etwa 235 bis 275, enthält etwa 40 bis 50 % Monoglyceride, verfügt über einen Gehalt an freiem Glycerin von maximal 2 %, hat einen Schmelzpunkt von etwa 24 bis 26°C, enthält nichtverseifbare Bestandteile von maximal 0,3 % und verfügt über eine Peroxidzahl von maximal 1.

Sorbitanfettsäureester der verschiedensten bekannten Arten, wie sie beispielsweise unter der Warenbezeichnung Span im Handel erhältlich sind, und hierzu gehören beispielsweise Sorbitanmonolaurylester, Sorbitanmonopalmitylester, Sorbitanmonostearylester, Sorbitantristearylester, Sorbitanmonooleylester und Sorbitantrioleylester, und hierzu wird beispielsweise auf Lexikon der Hilfsstoffe, 3. Auflage, Seiten 1139 bis 1140 (1989) von Fiedler verwiesen.

Pentaerythritfettsäure und Polyalkylenglykolether, wie Pentaerythritdioleat, Pentaerythritdestearat, Pentaerythritmonolaurat, Pentaerythritpolyglykolether und Pentaerythritmonostearat und auch Pentaerythritfettsäureester, wozu auf Lexikon der Hilfsstoffe, 3. Auflage, Seiten 923 bis 924 (1989) von Fiedler verwiesen wird.

Monoglyceride, wie Glycerinmonooleat, Glycerinmonopalmitat und Glycerinmonostearat, wie sie beispielsweise unter den Warenbezeichnungen Myvatex, Myvaplex und Myverol bekannt und im Handel erhältlich sind, wozu auf Lexikon der Hilfsstoffe, 3. Auflage, Seite 836 (1989) von Fiedler verwiesen wird, und acetylierte, beispielsweise monoacetylierte und diacetylierte, Monoglyceride, wie sie beispielsweise unter der Warenbezeichnung Myvacet bekannt und im Handel erhältlich sind, wozu auf Lexikon der Hilfsstoffe, 3. Auflage, Seite 835 (1989) von Fiedler verwiesen wird.

Mono- und Difettsäureester von Propylenglykol, wie Propylenglykoldicaprylat, Propylenglykoldilaurat, Propylenglykolhydroxystearat, Propylenglykolisostearat, Propylenglykollaurat, Propylenglykolricinoleat, Propylenglykolstearat und der-

gleichen, wozu auf Lexikon der Hilfsstoffe, 3. Auflage, Seiten 1013 ff. (1989) von Fiedler hingewiesen wird. Besonders bevorzugt ist Propylenglykolcaprylsäure-caprinsäurediester, der unter der Warenbezeichnung Miglyol 840 bekannt und im Handel erhältlich ist, wozu auf Lexikon der Hilfsstoffe, 3. Auflage, Seite 809 (1989) von Fiedler verwiesen wird. Miglyol 840 hat einen Fettsäuregehalt von C_6 maximal etwa 3 Prozent, C_8 etwa 65 bis 80 Prozent, C_{10} etwa 15 bis 30 Prozent und C_{12} maximal 3 Prozent, und weist eine Säurezahl von maximal 0,1, eine Verseifungszahl von etwa 320 bis 340 und eine Iodzahl von maximal 1 auf.

Weitere geeignete Produkte dieser Klasse sind Capmul MCT[(1)], Captex 300[(1)], Captex 800[(1)], Neobee M5[(2)] und Mazol 1400[(3)] Imwitor[(4)]

[(1)] = Capital City Products, P.O.Box 569, Columbus, OH, V.St.A.
[(2)] = Stepan, PVO Dept., 100 West Hunter Ave., Maywood, NJ 07607, V.St.A.
[(3)] = Mazer Chemicals, 3938 Porett Drive, Gurnee, IL, V.St.A,
[(4)] = Hüls AG, 14370 Marl, Deutschland

Weitere Colösungsmittel sind Benzylalkohol, der gleichzeitig als Konservierungsmittel dienen kann, Alkohole wie Ethanol, Glykol, Glycerin, cyclische Carbonate wie Propylencarbonat. Die Colösungsmittel liegen in Konzentrationen von 30-85 Gew.-%.

Weitere Zusätze sind Stabilisatoren wie Butylhydroxyanisol (BHA), Butylhydroxytoluol (BHT) oder Propylgallat von insgesamt bis zu 1000 ppm. Besonders geeignete Stabilisatorkombinationen und -konzentrationen sind z.B. 100 ppm BHA oder 100 ppm BHA plus 150 ppm Propylgallat oder 200 ppm BHA plus 100 ppm Propylgallat.

Die Viskosität der erfindungsgemäßen Formulierungen liegt zwischen 25 bis 60 mPa.s (20°C), bevorzugt zwischen 30 bis 55 mPa.s (20°C), besonders bevorzugt zwischen 35 und 51 mPa.s (20°C).

Die folgenden Beispiele erläutern die Erfindung.

Anmerkung:

V/V = $\frac{\text{Volume}}{\text{Volume}}$ entspricht Volumenprozent

M/V = $\frac{\text{Masse}}{\text{Volume}}$

n

1 % M/V heißt z.B. 10 mg Wirkstoff in 1 ml Lösung.

Beispiel 1

a)	Miglyol® 812	q.s.100 % V/V	b)	Miglyol® 812	q.s. 100 % V/V
	Rizinusöl	20 % V/V		Rizinusöl	20 % V/V
	Benzylalkohol	2 % V/V		Benzylalkohol	2 % V/V
	Ivermectin	1 % M/V		Ivermectin	2 % M/V
	Dichte:	0,954 g/ml		Dichte:	0,956 g/ml
	Viskosität:	48 mPa.s bei 20°C 95 mPa.s bei 5°C		Viskosität:	48 mPa.s bei 20°C 105 mPa.s bei 5°C

Beispiel 2

a)	Miglyol® 812	q.s.100 % V/V	b)	Miglyol® 812	q.s.100 % V/V
	Rizinusöl	20 % V/V		Rizinusöl	20 % V/V
	Propylencarbonat	3 % V/V		Propylencarbonat	3 % V/V
	Benzylalkohol	2 % V/V		Benzylalkohol	2 % V/V
	Ivermectin	1 % M/V		Ivermectin	2 % M/V
	Dichte:	0,962 g/ml		Dichte:	0,964 g/ml
	Viskosität:	42 mPa.s bei 20°C 91 mPa.s bei 5°C		Viskosität:	44 mPa.s bei 20°C 97 mPa.s bei 5°C

Beispiel 3

a)	Miglyol® 812	q.s. 100% V/V	b)	Miglyol® 812	q.s. 100 % V/V
	Rizinusöl	20 % V/V		Rizinusöl	20 % V/V
	Ivermectin	1 % M/V		Ivermectin	2 % M/V
	Dichte:	0,952 g/ml		Dichte:	0,954 g/ml
	Viskosität:	51 mPa.s bei 20°C 105 mPa.s bei 5°C		Viskosität:	51 mPa.s bei 20°C 117 mPa.s bei 5°C

Beispiel 4

a)	Miglyol® 812	q.s. 100 % V/V	b)	Miglyol® 812	q.s. 100 % V/V
	Rizinusöl	35 % V/V		Rizinusöl	35 % V/V
	Ivermectin	1 % M/V		Ivermectin	2 % M/V
	Dichte:	0,939 g/ml		Dichte:	0,941 g/ml
	Viskosität:	38 mPa.s bei 20°C 75 mPa.s bei 5°C		Viskosität:	42 mPa.s bei 20°C 76 mPa.s bei 5°C

Beispiel 5

a)	Ethyloleat	q.s. 100 % V/V	b)	Ethyloleat	q.s. 100 % V/V
	Rizinusöl	45 % V/V		Rizinusöl	45 % V/V
	Ivermectin	1 % M/V		Ivermectin	2 % M/V
	Dichte:	0,916 g/ml		Dichte:	0,918 g/ml
	Viskosität:	40 mPa.s bei 20°C 91 mPa.s bei 5°C		Viskosität:	49 mPa.s bei 20°C 98 mPa.s bei 5°C

Beispiel 6

a)	Miglyol® 840	q.s.100 % V/V	b)	Miglyol® 840	q.s 100 % V/V
	Rizinusöl	35 % V/V		Rizinusöl	35 % V/V
	Propylenglykol	5 % V/V		Propylenglykol	5 % V/V
	Benzylalkohol	5 % V/V		Benzylalkohol	5 % V/V
	Ivermectin	1 % M/V		Ivermectin	2 % M/V
	Dichte:	0,952 g/ml		Dichte:	0,954 g/ml
	Viskosität:	36 mPa.s bei 20°C 76 mPa.s bei 5°C		Viskosität:	38 mPa.s bei ~~20~~°C 81 mPa.s bei 5°C

Beispiel 7

a)	Ethyloleat	q.s. 100 % V/V
	Rizinusöl	40 % V/V
	Propylenglykol	5 % V/V
	Benzylalkohol	5 % V/V
	Ivermectin	1 % M/V
	Dichte:	0,926 g/ml
	Viskosität:	34 mPa.s bei 20°C 70 mPa.s bei 5°C

Beispiel 8

a)	Miglyol® 840	q.s. 100 % V/V
	Rizinusöl	35 % V/V
	Benzylalkohol	20 % V/V
	Ivermectin	1 % M/V
	Dichte:	0,965 g/ml
	Viskosität:	28 mPa.s bei 20°C 56 mPa.s bei 5°C

Beispiel 9

a)	Miglyol® 840	q.s. 100 % V/V
	Rizinusöl	35 % V/V
	Propylencarbonat	10 % V/V
	Benzylalkohol	5 % V/V
	Ivermectin	1 % M/V

Dichte:	0,975 g/ml
Viskosität	27 mPa.s bei 20°C 53 mPa.s bei 5°C

Beispiel 10

a)	Imwitor® 408	q.s. 100 % V/V
	Rizinusöl	30 % V/V
	Ivermectin	1 % M/V
	Dichte	0,953 g/ml
	Viskosität	30 mPa.s bei 20°C 66 mPa.s bei 5°C

Imwitor® ist ein Markenname der Hüls AG. Bei Imwitor® 408 handelt es sich um 1,2-Propandiol-mono-dicaprylat (INCI (CTFA)-Bezeichnung). Laut vorläufiger Produktinformation enthält Imwitor® 408 ca. 10 % freies Propylenglykol und ca. 50 % Monoglyceride. Es zeigt ein hohes Lösungsvermögen für Ivermectin (>20 % M/V).

Allgemeine Herstellvorschrift für die Beispiele 1 bis 10 als sterile Lösungen zur Injektion:

Die Formulierhilfsstoffe werden in einen Edelstahlbehälter eingewogen und unter Rühren homogenisiert. Unter weiterem Rühren wird das Ivermectin eingebracht. Die Mischung wird auf 40 bis 50°C erwärmt, um die Auflösung des Wirkstoffs zu beschleunigen (möglichst unter Stickstoffbegasung). Nach vollständiger Auflösung wird bei gleicher Temperatur über ein 0,22 µm Filter sterilfiltriert (in der Regel wird ein 0,45 µm oder 1 µm Filter vorgeschaltet). Es folgt aseptische Abfüllung in Braunglasflaschen.

Die so hergestellten Formulierungen sind bei der Anwendung am Rind hervorragend verträglich. Sie sind außerdem über mindestens 6 Wochen bei Temperaturen zwischen 4°C und 60°C lagerstabil.

Patentansprüche

1. Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis von Rizinusöl.

2. Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, daß sie folgende Zusammensetzung haben:

   1. Wirkstoff 0,1 bis 10 Gew.-%

   2. Rizinusöl 15 bis 50 Gew.-%

   3. Co-Lösungsmittel aus der Reihe pflanzlicher oder synthetischer Fettsäureester ein- oder mehrwertiger Alkohole, aliphatischer oder aromatischer Alkohole, cyclischer Carbonate in Konzentrationen von 30 bis 85 Gew.-%

   4. gegebenenfalls weitere Hilfsstoffe.

3. Formulierungen gemäß Anspruch 1 der folgenden Zusammensetzung:
   0,1 bis 10 % M/V eines Avermectins oder Milbemycins in einem Lösungsmittel bestehend aus 15 bis 50 % V/V Rizinusöl, sowie 30 bis 85 % V/V eines mittelkettigen Triglycerids und/oder Propylenglykol-octanoat/-decanoat und/oder Ethyloleat und 0 bis 30 % V/V eines oder eines Gemisches aus den Lösungsmitteln Benzylalkohol, Propylenglykol oder Propylencarbonat, sowie gegebenenfalls bis zu 1000 ppm Stabilisatoren.

4. Formulierungen gemäß Anspruch 1 der folgenden Zusammensetzung:
   20 bis 45 % V/V Rizinusöl, 45 bis 80 % V/V mittelkettige Triglyceride oder Propylenglykol-octanoat/decanoat oder Ethyloleat und 0 bis 20 % V/V Benzylalkohol, 0 bis 10 % V/V Propylenglykol oder Propylencarbonat sowie gegebenenfalls bis zu 500 ppm Stabilisatoren.

5. Verfahren zur Herstellung der Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, daß man den Wirkstoff mit Rizinusöl mischt und die Colösungsmittel zufügt oder, daß man den Wirkstoff in einer Mischung aus Rizinusöl und den Colösungsmitteln auflöst.

6. Verwendung von Rizinusöl zur Herstellung einer Formulierung gemäß Anspruch 1.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/01569

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/35 A61K47/44

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	EP 0 303 933 A (BAYER AG) 22 February 1989 see claim 1 see page 8, line 31 - line 32 see page 8, line 37 - page 9, line 23	1-6
A	WO 94 08566 A (MICRO VESICULAR SYSTEMS) 28 April 1994 see claims 1,7,8,13-15	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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1

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 1997	24.07.97

Name and mailing address of the ISA	Authorized officer
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	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/EP 97/01569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 303933 A	22-02-89	DE 3727648 A	02-03-89
		AU 2114088 A	23-02-89
		JP 1068378 A	14-03-89
		US 4916120 A	10-04-90
WO 9408566 A	28-04-94	AU 5330294 A	09-05-94
		US 5510117 A	23-04-96

INTERNATIONALER RECHERCHENBERICHT

Interne des Aktenzeichen
PCT/EP 97/01569

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K31/35 A61K47/44

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP 0 303 933 A (BAYER AG) 22.Februar 1989 siehe Anspruch 1 siehe Seite 8, Zeile 31 - Zeile 32 siehe Seite 8, Zeile 37 - Seite 9, Zeile 23 ---	1-6
A	WO 94 08566 A (MICRO VESICULAR SYSTEMS) 28.April 1994 siehe Ansprüche 1,7,8,13-15 -----	1,6

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :
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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
11.Juli 1997	24. 07. 97

Name und Postanschrift der Internationale Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ventura Amat, A

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INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Interr ales Aktenzeichen
PCT/EP 97/01569

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 303933 A	22-02-89	DE 3727648 A	02-03-89
		AU 2114088 A	23-02-89
		JP 1068378 A	14-03-89
		US 4916120 A	10-04-90
WO 9408566 A	28-04-94	AU 5330294 A	09-05-94
		US 5510117 A	23-04-96

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/48, 9/107, 31/565, 31/57 — A1

(11) International Publication Number: **WO 97/40823**

(43) International Publication Date: 6 November 1997 (06.11.97)

(21) International Application Number: PCT/GB97/01247

(22) International Filing Date: 28 April 1997 (28.04.97)

(30) Priority Data:
9608719.2 26 April 1996 (26.04.96) GB

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), 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: ORAL PHARMACEUTICAL COMPOSITIONS CONTAINING SEX HORMONES

(57) Abstract

A pharmaceutical composition comprising: a hydrophobic drug, a digestible oil selected from triglycerides or propylene glycol esters of medium chain length (C_8-C_{12}) and/or long chain length (C_{13}-C_{22}) fatty acids; and propylene glycol monolaurate, a lipophilic surfactant which comprises a glyceride of a C_5 to C_{10} fatty acid and a hydrophilic surfactant which is a polyoxyethylene hydrogenated castor oil, wherein the digestible oil is present in an amount on the range from 3.0 to 12.0 % by weight of the composition and the weight ratio of hydrophilic surfactant to lipophilic surfactant is in the range 1:1.5 to 1:2.5. Suitable hydrophobic drugs includes sex hormones such as progesterone, oestradiol and testosterone.

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ORAL PHARMACEUTICAL COMPOSITIONS CONTAINING SEX HORMONES

This invention relates to pharmaceutical compositions for oral administration and in particular to pharmaceutical compositions comprising sex hormones, such as progesterone, oestradiol and testosterone.

The demand for hormonal preparations to treat menopausal symptoms has been growing rapidly as evidence has accumulated of the benefits of hormone replacement therapy for both symptomatic relief of menopausal symptoms and the prevention of osteoporosis. It is estimated that in the United Kingdom 25% of women suffer from osteoporosis. A preferred treatment for the symptoms and complications of the menopause is a cyclical treatment regimen of an oestrogen alone or a combination of an oestrogen and a progestogen. Most products available, however, contain oestrogens and progestogens from either non-human animal sources or which are synthetic analogues of human hormones.

Progesterone is a naturally occurring female progestogen. Synthetic progestogens have been used for many years as contraceptives and for preventing endometrial hyperplasia in women receiving oestrogens as hormone replacement therapy. Natural progesterone has not been widely used because of its poor oral bioavailability.

Progesterone has traditionally been administered intramuscularly or by the vaginal or rectal route in order to avoid the high rate of "first pass" hepatic metabolism for the drug. Such methods of administration are not universally popular however, and an effective oral dosage form is required. A suspension of micronised progesterone in oil encapsulated in a softgel has recently been available but, as for solid dosage forms, dissolution is still required in vivo and limits the rate of absorption, particularly as the aqueous solubility of progesterone is very low. Gradual dissolution and absorption of progesterone from a suspension provides a

steady flow of the drug to the liver where it is extensively metabolised, thereby limiting the amount of the dose reaching the systemic circulation. Increasing the rate of drug absorption beyond the rate of metabolism in the liver would be expected to result in increased oral bioavailability.

Testosterone, generally in the form of a testosterone ester, has also been administered therapeutically, e.g. in hormone replacement treatments. Testosterone has been applied by intramuscular injection, implants and orally, e.g. in the form of capsules.

PCT/US90/00721 discloses pharmaceutical compositions for oral administration comprising a therapeutically effective amount of a pharmaceutical compound, an organic solvent and an oil. A solution formulation comprising ethanol, palm oil, polyethylene glycol fatty acid ester, progesterone and N-methyl-2-pyrrolidine (organic solvent) is disclosed. The formulation exhibits improved bioavailability compared to a formulation of micronised progesterone in peanut oil. However, the high quantity of organic solvent present in the formulation is undesirable for use in softgel capsules as it is likely to cause stability problems.

US-A-4963540 discloses pharmaceutical compositions which may be filled in capsules, comprising micronised progesterone in an oil vehicle which is high in glycerides of polyunsaturated fatty acids. It is stated that micronised progesterone particles suspended in such a vehicle are more readily absorbed into the bloodstream than other types of oral progesterone formulations.

WO95/24893 discloses a carrier system for a hydrophobic drug which comprises a digestible oil and a pharmaceutically acceptable surfactant for dispersing the oil <u>in vivo</u> upon administration of the carrier system, said surfactant comprising a hydrophilic surfactant component, and being such that it does not substantially inhibit the lipolysis of the digestible oil. The

surfactant generally comprises:

(a) a hydrophilic surfactant component which substantially inhibits the in vivo lipolysis of said digestible oil, and

(b) a lipophilic surfactant component capable of at least substantially reducing said inhibitory effect of said hydrophilic surfactant component.

The generally preferred range of digestible oil in the carrier system is 10 to 90% with the more preferred range being 20 to 60%, most preferably 25 to 45%.

Several formulations comprising dissolved progesterone are disclosed in which ethanol is present but the maximum concentration of progesterone achieved was 4% by weight. In order to achieve a dose of 50mg of progesterone completely dissolved in the formulation in a softgel capsule it is necessary to employ a large (20 oblong) capsule size or divide the dose into two smaller capsules. Neither of these options is conducive to patient compliance.

It has now been found that particular combinations of digestible oil and mixtures of lipophilic and hydrophilic surfactants provide a carrier system which is capable of solubilising significant amounts of hydrophobic drugs, such as, progesterone.

According to one aspect of the present invention there is provided a pharmaceutical composition comprising:

a hydrophobic drug,

a digestible oil selected from triglycerides or propylene glycol esters of medium chain length (C_8-C_{12}) and/or long chain length (C_{13}-C_{22}) fatty acids; and propylene glycol monolaurate,

a lipophilic surfactant which comprises a glyceride of a C_5 to C_{10} fatty acid and

a hydrophilic surfactant which is a polyoxyethylene hydrogenated castor oil,

wherein the digestible oil is present in an amount in the

range from 3.0 to 12.0% by weight of the composition and the weight ratio of hydrophilic surfactant to lipophilic surfactant is in the range 1 : 1.5 to 1 : 2.5.

The formulations of the invention allow the drug to be completely solubilised in the liquid formulation. As a solution the drug is presented to the body in the most available form, avoiding the problems of slow disintegration and dissolution associated with other solid oral dosage formulations. This also obviates the need for micronised progesterone and subsequent control of the drug particle size. The formulations may be readily filled in hard or soft capsules.

The blend of digestible oil and surfactants used in the invention provides good solubilisation of the hydrophobic drug. The improved solvent power may be exploited by the formulators in various different ways. It is possible to employ a smaller capsule size to deliver the same drug dose compared with similar formulations in the prior art. Alternatively, or in addition, it is possible to reduce or eliminate ethanol and/or unsaturated compounds, such as maisine, which have been employed in prior art formulations to improve solubilisation of the drug.

The formulations of the invention have been designed to disperse immediately in aqueous environments such as the gastrointestinal tract, forming fine emulsions or microemulsions. In addition, the liquid excipients are chosen such that the emulsified formulation undergoes the natural rapid process of fat digestion (lipolysis). The submicroscopic mixed micelles formed by this process incorporate the products of vehicle lipolysis and solubilised drug. Solubilised drug leaves the microemulsion droplets, the vesicles and the micelles by diffusion. The surface area is vast so the diffusion process is very rapid. Any remaining solubilised drug in the micelles is released when the micelles deaggregate at the intestinal wall. Absorption of progesterone across

the gastrointestinal wall in association with these mixed micelles is thought to contribute to the increase in drug bioavailability.

Hydrophobic drugs of interest in the present invention are sex hormones, particularly progesterone, oestradiol and testosterone. The invention allows formulations containing in excess of 5% by weight, preferably more than 6% by weight of progesterone in solution to be prepared which allows 50mg dose of progesterone to be encapsulated in softgel capsule, size 12 oblong which is considerably smaller than the size 20 oblong required to deliver 50mg of progesterone in the formulations disclosed in WO95/2493.

Furthermore, the invention allows ethanol to be completely eliminated from the formulations containing hydrophobic drugs. For example, an ethanol free formulation containing progesterone in solution and providing a 25mg dose in a softgel capsule may be formulated and filled into a size 9.5 oblong.

The reference to capsule sizes and shapes herein refer to softgel capsules. The capsule size provides an indication of the nominal fill volume (NFV). Examples of capsule sizes include:

Capsule Size	NFV (minims)	NFV (cm^3)
4	3.0 - 4.0	0.185 - 0.246
9.5	7.5 - 9.5	0.462 - 0.585
20	16 - 20	0.986 - 1.232
10	7.5 - 10.0	0.462 - 0.616
18	15.0 - 18.0	0.924 - 1.109

The compositions of the invention employ smaller amounts of digestible oil than used in WO92/24893. Generally 3 to 12%, preferably 4 to 7. The preferred digestible oil is fractionated coconut oil although other digestible oils, such as, peanut oil, soyabean oil,

propylene glycol monolaurate and propylene glycol ester of fractionated coconut oil which is commercially available under the trade name Miglyol 840 may be used.

A blend of hydrophilic and lipophilic surfactants is present in the composition of the invention. The hydrophilic surfactant comprises a polyoxyethylene hydrogenated castor oil, preferably polyoxyethylene (40) hydrogenated castor oil, such as the product commercially available under the trade name Cremophor RH40. The lipophilic surfactant is preferably a mixture of glyceryl mono-and di-caprylate, such as the product commercially available under the trade name Imwitor 988. Other suitable lipophilic surfactants include a mixture of glyceryl mono- and dicaprates in combination with glyceryl mono- and di-caprylates. Such products are commercially available under the trade names Imwitor 742 and Capmul MCM.

The weight ratio of hydrophilic to lipophilic surfactant is important to achieve optimum solubilisation of the drugs. The weight ratio of hydrophilic to lipophilic surfactant is generally in the range from 1 : 1.5 to 1 : 2.5, usually 1 : 1.7 to 1 : 2.1. For progesterone and oestradiol formulations the ratio is preferably 1 : 1.80 to 1 : 1.90, most preferably about 1.85. Testosterone may be used in larger concentrations e.g. 8 to 16% by weight and the preferred weight ratio of hydrophilic to lipophilic surfactant is in the range 1 : 1.7 to 1 : 2.1.

The compositions may additionally comprise a co-solvent, such as ethanol. The presence of ethanol assists in increasing the concentration of drug which may be dissolved thereby allowing smaller volumes of formulation to achieve a desired unit dose. However, the presence of ethanol may result in an increased level of shell-fill interactions in capsules compared to formulations in which ethanol is absent. In addition ethanol can complicate the manufacturing process and

packaging costs can increase where the final package must be impervious to ethanol. Formulations of the invention may be ethanol-free and still provide acceptable dosage levels of drug. The effective ratio of hydrophilic to lipophilic surfactant is not affected by the presence of ethanol.

The formulations of the invention do not require the presence of unsaturated components to solubilise the drug. Thus, compounds, such as Maisine 35-1, which could potentially react with other excipients or the drug itself, may be avoided. Additionally, unsaturated compounds could lead to cross-linking of the gelatin of capsules and ultimately a significantly increased disintegration time, possibly leading to poor adsorption. Preferably, the formulations are free from additives which are unsaturated compounds.

Suitable progesterone formulations containing ethanol in accordance with the invention comprise:

at least 5% by weight of progesterone
40 to 50% by weight of lipophilic surfactants
20 to 30% by weight of hydrophilic surfactants
3 to 10% by weight of digestible oil
15 to 25% by weight of ethanol.

Preferred formulations comprise:

5.5 to 6.5% by weight or progesterone
43 to 45% by weight of lipophilic surfactants
23 to 25% by weight of hydrophilic surfactants
4 to 9 by weight of digestible oil
18 to 20% by weight of ethanol.

A particularly preferred formulation comprises about:

6 parts by weight of progesterone
45 parts by weight of lipophilic surfactants
24 parts by weight of hydrophilic surfactants
4.5 parts by weight of digestible oil
20 parts by weight of ethanol.

Suitable ethanol-free formulations in accordance

with the invention comprise a pharmaceutical composition comprising:

from 4 to 5% by weight of progesterone
55 to 60% by weight of lipophilic surfactants
30 to 35% by weight of hydrophilic surfactants
3 to 10% by weight of digestible oil.

A preferred formulation comprises about:

4.5 parts by weight of progesterone
58 parts by weight of lipophilic surfactants
31.5 parts by weight of hydrophilic surfactants
6 parts by weight of digestible oil.

The ethanol-containing and ethanol-free progesterone formulations may additionally comprise from 0.02 to 0.4% oestradiol without substantially altering the ratio of the other components.

The invention also provides ethanol-containing oestradiol formulations comprising:

0.05 to 2% by weight of oestradiol
45 to 50% by weight of lipophilic surfactants
22 to 27% by weight of hydrophilic surfactants
3 to 10% by weight of digestible oil
15 to 25% by weight of ethanol.

A preferred oestradiol formulation comprises about:

1 part by weight of oestradiol
48 parts by weight of lipophilic surfactants
26 parts by weight of hydrophilic surfactants
5 parts by weight of digestible oil
21 parts by weight of ethanol.

Ethanol-free oestradiol formulation in accordance with the invention comprise:

0.05 to 2% by weight of oestradiol
58 to 62% by weight of lipophilic surfactants
30 to 35% by weight of hydrophilic surfactants
5 to 7% by weight of digestible oil.

A preferred oestradiol formulation comprises about:

1 part by weight oestradiol
60 parts by weight of lipophilic surfactants

33 parts by weight of hydrophilic surfactants
6 parts by weight of digestible oil.

Suitable testosterone formulations in accordance with the invention comprise:

4 to 18% by weight of testosterone
40 to 48% by weight of lipophilic surfactants
20 to 25% by weight of hydrophilic surfactants
7 to 10% by weight of digestible oil
about 15% by weight of ethanol.

The formulations of the invention may comprise minor amounts of other components e.g. antioxidants.

In all of the above formulations the preferred components are fractionated coconut oil, Imwitor 988 and Cremophor RH40.

The formulation of the invention spontaneously form microemulsions when contacted with aqueous media and maintain the benefits of the composition disclosed in W095/24893 maintaining lipolysis and bioavailability of the drug.

The composition of the invention may readily be prepared by known methods, such as described in W095/24893. The compositions may be encapsulated in softgel or hardshell capsules. Methods of softgel encapsulation are disclosed in Theory and Practice of Industrial Pharmacy - Lachman & Leibermann, 2nd Edition, published by Henry Kimpton Publishers, London. Methods of liquid-fill hardshell encapsulation are disclosed in Hardcapsules - Development and Technology - Edited by K. Ridgeway, published by Pharmaceutical Press 1987.

The invention will now be illustrated by the following Examples.

The formulations reported in the following Tables in which all figures are in parts by weight were prepared.

Example	Comparative Example 5 WO95/24893	1	2	3
Progesterone USP	4.52	5.56	5.56	6.15
Imwitor 988	25.79	43.44		45.27
Imwitor 742			43.44	
Cremophor RH40	25.79	23.42	23.42	24.40
Maisine 35-1	8.60			
Ethanol USP/BP	18.10	18.89	18.89	19.68
Frac. Coconut Oil BP	17.19	8.69	8.69	4.50

Example	4	5	6	7	8
Progesterone USP	4.50				
Oestradiol USP		1.01	1.01	1.01	1.01
Imwitor 988	58.29	47.74	47.73	60.41	60.39
Cremophor RH40	31.42	25.74	25.73	32.57	32.56
Ethanol USP/BP		20.76	20.75		
Frac. Coconut Oil BP	5.79	4.75	4.75	6.01	6.01
Tocopherols			0.03		0.03

Example	9	10	11	12	13	14
Oestradiol USP	0.09	0.18	0.06	0.12	0.25	0.045
Progesterone USP	4.50	4.50	6.14	6.14	6.14	4.500
Imwitor 988	58.20	58.11	45.27	45.21	45.15	58.245
Cremophor RH40	31.42	31.42	24.37	24.37	24.34	31.420
Ethanol			19.66	19.66	19.63	
Frac. Coconut Oil BP	5.79	5.79	4.50	4.50	4.49	5.790

The formulation of each Example comprised stable, solutions of the drug.

The formulations may be filled into softgel capsules to provide a dosage form as follows:

Example	Dose/Capsule	Softgel Capsule Size
Comparative	50mg progesterone	20 oblong
1	50mg progesterone	12 oblong
2	50mg progesterone	12 oblong
3	50mg progesterone	12 oblong
4	25mg progesterone 50mg progesterone	9.5 oblong or 10 oval 18 oblong
5	2mg oestradiol	4 oblong
6	2mg oestradiol	4 oblong
7	2mg oestradiol	4 oblong
8	2mg oestradiol	4 oblong
9	0.5mg oestradiol 25mg progesterone 1mg oestradiol 50mg progesterone	9.5 oblong or 10 oval 18 oblong
10	1mg oestradiol 25mg progesterone	9.5 oblong or 10 oval
11	0.5mg oestradiol 50mg progesterone	12 oblong
12	1mg oestradiol 50mg progesterone	12 oblong
13	2mg oestradiol 50mg progesterone	12 oblong
14	0.5mg oestradiol 50mg progesterone 0.25mg oestradiol 25mg progesterone	18 oblong 9.5 oblong or 10 oval

Relative Rates of Lipolysis

The relative rates of lipolysis for formulations of the Comparative Example and Examples 3 and 4 were measured in accordance with the in vitro test procedure described in W095/24893. The results are reported in Figure 1 of the accompanying drawings which represents a plot of NaOH dispensed against time for the formulations. The composition of the invention, both with and without ethanol indicate effective lipolysis is maintained.

Bioavailability Study

The bioavailability of progesterone from the formulations of the Comparative Example delivered in a 20 oblong softgel capsule and Example 3 delivered in a 12 oblong softgel capsule was measured. The results of the study are reported in Figure 2 of the accompanying drawings which represent a plot of mean serum concentration of progesterone against time for following the administration to 12 subjects of a single oral dose of each softgel capsule containing the progesterone. It will be seen the bioavailability of the formulation of the invention is substantially identical to the Comparative Example.

Examples 15 to 20

The oestradiol formulation reported in the following Table were prepared in which all figures are in parts by weight. All formulations were in the form of solutions of oestradiol.

Example	15	16	17	18	19	20
Oestradiol USP	0.047	0.094	0.188	0.033	0.066	0.132
Imwitor 988	60.993	60.946	60.852	48.197	48.164	48.098
Cremophor RH40	32.900	32.900	32.900	26.000	26.000	26.000
Ethanol USP/BP				20.970	20.970	20.970
Frac. Coconut Oil BP	6.060	6.060	6.060	4.800	4.800	4.800

The formulations were filled into softgel capsules as follows:

Example 15 0.25mg oestradiol (fill weight of 531mg) in 9.5 oblong or 10 oval capsule.

Example 16 0.5mg oestradiol (fill weight of 531mg) in 9.5 oblong or 10 oval capsule.

Example 17 1.0mg oestradiol (fill weight of 531mg) in 9.5 oblong or 10 oval capsule.

Example 18 0.25mg oestradiol (fill weight of 763mg) in 12 oblong capsule.

Example 19 0.5mg oestradiol (fill weight of 763mg) in 12 oblong capsule.

Example 20 1.0mg oestradiol (fill weight of 763mg) in 12 oblong capsule.

Examples 21 to 38

The following Table, in which all figures are in parts by weight, illustrate testosterone formulations in accordance with the invention. Examples 21 to 26 may be encapsulated to provide a dose of 20mg, Examples 27 to 32 may be encapsulated to provide a dose of 40mg and Examples 33 to 38 may be encapsulated to provide a dose of 80mg.

Example	21	22	23	24	25	26
Testosterone undecanoate	4	4	4	4	4	4
Imwitor 988	46	-	-	46	-	-
Imwitor 742	-	46	-	-	46	-
Capmul MCM	-	-	46	-	-	46
Cremophor RH40	25	25	25	-	-	-
Tween 80	-	-	-	25	25	25
Miglyol	10	10	10	10	10	10
Ethanol	15	15	15	15	15	15

Example	27	28	29	30	31	32
Testosterone undecanoate	8	8	8	8	8	8
Imwitor 988	44	-	-	44	-	-
Imwitor 742	-	44	-	-	44	-
Capmul MCM	-	-	44	-	-	44
Cremophor RH40	24	24	24	-	-	-
Tween 80	-	-	-	24	24	24
Miglyol	9	9	9	9	9	9
Ethanol	15	15	15	15	15	15

Example	33	34	35	36	37	38
Testosterone undecanoate	16	16	16	16	16	16
Imwitor 988	41	-	-	41	-	-
Imwitor 742	-	41	-	-	41	-
Capmul MCM	-	-	41	-	-	41
Cremophor RH40	20	20	20	-	-	-
Tween 80	-	-	-	20	20	20
Miglyol	8	8	8	8	8	8
Ethanol	15	15	15	15	15	15

CLAIMS

1. A pharmaceutical composition comprising:

a hydrophobic drug,

a digestible oil selected from triglycerides or propylene glycol esters of medium chain length (C_8-C_{12}) and/or long chain length (C_{13}-C_{22}) fatty acids; and propylene glycol monolaurate,

a lipophilic surfactant which comprises a glyceride of a C_5 to C_{10} fatty acid and

a hydrophilic surfactant which is a polyoxyethylene hydrogenated castor oil,

wherein the digestible oil is present in an amount in the range from 3.0 to 12.0% by weight of the composition and the weight ratio of hydrophilic surfactant to lipophilic surfactant is in the range 1 : 1.5 to 1 : 2.5.

2. A pharmaceutical composition as claimed in Claim 1 in which the hydrophobic drug is dissolved and is selected from progesterone, oestradiol, testosterone and mixture of progesterone and oestradiol.

3. A pharmaceutical composition comprising:

at least 5% by weight of progesterone
40 to 50% by weight of lipophilic surfactants
20 to 30% by weight of hydrophilic surfactants
3 to 10% by weight of digestible oil
15 to 25% by weight of ethanol.

4. A pharmaceutical composition as claimed in Claim 3 comprising:

5.5 to 6.5% by weight or progesterone
43 to 45% by weight of lipophilic surfactants
23 to 25% by weight of hydrophilic surfactants
4 to 9% by weight of digestible oil
18 to 20% by weight of ethanol.

5. A pharmaceutical composition as claimed in Claim 4 comprising about:

6 parts by weight of progesterone
45 parts by weight of lipophilic surfactants
24 parts by weight of hydrophilic surfactants
4.5 parts by weight of digestible oil
20 parts by weight of ethanol.

6. A pharmaceutical composition comprising:

4 to 5% by weight of progesterone
55 to 60% by weight of lipophilic surfactants
30 to 35% by weight of hydrophilic surfactants
3 to 10% by weight of digestible oil.

7. A pharmaceutical composition as claimed in Claim 6 comprising about:

4.5 parts by weight of progesterone
58 parts by weight of lipophilic surfactants
31.5% parts by weight of hydrophilic surfactants
6% parts by weight of digestible oil.

8. A pharmaceutical composition as claimed in any one of Claims 3 to 7 which additionally comprises from 0.02 to 2.0% oestradiol.

9. A pharmaceutical composition comprising:

0.05 to 2% by weight of oestradiol
45 to 50% by weight of lipophilic surfactants
22 to 27% by weight of hydrophilic surfactants
3 to 10% by weight of digestible oil
15 to 25% by weight of ethanol.

10. A pharmaceutical composition as claimed in Claim 9 comprising about:

1 part by weight of oestradiol
48 parts by weight of lipophilic surfactants
26 parts by weight of hydrophilic surfactants
5 parts by weight of digestible oil
21 parts by weight of ethanol.

11. A pharmaceutical composition comprising:

0.05 to 2% by weight of oestradiol
58 to 62% by weight of lipophilic surfactants
30 to 35% by weight of hydrophilic surfactants
5 to 7% by weight of digestible oil.

12. A pharmaceutical composition as claimed in Claim 11 comprising about:

1 part by weight oestradiol
60 parts by weight of lipophilic surfactants
33 parts by weight of hydrophilic surfactants
6 parts by weight of digestible oil.

13. A pharmaceutical composition comprising:

4 to 18% by weight of testosterone
40 to 48% by weight of lipophilic surfactants
20 to 25% by weight of hydrophilic surfactants
7 to 10% by weight of digestible oil
about 15% by weight of ethanol.

14. A pharmaceutical composition as claimed in any preceding claim in which the digestible oil is fractionated coconut oil.

15. A pharmaceutical composition as claimed in any preceding Claim in which the lipophilic surfactant comprises a mixture of glyceryl mono- and di-caprylate.

16. A pharmaceutical composition as claimed in Claim 15 in which the lipophilic surfactant additionally comprises a mixture of glyceryl mono-and di-caprate.

17. A pharmaceutical composition as claimed in any preceding Claim in which the hydrophilic surfactant comprises polyoxyethylene (40) hydrogenated castor oil.

18. A pharmaceutical composition as claimed in Claim 1 or Claim 2 which additionally comprises up to 25% by weight of the composition of ethanol.

19. A pharmaceutical composition as claimed in any preceding Claim in which the weight ratio of hydrophilic surfactants to lipophilic surfactants is in the range 1 : 1.5 to 1 : 2.5.

20. A pharmaceutical composition as claimed in Claim 18 in which the weight ratio of hydrophilic surfactants to lipophilic surfactants is in the range 1 : 1.80 to 1 : 1.90.

21. A pharmaceutical composition as claimed in Claim 19 in which the weight ratio of hydrophilic surfactants to lipophilic surfactants is about 1 : 1.85.

22. A pharmaceutical composition as claimed in Claim 1 or Claim 2 which is free of ethanol.

23. A pharmaceutical composition as claimed in Claim 1 or Claim 2 which is free of additives which are unsaturated compounds.

24. A hard or soft capsule filled with a pharmaceutical composition as claimed in any preceding Claim.

25. A softgel capsule as claimed in Claim 24 comprising a capsule of size 12 oblong containing 50mg of progesterone.

26. A softgel capsule as claimed in Claim 24 comprising a capsule of size 9.5 oblong or 10 oval containing 25mg progesterone in an ethanol-free formulation.

27. A softgel capsule as claimed in Claim 25 or Claim 26 in which the capsule additionally contains from 0.25 to 2mg of oestradiol.

28. A softgel capsule as claimed in Claim 24 containing from 20 to 80mg testosterone.

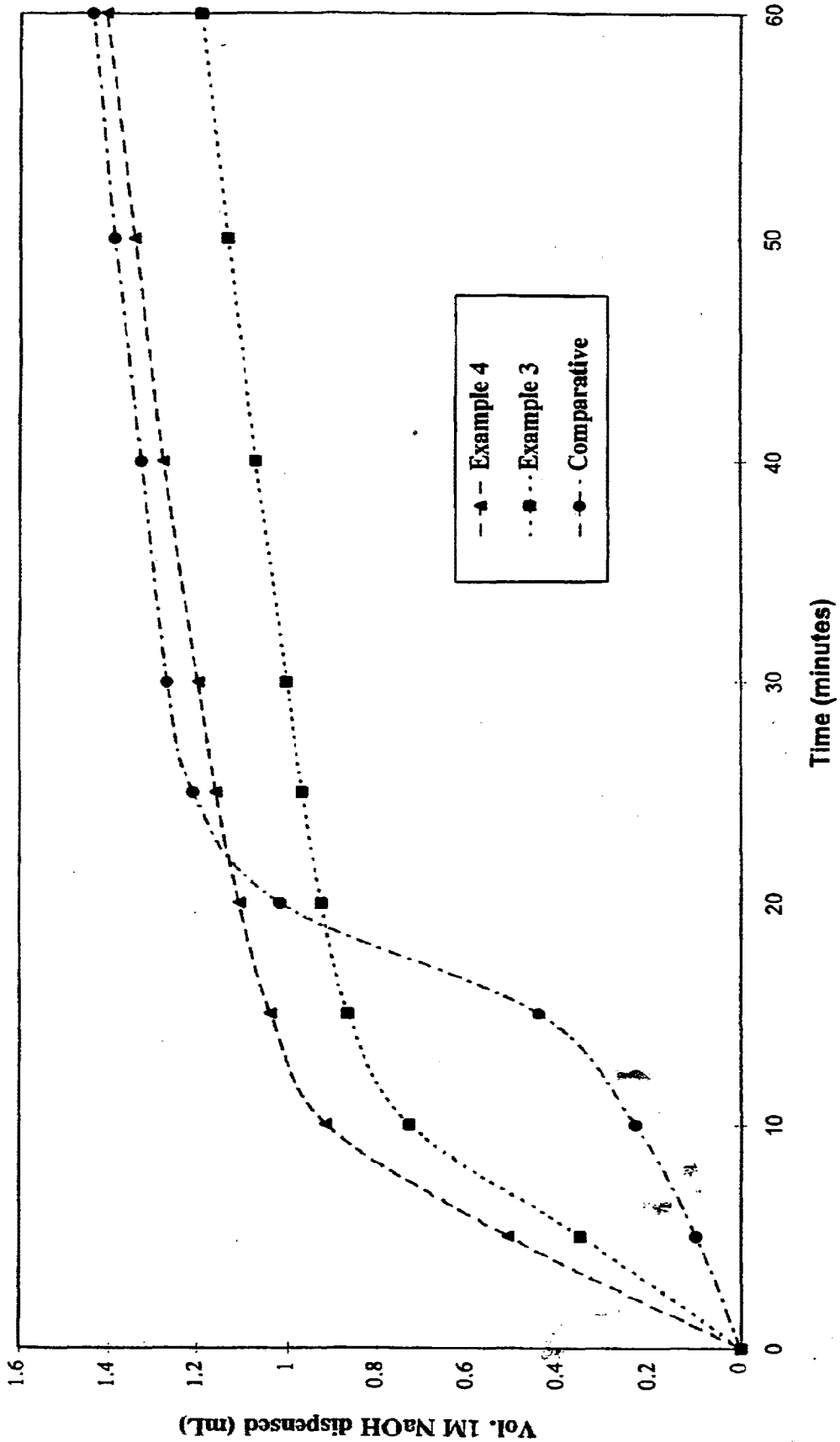

FIGURE 1

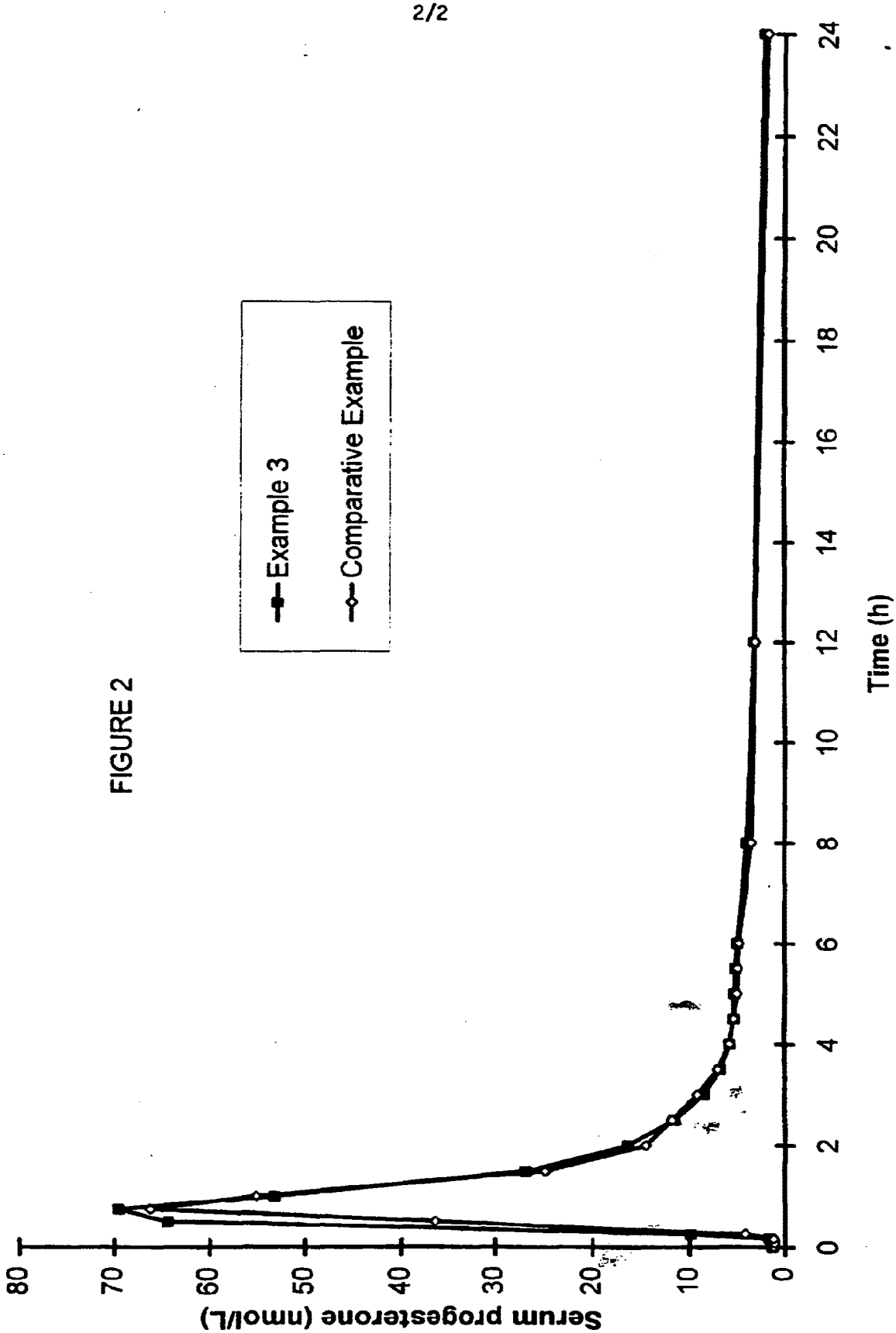

FIGURE 2

INTERNATIONAL SEARCH REPORT

In .tional Application No
PCT/GB 97/01247

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/48 A61K9/107 A61K31/565 A61K31/57

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 95 24893 A (R.P. SCHERER LIMITED) 21 September 1995 cited in the application see the whole document	1-3,6, 12, 14-17, 19-21, 24-26

☐ Further documents are listed in the continuation of box C.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 1997	01. 09. 97

Name and mailing address of the ISA	Authorized officer
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	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 97/01247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9524893 A	21-09-95	AU 1897495 A	03-10-95
		CA 2185347 A	21-09-95
		EP 0750495 A	02-01-97
		US 5645856 A	08-07-97

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 : A61K 31/71, 47/10, 47/14, 47/44 — A1

(11) Internationale Veröffentlichungsnummer: **WO 98/11902**

(43) Internationales Veröffentlichungsdatum: 26. März 1998 (26.03.98)

(21) Internationales Aktenzeichen: PCT/EP97/04867

(22) Internationales Anmeldedatum: 8. September 1997 (08.09.97)

(30) Prioritätsdaten:
196 38 045.6 18. September 1996 (18.09.96) DE

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(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, 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, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches 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).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: INJECTABLE FORMULATIONS OF AVERMECTINS AND MILBEMYCINS

(54) Bezeichnung: INJEKTIONSFORMULIERUNGEN VON AVERMECTINEN UND MILBEMYCINEN

(57) Abstract

The present application concerns injectable formulations of avermectins and milbemycins based on a solvent mixture which contains sesame seed oil, medium-chain triglycerides, glycol esters or fatty acid esters and another solvent of the series of monovalent or polyvalent aliphatic or aromatic alcohols and their derivatives (for example cyclic carbonates, acetates, acetals and ketals) or castor oil.

(57) Zusammenfassung

Vorliegende Anmeldung betrifft Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis eines Lösungsmittelgemischs, enthaltend Sesamöl, mittelkettige Triglyceride, Glycolester oder Fettsäureester und ein weiteres Solvenz aus der Reihe ein- oder mehrwertiger aliphatischer oder aromatischer Alkohole und deren Derivate (z.B. cyclische Carbonate; Acetate; Acetale; Ketale) oder Rizinusöl.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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Injektionsformulierungen von Avermectinen und Milbemycinen

Die Erfindung betrifft neue Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis von Lösungsmittelmischungen, die Sesamöl enthalten.

Injektionsformulierungen von Ivermectin sind bekannt aus EP-A 146 414. Die Formulierungen enthalten ein Lösemittelgemisch aus Propylenglykol und Glycerinformal im Verhältnis 60:40 V/V. Von Propylenglykol ist bekannt, daß es in bestimmten Konzentrationen lokale Unverträglichkeiten hervorrufen kann (siehe Review: B. Kruss, Acta Pharm. Technol. 35(4) (1989) 187-196). Auch kann es zur Ausfällung des wasserunlöslichen Wirkstoffs Ivermectin im Gewebe um die Applikationsstelle kommen. So wurden bei der Anwendung entsprechender Formulierungen deutliche Schwellungen und Gewebeunverträglichkeiten an den Injektionsstellen beobachtet, die sich zum Teil erst nach mehreren Wochen zurückbildeten.

Injektionsformulierungen bestimmter Avermectine sind bekannt aus EP-A 393 890. Es handelt sich um ölige Formulierungen auf Basis von Sesamöl und Ethyloleat im Verhältnis 90:10 V/V. Diese Formulierungen sind verträglich, haben aber den Nachteil, daß die Löslichkeit für Avermectine/Milbemycine oft nicht ausreicht, um eine für die Anwendung gewünschte Konzentration von 1 % M/V oder höher zu erreichen. In der Regel erhält man bei erhöhten Temperaturbedingungen ($T \geq 80°C$) übersättigte 1 % M/V-Lösungen, die bei tieferen Temperaturen auf Dauer wieder auskristallisieren.

Weitere Injektionsformulierungen von Avermectinen sind bekannt aus EP-A 45 655. Die dort beschriebenen Formulierungen enthalten verhältnismäßig hohe Anteile an Emulgatoren und sind zum Teil wenig verträglich.

Injektionsformulierungen von Avermectinen, die Triacetin (Glycerintriacetat) enthalten, sind in EP-A 413 538 beschrieben. In EP-A 535 734 werden Injektionsformulierungen von Avermectinen auf Basis von Triacetin und hydriertem Rizinusöl beschrieben.

Weitere Formulierungen zur Injektion von Milbemycinen und Avermectinen sind in EP-A 525 307 beschrieben. Die Herstellung der Formulierungen erfolgt, indem Glycerintristearat mit dem Wirkstoff geschmolzen und mit einem öligen neutralen Triglycerid vermischt und unter Verwendung von z.B. Methylcellulose und Salzen

emulgiert wird. Die durchschnittliche Partikelgröße in der so erhaltenen Mikroemulsion soll zwischen 25 und 300 µm liegen.

Gegenstand der vorliegenden Erfindung sind Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis eines Lösungsmittelgemischs, enthaltend Sesamöl, mittelkettige Triglyceride oder Glycolester oder Fettsäureester und einem weiteren Solvenz.

Die Formulierungen enthalten bevorzugt

1. Wirkstoff 0,2 bis 5 % M/V;

2. Sesamöl 60 bis 90 % V/V;

3. mittelkettige Triglyceride oder Glycolester oder Fettsäureester 10 bis 30 Vol.-%;

4. 1 bis 20 Vol.-% Benzylalkohol oder Propylenglykol oder andere geeignete aliphatische oder aromatische ein- oder mehrwertige Alkohole und deren Derivate (z.B. cyclische Carbonate, Acetate, Acetale/Ketale) oder Rizinusöl;

5. gegebenenfalls weitere Hilfsstoffe.

Die erfindungsgemäßen Formulierungen weisen eine hervorragende Löslichkeit für die Wirkstoffe auf.

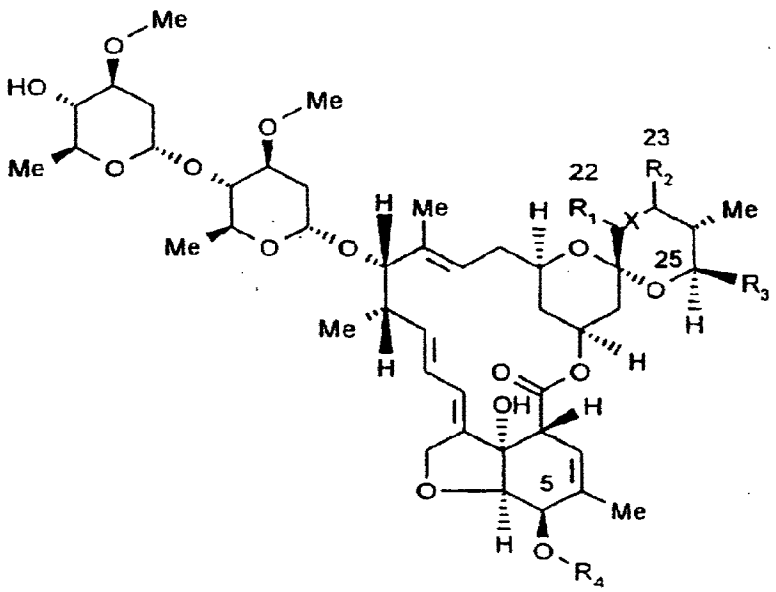
Die hohe Viskosität von Sesamöl kann durch Zusatz von mittelkettigen Triglyceriden oder Propylenglykol-octanoat/decanoat oder besonders Ethyloleat auf ein gewünschtes niedriges Maß eingestellt werden. Zusätzlich kann durch Addition von kleineren Volumina hydrophiler Lösemittel wie Benzylalkohol, Propylenglykol oder Propylencarbonat unter Beibehaltung eines einphasigen Systems die Löslichkeit des Wirkstoffs verbessert, die Viskosität weiter herabgesetzt und die Bioverfügbarkeit des Wirkstoffs verbessert werden. Als einziges Triglycerid weist Rizinusöl ein hohes Lösepotential für die in Frage stehenden Wirkstoffe auf.

Die in den erfindungsgemäßen Formulierungen eingesetzten Wirkstoffe sind bekannt.

Avermectine wurden aus dem Mikroorganismus Streptomyces avermitilis als mikrobielle Metabolite isoliert (US-Pat. 4 310 519) und können im wesentlichen als Gemisch, bestehend aus den acht Komponenten A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b}, B_{2a} und B_{2b}, auftreten (I. Putter et al. Experentia 37 (1981) S. 963, Birkhäuser Verlag (Schweiz)). Daneben besitzen auch die synthetischen Derivate, insbesondere das 22,23 Dihydroavermectin B_1 (Ivermectin), Interesse (US-Pat. 4 199 569). Milbemycin B-41 D wurde fermentativ aus Streptomyces hygroscopicus isoliert (vgl. "Milbemycin: Discovery and Development" I. Junya et al. Annu. Rep. Sankyo Res. Lab. 45 (1993), S. 1-98; JP-Pat. 8 378 549; GB 1 390 336).

Die Verwendung der Avermectine, z.B. 22,23-Dihydroavermectine B_1 (Ivermectin), und Milbemycine als Endoparasitizide ist bekannt und Gegenstand zahlreicher Patentanmeldungen sowie Übersichtsartikel (z.B. Biologische Wirkungen in: "Ivermectin and Abamectin" W.C. Campbell, Ed., Springer Verlag, New York, N.Y., 1989; "Avermectins and Milbemycins Part II" H.G. Davies et al. Chem. Soc. Rev. 20 (1991) S. 271-339; Chemische Modifikationen in: G. Lukacs et al. (Eds.), Springer Verlag, New York, (1990), Chapter 3; Cydectin® [Moxidectin und Derivate]: G.T. Carter et al. J. Chem. Soc. Chem. Com-mun. (1987), S. 402-404); EP 423 445-A1) "Doramectin - a potent novel endectozide" A.C. Goudie et al. Vet. Parasitol. 49 (1993), S. 5-15).

Besonders hervorgehoben seien Avermectine und deren Derivate der allgemeinen Formel (I)



(I),

in welcher

die Reste R^1 bis R^4 die in der nachfolgenden Tabelle 1 angegebene Bedeutung haben und X für eine Einfach- oder Doppelbindung zwischen der C_{22}- und C_{23}-Position (-$C_{22}R^1$-X-$C_{23}R^2$-) stehen kann.

Im Falle einer Doppelbindung befinden sich keine Substituenten (R^1, R^2) an der C_{22}- und C_{23}-Position.

Tabelle 1

Makrocyclisches Lacton	$-C_{22}R^1-X-C_{23}R^2-$	R^3	R^4
Avermectin A_{1a}	-CH=CH-	-sec-Bu	-Me
Avermectin A_{1b}	-CH=CH-	-iso-Pr	-Me
Avermectin A_{2a}	$-CH_2-CHOH-$	-sec-Bu	-Me
Avermectin A_{2b}	$-CH_2-CHOH-$	-iso-Pr	-Me
Avermectin B_{1a}	-CH=CH-	-sec-Bu	-H
Avermectin B_{1b}	-CH=CH-	-iso-Pr	-H
Avermectin B_{2a}	$-CH_2-CHOH-$	-sec-Bu	-H
Avermectin B_{2b}	$-CH_2-CHOH-$	-iso-Pr	-H
22,23-Dihydroavermectin B_{1a}	$-CH_2-CH_2-$	-sec-Bu	-H
22,23-Dihydroavermectin B_{1b}	$-CH_2-CH_2-$	-iso-Pr	-H
Doramectin	-CH=CH-	-Chx	-H

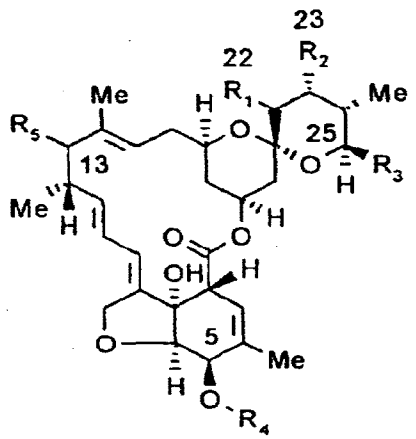
22,23-Dihydroavermectin B_1 steht für Ivermectin;
sec-Bu = sekundär Butyl; iso-Pr = Isopropyl; Chx = Cyclohexyl; -Me = Methyl

Die Avermectine und 22,23-Dihydroavermectine B_1 (Ivermectin) der allgemeinen Formel (I) werden in der Regel als Gemische eingesetzt. Von besonderem Interesse ist hierbei das Produkt Abamectin, das die Avermectine B_1 enthält, und deren Hydrierungsprodukte, die 22,23-Dihydroavermectine B_1 (Ivermectin).

Die mit "b" bezeichneten Verbindungen der makrocyclischen Lactone, die in der C_{25}-Position einen iso-Propylrest besitzen, müssen nicht notwendigerweise von den "a" Verbindungen, welche eine sec-Butylgruppe in der C_{25}-Position haben, getrennt werden. Es wird generell das Gemisch beider Substanzen, bestehend aus > 80 % sec-Butylderivat (B_{1a}) und < 20 % iso-Propylderivat (B_{1b}) isoliert, und kann erfindungsgemäß verwendet werden. Zudem können bei den Stereoisomeren die Substituenten in der C_{13}- und C_{23}-Position sowohl α- als auch ß-ständig am Ringsystem angeordnet sein, d. h. sich oberhalb oder unterhalb der Molekülebene befinden. In jedem Fall werden alle Stereoisomeren erfindungsgemäß berücksichtigt.

Besonders genannt seien die Milbemycine. Die Milbemycine haben die gleiche makrolide Ringstruktur wie die Avermectine oder 22,23-Dihydroavermectine B_1 (Ivermectine), tragen aber keinen Substituenten (d.h. fehlendes Oleandrose-Disaccharidfragment) in Position 13 (R^5 = Wasserstoff).

Beispielhaft seien als Milbemycine aus der Klasse der macrocyclischen Lactone die Verbindungen mit der allgemeinen Formel (II) genannt

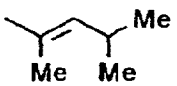
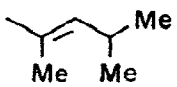


(II)

in welcher

die Reste R^1 bis R^5 die in der nachfolgenden Tabelle 2 angegebene Bedeutung haben:

Tabelle 2

Makrocyclisches Lacton	R^1	R^2	R^3	R^4	R^5
Milbemycin B41 D	-H	-H	-iso-Pr	-H	-H
Nemadectin	-H	-OH		-H	-H
Moxidectin	-H	=N-O-Me		-H	-H

iso-Pr = Isopropyl

Ganz besonders hervorgehoben seien die Wirkstoffe

Avermectin B_{1a}/B_{1b} (Abamectin),
22,23-Dihydroavermectin B_{1a}/B_{1b} (Ivermectin),
Doramectin,
Moxidectin.

Die Wirkstoffe liegen in den erfindungsgemäßen Formulierungen in Konzentrationen von 0,2 bis 5 %, bevorzugt von 0,5 bis 2 %, besonders bevorzugt 1 % M/V vor.

Das in den erfindungsgemäßen Formulierungen eingesetzte Sesamöl (60 bis 90 % V/V) ist bekannt.

Die in den erfindungsgemäßen Formulierungen eingesetzten Viskositätserniedriger, insbesondere Ethyloleat, sind bekannt.

Gute und als Bestandteil von Injektabilia einsetzbare weitere Lösungsmittel für die Wirkstoffe sind namentlich Benzylalkohol, Propylenglykol, Glycerinformal, Propylencarbonat, Triacetin, die Myvacete® (Warenzeichen von Eastman), Propylengly-

koldiacetat, Polyethylenglykol 400, Tetraglykol sowie Rizinusöl. Besonders bevorzugt sind Benzylalkohol (1 bis 5 % V/V) und Rizinusöl (10 bis 20 % V/V).

Die Löslichkeit von Ivermectin beträgt in Benzylalkohol > 40 Gew.-%, in Rizinusöl ~ 4 Gew.-%.

Weitere Zusätze zu den erfindungsgemäßen Formulierungen sind Stabilisatoren wie Butylhydroxyanisol (BHA), Butylhydroxytoluol (BHT) oder Propylgallat von insgesamt bis zu 1000 ppm. Besonders geeignete Stabilisatorkombinationen und -konzentrationen sind z.B. 100 ppm BHA oder 100 ppm BHA plus 150 ppm Propylgallat oder 200 ppm BHA plus 100 ppm Propylgallat.

Die Viskosität der erfindungsgemäßen Formulierungen liegt zwischen 20 bis 60 mPa.s (20°C), bevorzugt zwischen 25 bis 55 mPa.s (20°C), besonders bevorzugt zwischen 30 und 51 mPa.s (20°C).

Die folgenden Beispiele erläutern die Erfindung.

Anmerkung:

$$V/V = \frac{\text{Volumen}}{\text{Volumen}}$$ entspricht Volumenprozent

$$M/V = \frac{\text{Masse}}{\text{Volumen}}$$

1 % M/V heißt z.B. 10 mg Wirkstoff in 1 ml Lösung.

Beispiel 1

Sesamöl	q.s. 100 % V/V	
Ethyloleat	10 % V/V	
Benzylalkohol	2 % V/V	
Ivermectin	1 % M/V	
Butylhydroxyanisol (BHA)	100 ppm	(≙ 0,01 % M/V)
Dichte:	0,922 g/ml	
Viskosität:	44 mPa.s bei 20°C	
	85 mPa.s bei 5°C	
	24 mPa.s bei 39°C	

Beispiel 2

Sesamöl	q.s. 100 % V/V	
Ethyloleat	20 % V/V	
Rizinusöl	10 % V/V	
Ivermectin	1 % M/V	
Butylhydroxyanisol (BHA)	100 ppm	(≙ 0,01 % M/V)
Dichte:	0,927 g/ml	
Viskosität:	38 mPa.s bei 20°C	
	83 mPa.s bei 5°C	

Allgemeine Herstellvorschrift für die Beispiele 1 und 2 als sterile Lösungen zur Injektion:

Sesamöl und Ethyloleat, mit 100 ppm BHA versehen, werden in einen Edelstahlbehälter eingewogen und unter Rühren homogenisiert. Unter weiterem Rühren wird das Ivermectin, in Benzylalkohol oder Rizinusöl gelöst bzw. angelöst, eingebracht. Die Mischung wird auf 40 bis 60°C erwärmt, um die rasche, vollständige Auflösung des Wirkstoffs zu garantieren (alles unter Stickstoffbegasung).

Dann wird bei gleicher Temperatur über ein 0,22 µm Filter sterilfiltriert (in der Regel wird ein 0,45 µm oder 1 µm Filter vorgeschaltet). Es folgt aseptische Abfüllung in Braunglasflaschen.

Die so hergestellten Formulierungen sind bei der Anwendung am Rind hervorragend verträglich. Sie sind außerdem über mindestens 6 Wochen bei Temperaturen von 60°C lagerstabil.

Patentansprüche

1. Injektionsformulierungen von Avermectinen und Milbemycinen auf Basis eines Lösungsmittelgemischs, enthaltend Sesamöl, mittelkettige Triglyceride, Glycolester oder Fettsäureester und ein weiteres Solvenz aus der Reihe ein- oder mehrwertiger aliphatischer oder aromatischer Alkohole und deren Derivate (z.B. cyclische Carbonate; Acetate; Acetale; Ketale) oder Rizinusöl.

2. Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, daß sie folgende Zusammensetzung haben:

   1. Wirkstoff 0,2 bis 5 % M/V;

   2. Sesamöl 60 bis 90 % V/V;

   3. 10 bis 30 Vol.-% mittelkettige Triglyceride oder Glycolester oder Fettsäureester;

   4. 1 bis 20 % Co-Lösungsmittel aus der Reihe ein- oder mehrwertiger aliphatischer oder aromatischer Alkohole und deren Derivate oder Rizinusöl;

   5. gegebenenfalls weitere Hilfsstoffe.

3. Formulierungen gemäß Anspruch 1 der folgenden Zusammensetzung: 0,2 bis 5 % M/V eines Avermectins oder Milbemycins in einem Lösungsmittelgemisch bestehend aus 60 bis 90 % V/V Sesamöl, sowie 10 bis 30 % V/V Ethyloleat oder Miglyol®812 oder Miglyol®840 und 1 bis 5 % V/V Benzylalkohol oder 10 bis 20 % V/V Rizinusöl sowie gegebenenfalls bis zu 1000 ppm Stabilisatoren.

4. Formulierungen gemäß Anspruch 1 der folgenden Zusammensetzung: 1 % M/V Ivermectin, 65 bis 90 % V/V Sesamöl, 10 bis 20 % V/V Ethyloleat und 1 bis 3 % V/V Benzylalkohol oder 10 % V/V Rizinusöl sowie gegebenenfalls bis zu 500 ppm Stabilisatoren.

5. Verfahren zur Herstellung der Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, daß man den Wirkstoff in Rizinusöl oder Benzylalkohol (an)löst und die restlichen Lösungsmittel zufügt oder, daß man den Wirkstoff in einer Mischung aus allen drei Lösungsmitteln auflöst.

6. Verwendung von Rizinusöl oder Benzylalkohol als Lösungsverbesserer in einer Formulierung gemäß Anspruch 1.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/04867

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/71 A61K47/10 A61K47/14 A61K47/44

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 minimumdocumentation 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.
Y	EP 0 393 890 A (PFIZER) 24 October 1990 cited in the application see the whole document	1-6
Y	EP 0 525 307 A (AMERICAN CYANAMID) 3 February 1993 cited in the application see claims see example 2	1-6
Y	EP 0 535 734 A (MERCK) 7 April 1993 cited in the application see claims 1,8	1-6
Y	GB 2 275 193 A (MERCK) 24 August 1994 see examples 8,9	1-6

-/--

[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 publicationdate 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 theinternational search	Date of mailing of the international search report
27 January 1998	03/02/1998

Name and mailing address of the ISA	Authorized officer
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	Scarponi, U

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

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/04867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 045 655 A (MERCK) 10 February 1982 cited in the application see the whole document	1-6
A	EP 0 146 414 A (MERCK) 26 June 1985 cited in the application see the whole document	1-6
A	EP 0 413 538 A (MERCK) 20 February 1991 cited in the application see the whole document	1-6
Y,P	WO 97 11709 A (ASHMONT) 3 April 1997 see claims	1-6
E	WO 97 37653 A (BAYER) 16 October 1997 see the whole document	1-6

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

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Intern... ...al Application No
PCT/EP 97/04867

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 393890 A	24-10-90	SG 27894 A	17-03-95
		AP 133 A	05-06-91
		AU 609660 B	02-05-91
		AU 5311990 A	08-11-90
		BG 60543 B	28-08-95
		CA 2014157 A,C	11-10-90
		CN 1046282 A	24-10-90
		CY 1777 A	20-10-95
		EG 18956 A	30-04-94
		ES 2052173 T	01-07-94
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		HK 39294 A	06-05-94
		HU 9500135 A	28-07-95
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		JP 1921370 C	07-04-95
		JP 2290820 A	30-11-90
		JP 6047548 B	22-06-94
		MX 20250 A	01-11-93
		NO 175882 B	19-09-94
		OA 9203 A	30-06-92
		PT 93697 B	30-08-96
		SU 1836084 A	23-08-93
EP 525307 A	03-02-93	AT 134873 T	15-03-96
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		DE 69208765 T	26-09-96
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		JP 5246893 A	24-09-93
		JP 6072108 B	14-09-94
		ZA 9207457 A	07-04-93

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Interna...nal Application No
PCT/EP 97/04867

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2275193 A	24-08-94	NONE	
EP 45655 A	10-02-82	AR 229354 A	29-07-83
		AU 551280 B	24-04-86
		AU 7361281 A	11-02-82
		CA 1162857 A	28-02-84
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		JP 1801578 C	12-11-93
		JP 5007371 B	28-01-93
		JP 57065330 A	20-04-82
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EP 146414 A	26-06-85	AU 560864 B	16-04-87
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		HK 5091 A	18-01-91
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		JP 6023100 B	30-03-94
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		US 4853372 A	01-08-89
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		AU 6094690 A	14-02-91
		CA 2022892 A	15-02-91
		DE 69003906 D	18-11-93
		DE 69003906 T	05-05-94
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		AU 7100296 A	17-04-97
WO 9737653 A	16-10-97	DE 19613972 A	16-10-97
		AU 2506697 A	29-10-97

INTERNATIONALER RECHERCHENBERICHT

Intern ales Aktenzeichen
PCT/EP 97/04867

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K31/71 A61K47/10 A61K47/14 A61K47/44

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	EP 0 393 890 A (PFIZER) 24.Oktober 1990 in der Anmeldung erwähnt siehe das ganze Dokument ---	1-6
Y	EP 0 525 307 A (AMERICAN CYANAMID) 3.Februar 1993 in der Anmeldung erwähnt siehe Ansprüche siehe Beispiel 2 ---	1-6
Y	EP 0 535 734 A (MERCK) 7.April 1993 in der Anmeldung erwähnt siehe Ansprüche 1,8 ---	1-6
Y	GB 2 275 193 A (MERCK) 24.August 1994 siehe Beispiele 8,9 --- -/--	1-6

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
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"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

1

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
27.Januar 1998	03/02/1998

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scarponi, U

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Intern ...ales Aktenzeichen
PCT/EP 97/04867

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 045 655 A (MERCK) 10.Februar 1982 in der Anmeldung erwähnt siehe das ganze Dokument	1-6
A	EP 0 146 414 A (MERCK) 26.Juni 1985 in der Anmeldung erwähnt siehe das ganze Dokument	1-6
A	EP 0 413 538 A (MERCK) 20.Februar 1991 in der Anmeldung erwähnt siehe das ganze Dokument	1-6
Y,P	WO 97 11709 A (ASHMONT) 3.April 1997 siehe Ansprüche	1-6
E	WO 97 37653 A (BAYER) 16.Oktober 1997 siehe das ganze Dokument	1-6

Formblatt PCT/ISA/210 (Fortsetzung von Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichung, die zur selben Patentfamilie gehören

Interna' ...les Aktenzeichen
PCT/EP 97/04867

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 393890 A	24-10-90	SG 27894 A	17-03-95
		AP 133 A	05-06-91
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		AU 5311990 A	08-11-90
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		CA 2014157 A,C	11-10-90
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		ES 2052173 T	01-07-94
		FI 92015 B	15-06-94
		HK 39294 A	06-05-94
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		JP 2290820 A	30-11-90
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		MX 20250 A	01-11-93
		NO 175882 B	19-09-94
		OA 9203 A	30-06-92
		PT 93697 B	30-08-96
		SU 1836084 A	23-08-93
EP 525307 A	03-02-93	AT 134873 T	15-03-96
		AU 651229 B	14-07-94
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		ES 2086022 T	16-06-96
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		JP 5194211 A	03-08-93
		MX 9204135 A	01-01-93
		NZ 243619 A	22-12-94
EP 535734 A	07-04-93	AU 2603792 A	01-04-93
		JP 5246893 A	24-09-93
		JP 6072108 B	14-09-94
		ZA 9207457 A	07-04-93

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichung, die zur selben Patentfamilie gehören

Interna[illegible]ales Aktenzeichen
PCT/EP 97/04867

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
GB 2275193 A	24-08-94	KEINE	
EP 45655 A	10-02-82	AR 229354 A	29-07-83
		AU 551280 B	24-04-86
		AU 7361281 A	11-02-82
		CA 1162857 A	28-02-84
		DK 345081 A,B,	05-02-82
		JP 1801578 C	12-11-93
		JP 5007371 B	28-01-93
		JP 57065330 A	20-04-82
		OA 6863 A	28-02-83
		US 4389397 A	21-06-83
EP 146414 A	26-06-85	AU 560864 B	16-04-87
		AU 3702484 A	04-07-85
		CA 1267844 A	17-04-90
		DK 619784 A,B,	23-06-85
		HK 5091 A	18-01-91
		JP 1900831 C	27-01-95
		JP 6023100 B	30-03-94
		JP 60169415 A	02-09-85
		US 4853372 A	01-08-89
EP 413538 A	20-02-91	AU 627610 B	27-08-92
		AU 6094690 A	14-02-91
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		DE 69003906 T	05-05-94
		JP 3169812 A	23-07-91
WO 9711709 A	03-04-97	NZ 280085 A	22-09-97
		AU 7100296 A	17-04-97
WO 9737653 A	16-10-97	DE 19613972 A	16-10-97
		AU 2506697 A	29-10-97

#7 mg 3/5/02

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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TECH CENTER 1600/2900

CHANGE OF ADDRESS/POWER OF ATTORNEY

FILE LOCATION 16G4 SERIAL NUMBER 09756291 PATENT NUMBER

THE CORRESPONDENCE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 9629

THE PRACTITIONERS OF RECORD HAVE BEEN CHANGED TO CUSTOMER # 9629

THE FEE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 9629

ON 02/07/02 THE ADDRESS OF RECORD FOR CUSTOMER NUMBER 9629 IS:

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON DC 20004

AND THE PRACTITIONERS OF RECORD FOR CUSTOMER NUMBER 9629 ARE:

16773	20534	25323	27890	30191	30988	32541	32676	33652	33701
33818	34658	35035	35861	36317	36787	37028	37525	38708	39887
40411	40420	40506	40541	40586	40624	40940	41023	41040	41146
41161	42030	42621	42623	42788	43210	43337	43371	43378	43690
43694	43782	43828	43877	44478	44479	45206	45397	45807	45841
46277	46340	46553	46840	46882	47142	47269	47278	47300	47302
47304	47362	47630	48107	48183	48463	48513	49086	49088	

PTO INSTRUCTIONS: PLEASE TAKE THE FOLLOWING ACTION WHEN THE CORRESPONDENCE ADDRESS HAS BEEN CHANGED TO CUSTOMER NUMBER: RECORD, ON THE NEXT AVAILABLE CONTENTS LINE OF THE FILE JACKET, 'ADDRESS CHANGE TO CUSTOMER NUMBER'. LINE THROUGH THE OLD ADDRESS ON THE FILE JACKET LABEL AND ENTER ONLY THE 'CUSTOMER NUMBER' AS THE NEW ADDRESS. FILE THIS LETTER IN THE FILE JACKET. WHEN ABOVE CHANGES ARE ONLY TO FEE ADDRESS AND/OR PRACTITIONERS OF RECORD, FILE LETTER IN THE FILE JACKET.
THIS FILE IS ASSIGNED TO GAU 1617.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

9629 7590 03/13/2002

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	9

DATE MAILED: 03/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/756,291	Applicant(s) EVANS ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of the invention of Group II, claims 21-22 and the specie of disease state, breast cancer, in Paper No. 6, received February 1, 2002 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-20, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Claim Objections

Claims 21 and 22 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims 21 and 22 have not been further treated on the merits.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone

numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
March 7, 2002

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Atty. Dkt. No.	M#	Client Ref.
	056291-5004	Z70635/US

Applicant: Evans et al.

Appln. No.: 09/756,291

Filing Date: January 9, 2001

Examiner: Stiller, K. | Group Art Unit: ~~1617~~

Date: February 1, 2002 Page 1 of 3

RECEIVED FEB 06 2002 TECH CENTER 1600/2900

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
SH	AR	2,822,316	02/1958	Richter et al.			
	BR	2,983,649	05/1961	Ercoli et al.			
	CR	3,541,209	11/1970	Neumann et al.			
	DR	4,048,309	09/1977	Chen et al.			
	ER	4,048,310	09/1977	Chen et al.			
	FR	4,659,516	04/1987	Bowler et al.			
	GR	4,888,331	12/1989	Elger et al.			
	HR	5,095,129	03/1992	Ottow et al.			
SH	IR	5,183,814	02/1993	Dukes			

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
SH	JR	0 138 504	04/1985	EPA	Bowler et al.					
	KR	0 346 014	12/1989	EPA	Dukes					
	LR	6241	09/1968	France	Schering AK		X			
	MR	817,241	07/1959	GB	Francecso Vismara, S.p.A.					
	NR	1 569 286	06/1980	GB	Schering AK					
	OR	1 207 571	10/1970	GB	Takeda Chemical Industries, Ltd.					
	PR	1 126 892	09/68	GB	Schering AK					
	QR	681014	02/1968	South Africa	Kimbel					
SH	RR	682530	04/1968	South Africa	Ufer et al.					

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

SH	SR	Anschel, "Lösungsmittel und Lösungsvermittler in Injektionen", Pharm. Ind., 1965, Vol. 27 (11a), pp. 781-787			X
SH	TR	Davis et al., "17-Alpha-Hydroxyprogesterone-Caproate:...with Chemically Pure Progesterone", J. Clin. Endocrinol. And Metabolism, 1955, Vol. 15, pp. 923-930			
SH	UR	Dukes et al., "Antiuterotrophic effects of the pure antioestrogen ICI 182, 780 ...quantitative magnetic resonance imaging"; J. Endocrinology, 1992, Vol. 138, pp. 203-209			
SH	VR	Dukes et al., "Antiuterotrophic effects of pure antioestrogen. ICI 182,780, ...the uterus in ovariectomized monkeys", J. Endocrinology, 1992, Vol. 135, pp. 239-247			

Examiner [signature] Date Considered: 3/6/02

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Atty. Dkt. No.	M#	Client Ref.
	056291-5004	Z70635/US

Applicant: Evans et al.

Appln. No.: 09/756,291

Filing Date: January 9, 2001

Date: February 1, 2002 Page 2 of 3

Examiner: Stiller, K. Group Art Unit: 1617

RECEIVED FEB 06 2002 TECH CENTER 1600/2900

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	5,484,801	01/1996	Al-Razzak et al.			
	BR	5,733,902	03/1998	Schneider			
	CR	5,929,030	07/1999	Hamied et al.			
	DR						
	ER						
	FR						

OIPE FEB 07 2002 PATENT & TRADEMARK OFFICE

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
SM	GR	549118	03/1977	Soviet Union	Prokofeva		X			
	HR	676284	07/1979	Soviet Union	Bikkulov et al.		X			
	IR	WO 95/12383	05/1995	WIPO	Fang et al.		X			
	JR	WO 96/19997	07/1996	WIPO	Chwalisz et al.		X			
	KR	WO 97/21440	06/1997	WIPO	Ferdinando et al.					
	LR	WO 97/37653	10/1997	WIPO	Grosse-Bley et al.		X			
	MR	WO 97/40823	11/1997	WIPO	Perry et al.					
SM	NR	WO 98/11902	03/1998	WIPO	Grosse-Bley et al.		X			

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

SM	OR	Howell et al., "Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer", British Journal of Cancer, 1996, Vol. 74, pp. 300-308			
	PR	Martindale, 32nd Ed., "Alcohol", Pharmaceutical Press, 1999, pp. 1099-1101			
	QR	Martindale, 32nd Ed., "Benzoates" and "Benzyl Alcohol"; Pharmaceutical Press, 1999, pp. 1102-1104			
	RR	Martindale, 32nd Ed., "Caster Oil"; 32nd Ed., Pharmaceutical Press, 1999, p. 1560			
	SR	Migally, "Effect of Castor Oil and Benzyl Benzoate Used as a Vehicle for Antiandrogens on the Adrenal Cortex", Archives of Andrology 2, 1979 pp. 365-369			
	TR	Pellegrino, "Use of 17 α Hydroxyprogesterone Caproate in Threatened Abortion", Current Therapeutic Research, Vol. 4, No. 6, June, 1962, pp. 301-305			
SM	UR	Piver et al., "Medroxyprogesterone Acetate (Depo-Provera) vs. . . . Women with Metastatic Endometrial Adenocarcinoma", Cancer, Vol. 45, American Cancer Society, 1980, pp. 268-272			

Examiner [signature] Date Considered: 3/6/02

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449.(modified)
To: U.S. Department of Commerce
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Atty. Dkt. No.	M#	Client Ref.
	056291-5004	Z70635/US

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: Evans et al.

Appln. No.: 09/756,291

Filing Date: January 9, 2001

Date: February 1, 2002 Page 3 of 3

Examiner: Stiller, K. Group Art Unit: 1617

RECEIVED FEB 06 2002 TECH CENTER 1600/2900

OIPE JC177 FEB 01 2002 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	FR									
	GR									
	HR									
	IR									
	JR									
	KR									
	LR									
	MR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

SH	NR	Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, pp. 891-895
	OR	Sawada et al., "Estrogen Receptor Antagonist ICI182,780 Exacerbates Ischemic Injury in Female Mouse", Journal of Cerebral Blood Flow and Metabolism, Vol. 20. No. 1, 2000, pp. 112-118.
	PR	Vidal, Le Dictionnaire, "Benzo-Gynoestryl Retard", 1998 pg. 201
	QR	Vidal, Le Dictionnaire, "Gravibinan", 1995, pp 660-661
	RR	Vidal, Le Dictionnaire, "Parabolan", 1997, pg. 1245
	SR	Vidal, Le Dictionnaire, "Trophobolene", 1997, pp. 1706-1707
	TR	Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential", Cancer Research, 1991, Vol. 51, pp. 3867-3873
SH	UR	Waterton et al., "A Case of Adenomyosis in a Pigtailed Monkey...Treated with the Novel Pure Antiestrogen, ICI 182,780"; Laboratory Animal Science, 1993, Vol. 43, No. 3, 1993, pp. 247-251

Examiner [signature] Date Considered: 3/6/02

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Interview Summary	Application No.	Applicant(s)	
	09/756,291	EVANS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

All participants (applicant, applicant's representative, PTO personnel):

(1) *San-ming Hui*. (3)_____.

(2) *Mr. Donald Bird*. (4)_____.

Date of Interview: *07 March 2002* .

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____ .

Claim(s) discussed: *21 and 22* .

Identification of prior art discussed: *None* .

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The examiner has notified Mr. Bird, the attorney of record that all the claims drawn to the elected invention have improper multiple dependency. The examiner also requested the attorney to submit an amendment to correct the improper multiple dependency of the claims; however, the examiner was informed that such amendment would not be made at this time.* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☐ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

3/9/02

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

1617

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San Ming R.

Commissioner of Patents
Washington, D.C. 20231

Date: September 13, 2002

Sir:

AMENDMENT TRANSMITTAL FORM

1. Transmitted herewith is an Amendment responding to the Office Action dated March 13, 2002.

2. Additional papers enclosed:

- ☒ Second Information Disclosure Statement
- ☒ Third Information Disclosure Statement with Form PTO-1449 and 3 cited references
- ☐ Declaration of Biological Deposit
- ☐ Submission of "Sequence Listing", computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
- ☐ Drawings: ☐ Formal ☐ Informal (Correction)

1-WA/1862189.1

3. Extension of Time

The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136(a) apply.

☐ Applicant believes that no extension of time is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

☒ Applicant petitions for an extension of time, the fees for which are set out in 37 C.F.R. § 1.17(a), for the total number of months checked below:

Total Months Requested	Fee for Extension	[Fee for Small Entity]
☐ one month	$ 110.00	$ 55.00
☐ two months	$ 400.00	$ 200.00
☒ three months	$ 920.00	$ 460.00
☐ four months	$ 1,440.00	$ 720.00
☐ five months	$ 1,960.00	$ 980.00

If an additional extension of time is required, please consider this a Petition therefor.

☐ An extension for _____months has already been secured and the fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension of time fee due with this request: $920.00

4. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Fee Calculation (37 C.F.R. §1.16)

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		Highest No. Previously Paid	Present Extra	at Rate of	Total Fees
Total Claims (37 C.F.R. §1.16(c))	47	minus	29	18	x $18.00 each=	$ 324.00
Independent Claims (37 C.F.R.§1.16(b))	4	minus	3	0	x $84 each=	$ 84.00
[ ] First presentation of Multiple dependent claim(s)					$280.00	$ 0.00
SUB-TOTAL =						$ 0.00
Fee for 3 Month Extenstion of Time						$ 920.00
Fee for Two Information Disclosure Statements						$ 360.00
Reduction by ½ for filing by a small entity						$ 0.00
TOTAL FEE =						$ 1,688.00

5. Fee Payment

☒ The Commissioner is hereby authorized to charge $1,688.00 to Deposit Account No. 50-0310 for Additional Claims Fee ($324.00), Additional Independent Claims Fee ($84.00), Three-Month Extension of Time Fee ($920.00) and Fee for Two Information Disclosure Statements ($360.00).

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: September 13, 2002 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **009629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

#10/A
YC
9-24-02

PATENT
ATTORNEY DOCKET NO.: 056291-9004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San-ming

Commissioner of Patents
Washington, D.C. 20231

Date: September 13, 2002

Sir:

AMENDMENT AND RESPONSE

This is in response to the Office Action dated March 13, 2002, the time for responding to which has been extended to September 13, 2002 by the petition and authorization for fee payment submitted herewith. Please amend the claims as follows:

IN THE CLAIMS:

Please cancel claims 1-23, without waiver or prejudice, and add the following new claims 24-50:

24. A method of treating a benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle, whereby a

therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks after injection.

25. The method as claimed in claim 24 wherein the benign or malignant disease is breast cancer.

26. The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

27. The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

28. A method of treating a benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle whereby the formulation comprises at least 45mgml^{-1} of fulvestrant.

29. The method as claimed in claim 24 or 28 wherein the pharmaceutical formulation contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

30. The method as claimed in claim 29 wherein the pharmaceutical formulation contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

31. The method as claimed in claim 29 wherein the pharmaceutical formulation contains 15-25% w/v of a pharmaceutically acceptable alcohol.

32. The method as claimed in claim 29 wherein the pharmaceutical formulation contains 17-23%

33. The method as claimed in claim 24 or 28 wherein the pharmaceutical formulation contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

34. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

35. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

36. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

37. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

38. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

39. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

40. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 10-25% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

41. The method as claimed in claim 33 wherein the pharmaceutical formulation contains 12-18% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

42. The method as claimed in claim 24 or 28 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

43. The method as claimed in claim 24 or 28 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

44. The method as claimed in claim 43 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

45. The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$.

46. The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

47. The method as claimed in claim 46 wherein the total volume of the formulation is from 5 to 5.25ml, the total amount of fulvestrant in said volume of formulation is 250mg.

48. The method as claimed in claim 24 or 28 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

49. A method of treating a benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of a pharmaceutically-

acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

50. A method of treating a benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

REMARKS

Original claims 1-23 have been cancelled and new claims 24-50 presented above are directed specifically to the invention of elected Group II, The cancellation of claims 1-23 is without prejudice to applicants' right to prosecute the subject matter thereof in one or more divisional or continuing applications. Support for the limitations of new claims 24-50 is found throughout the specification, and in the original claims as filed. Entry of these claims is therefore believed to be in or and entry of the same is respectfully requested.

Elected claims 21 and 22 were objected to as being in improper multiple dependent form. This objection has been obviated by the cancellation of claims 21 and 22, and new claims 24-50 are believed to be in proper form in all respects.

The Examiner's attention is drawn to the Second and Third Information Disclosure Statements being filed herewith. It is respectfully requested that the Examiner consider the content of these Information Disclosure Statements at the time the above claims are examined on the merits.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

September 13, 2002 By: _____

Morgan Lewis & Bockius LLP
Customer No. **009629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
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Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

VERSION WITH MARKINGS TO SHOW CHANGES

IN THE CLAIMS:

Claims 1-23 have been cancelled.

New Claims 24-50 have been added.

PATENT
ATTORNEY DOCKET NO.: 086291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San-ming

September 13, 2002

Commissioner of Patents
Washington, D.C. 20231

Sir:

SECOND INFORMATION DISCLOSURE STATEMENT

Applicant wishes to make of record the following circumstances regarding the controlled, confidential and non-commercial testing of compositions meeting the definition of "pharmaceutical formulation", as used in the present method of treatment claims, which was carried out in the United States more than one year before the filing date of the present application in preparation for and during the testing (IND) phase of the regulatory review of such formulation by the FDA.

1. The elected invention as presently claimed is directed toward a method for treating a benign or malignant disease of the breast or reproductive tract of a human by intra-muscular injection of a particular pharmaceutical formulation comprising the active drug fulvestrant in a vehicle comprising ricinoleate, a pharmaceutically-acceptable alcohol, and a pharmaceutically-acceptable non-aqueous ester solvent miscible in ricinoleate, as detailed in the claims.

2. Fulvestrant is the international non-proprietary (generic) name for the compound 7-alpha-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3-5(10)-triene-3,17-beta-diol, which compound is encompassed by claims of U.S. Patent No. 4,659,516 issued to Bowler *et al.* in 1987 (hereinafter the "Bowler '516 patent").

3. The present specification acknowledges that fulvestrant is included among the steroid derivatives disclosed in European Patent Application No. 0 138 504 (corresponding to the Bowler '516 patent) as being effective antioestrogenic agents. The Bowler '516 patent notes at the bottom of column 7 that compositions of the disclosed steroid derivatives may be in a form suitable for oral or parenteral administration, and that compounds having antioestrogenic effect may have value in the treatment of, *e.g.*, anovulatory infertility, breast tumors and menstrual disorders.

4. However, certain characteristics of fulvestrant make it very difficult to formulate a pharmaceutically acceptable and effective composition for administration to humans. In particular, fulvestrant is an extremely lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low, placing severe limitations on the manner and mechanism by which it can be administered.

5. Subsequent to grant of the Bowler '516 patent, applicants developed an injectable extended release formulation of fulvestrant by which it became feasible to effectively utilize the known pharmacological properties of fulvestrant in the treatment of benign or malignant diseases of the breast or reproductive tract in humans, as presently claimed. This injectable extended release formulation of fulvestrant was subjected to extensive *in*

vitro and *in vivo* testing in animals, and eventually in clinical trials as detailed below, leading up to the first FDA approval of this formulation in April 2002.

6. In brief chronology, fulvestrant was initially put into development by Imperial Chemical Industries PLC (hereinafter "ICI"), under the product designation ICI 182,780. Development of fulvestrant was continued by Zeneca Limited (formed from ICI in 1993) under the product designation ZD9238. By December 6, 1996, preliminary testing of an injectable formulation containing fulvestrant as active ingredient had progressed to the point that an IND (Investigational New Drug) application was filed with the FDA for FASLODEX® (fulvestrant) Injection. As of the January 5, 1997 effective date of the IND application, clinical testing could, for the first time, commence in human subjects in the United States.

7. Clinical testing under the IND continued on behalf of AstraZeneca (formed by merger in 1999) until it was believed that sufficient evidence of safety and efficacy of the formulation had been obtained, and on March 28, 2001 an NDA (New Drug Application) was submitted to the FDA. Meanwhile, the subject application for patent, Application No. 09/756,291, was filed in the United States on January 9, 2001, claiming priority from GB Application 0000313.7, filed January 10, 2000, and GB Application 0008837.7, filed April 12, 2000. Thereafter, on April 25, 2002, the NDA for the Faslodex (injectable fulvestrant formulation) was approved by the FDA, whereupon Faslodex was approved for commercial marketing for the treatment of certain breast cancers.

8. The injectable fulvestrant formulation constituting Faslodex comes within the definition of "pharmaceutical formulation" as used in the method of treatment claims presently

pending in this application. The April 25, 2002 approval date constitutes the earliest possible date for commercial marketing in the United States of a formulation for use in accordance with the present claims.

9. This FDA approval came after the present application was filed, and was the culmination of many years of testing and gathering of data on the injectable formulation of fulvestrant (ICI 182,780 or ZD9238), both in the United States and abroad, in animals and eventually in human clinical trials. As will be evident below, all such testing in the United States more than one year before this application was filed was carried out under agreements which imposed obligations of confidentiality on the involved institutions and/or investigators, gave AstraZeneca strict control over the permitted use and disposition of the test samples of formulation, and provided that AstraZeneca was entitled to all information or data derived from the testing.[1] Moreover, all persons enrolled in the clinical trials were advised of the experimental nature of the formulation, and acknowledged this in signed informed consent forms as a precondition to their enrollment. AstraZeneca received no payment for the samples, and was not otherwise compensated for the use of these samples in the clinical trials. Under these conditions and the applicable case law discussed later below, these tests of the fulvestrant formulation in the United States did not constitute a "public use" under 35 U.S.C. § 102(b) of the present invention because the tests were carried out under strict obligations of confidentiality, and the tests and the use and disposition of the formulation, remained

[1] Reference to AstraZeneca hereinafter should be understood to refer to AstraZeneca and/or its predecessors in interest, ICI and Zeneca, unless the context indicates otherwise.

under the control of AstraZeneca throughout the entire period. These tests did not place the formulation in the public domain or cause the public to believe that the formulation of the invention was freely available, and certainly did not constitute a commercial exploitation of the invention more than one year before this application was filed.

10. Prior to the January 5, 1997 effective date of the IND application, all testing of fulvestrant formulation in the United States was necessarily carried out *in vitro* or in animals, and therefore cannot come within the scope of the present method of treatment claims. Nevertheless, it should be noted that all such testing was carried out under strict conditions of confidentiality and limitations of use imposed by a Statement of Proposed Investigation (SOPI) form that each investigator was required to sign as a condition to receiving samples of fulvestrant formulation.

11. The SOPI forms used by ICI in the early 1990s required a statement of proposed use of the material (necessarily not including any use in humans) that had to be approved by ICI, and stated just above the required signature of the investigator:

"If samples are supplied, I undertake:-

1. to make available all results to ICI;
2. that the results will not be submitted for publication or disclosed in any other way prior to disclosure to ICI;
3. to use the samples only for the purposes described above and not to pass the samples or any portion thereof to any investigators for any other purpose;
4. not to use the samples for any commercial purpose or for any study requested by a commercial organization."

12. The SOPI forms used by Zeneca and AstraZeneca (even after the effective date of the IND, for any samples provided to investigators outside of formal protocols for clinical or compassionate use trials discussed below) similarly required a statement of proposed use of the material that had to be approved by Zeneca or AstraZeneca, and explicitly stated, "Laboratory studies/tests on animals only. (Not for human use)." Again, just above the signature of the investigator, the following undertaking was printed on each form:

"1. All results acquired as a direct result of the use of the sample(s) will be promptly furnished to AstraZeneca.

2. The results will not be submitted for publication or disclosed in any other way without prior consent from AstraZeneca, which will not be unreasonably withheld.

3. The sample(s) will only be used for the purpose described above and shall not be passed to a third party. Any unused material will be returned to AstraZeneca.

4. The sample(s) will not be used to support the development of any commercial product containing the compound(s) supplied by AstraZeneca.

5. AstraZeneca shall be granted first option of a license to all rights in any discoveries or inventions made as a direct result of the investigations described above (whether patentable or not). In particular, the option will include an option for a license under any patents and patent applications relating to the use of the sample(s).

6. AstraZeneca requires assurance from all external investigators that all studies carried out on behalf of AstraZeneca and/or involving AstraZeneca compounds are carried out in compliance with all animal welfare legislation, regulations and policies applicable in that country/state. Please let us have your confirmation in writing that this is the case. We would also like to receive any additional

information on your in-house animal welfare arrangements which you are able to provide."

13. It is understood that no investigator receiving fulvestrant formulation pursuant to a SOPI, at least in the United States and prior to the filing of the present application for patent, was informed of the components and/or proportions thereof constituting the injectable vehicle in which the fulvestrant was carried, and that no investigator publication of results approved by AstraZeneca included such a disclosure.

14. Two clinical studies involving Faslodex were carried out at least in part in the United States prior to the filing date of the present application for patent.

- Clinical Study 9238IL/0021 began, in the United States, in April 1997 and extended to June 2000; was carried out in 69 centers involving 414 patients; and had the objective of comparing the effect, in terms of time to progression, of two doses of Faslodex (125 and 250 mg) with one dose of Arimidex (1 mg) in postmenopausal women with advanced breast cancer.

- Clinical Study 9238IL/0025 began, in the United States, in November 1998 and extended to July 2001; was carried out in 32 centers involving 51 patients; and had the objective of comparing the effect, in terms of time to progression, of Faslodex (250 mg) with Nolvadex (20 mg) as first-line therapy in postmenopausal women with advanced breast cancer.

15. Each clinical study was carried out under a Clinical Study Agreement entered into by each Institution and Investigator taking part in the study.

16. A representative Clinical Study Agreement for Clinical Study 9238IL/0021 provided in relevant part:

> "The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol entitled "A Double-blind, Randomized, Multicenter Trial comparing the Efficacy and Tolerability of 125 and 250 mg of FASLODEX™ (Long-acting ICI 182,780) With 1 mg ARIMIDEX™ (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer" (hereinafter referred to as "Protocol"). Institution shall use its best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."
>
> * * * * *
>
> "ZENECA reserves the right to terminate this Agreement and Study at any time in its sole discretion upon thirty (30) days prior written notice. However, ZENECA may terminate this agreement upon five (5) days written notice for safety, regulatory or ethical reasons. In the event of termination, all unused Study materials shall be returned to ZENECA and ZENECA shall reimburse Institution for all actual costs reasonably incurred up until the effective termination date."
>
> * * * * *
>
> "All rights to all data, inventions or discoveries Institution may make or conceive in the course of their work for ZENECA in their performance under this Agreement and using product in accordance with the detailed protocol provided by ZENECA will be the property of ZENECA and will be assigned to ZENECA, and Institution will assist ZENECA, at ZENECA's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries in any country which ZENECA at ZENECA's option, desires to obtain patent protection. All control of and decisions regarding such patent filings and prosecution, whether U.S. or foreign, and all costs and fees associated therewith, shall be exercised and/or borne by ZENECA."

* * * * *

"It may be necessary for Zeneca to disclose to Institution certain information considered proprietary or confidential (hereinafter 'Confidential Information') to aid Institution in effecting or completing their performance under this Agreement. Institution agrees to maintain in confidence all Confidential Information Institution obtains from ZENECA relating to this Agreement and not to disclose any of said Confidential Information to a third party for a period of three (3) years after the termination of this Agreement without the prior written consent of ZENECA. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Institution obtain from some third party not under any obligation to ZENECA with respect to such information, or (iv) information which Institution already have in their possession, prior to any disclosure by ZENECA, as evidenced by written records, (v) is independently developed by Institution or (vi) is required by law or regulation to be disclosed, provided, however, that Institution notifies and consults with Zeneca prior to such disclosure.

"Subject to the provisions of confidentiality set forth in Section 6(d) above, ZENECA agrees to grant Institution the right to publish its findings in the scientific literature, provided that ZENECA shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. Upon request by ZENECA, in order to protect intellectual property rights, Institution agrees to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which ZENECA receives such final draft manuscripts. Institution agrees to implement any reasonable suggestions made to preserve ZENECA's

right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agrees to take appropriate cognizance of any other suggestions by ZENECA before any disclosure for publication or presentation."

17. A representative Clinical Study Agreement for Clinical Study 9238IL/0025 similarly provided in relevant part:

"The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol which is attached hereto as Exhibit A and incorporated herein by reference. Institution and Investigator shall use their best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."

* * * * *

"Zeneca reserves the right to terminate this Agreement and Study at any time in its sole discretion upon five (5) days prior written notice. In the event of termination, all unused Study materials shall be returned to Zeneca and Zeneca shall reimburse Institution and Investigator for all actual costs reasonably incurred up until the effective termination date."

* * * * *

"All rights to all data, inventions or discoveries Institution and Investigator may make or conceive in the course of their work for Zeneca in their performance under this Agreement will be the property of Zeneca and will be assigned to Zeneca, and Institution and Investigator will assist Zeneca, at Zeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries."

* * * * *

"It may be necessary for Zeneca to disclose to Investigator and Institution certain information considered proprietary or confidential (hereinafter "Confidential

Information") to aid Investigator and Institution in effecting or completing their performance under this Agreement. Confidential Information shall also include Study data; however, Investigator's and Institution's right to publish pursuant to Section (d) below* shall not be affected by this provision. Investigator and Institution agree to maintain in confidence all Confidential Information Investigator and Institution obtain from Zeneca relating to this Agreement and not to disclose any of said Confidential Information to a third party without the prior written consent of Zeneca. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Investigator and Institution obtain from some third party not under any obligation to Zeneca with respect to such information, or (iv) information which Investigator and Institution already have in their possession, prior to any disclosure by Zeneca, as evidenced by written records.

"Nothing herein shall prevent Investigator and Institution from complying with the legal obligation to disclose Confidential Information so long as Investigator and Institution (i) provide Zeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) take reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) afford Zeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator and Institution have sought to resist disclosure) or obtain protection for the information disclosed."

* * * * *

*[(d)] "Subject to the provisions of confidentiality set forth in Section 6(c) above, Zeneca agrees to grant Investigator and Institution the right to publish their findings in the scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Investigator and

Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator and Institution agree to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which Zeneca receives such final draft manuscripts. Investigator and Institution agree to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agree to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

* * * * *

"Zeneca shall be entitled to make copies, at Zeneca's expense, of any and all documents and data generated from the Study. In addition, Institution and Investigator agree to allow Zeneca to audit the Study records (including administrative files and source documents such as hospital charts, office records and written results of laboratory and diagnostic tests) of Institution and Investigator at mutually convenient times.

18. An additional clinical study involving Faslodex was commenced in the United States more than one year prior to the filing date of the present application for patent, being Clinical Study 9238IL/0037, a compassionate-use trial under a protocol initially entitled "An Open-label, Treatment-use Protocol of 250 mg of FASLODEX™ (Long-acting ICI 182,780) in Postmenopausal Women With Advanced Breast Cancer." It is understood that as of one year prior to the filing date of this application, seven subjects had been enrolled in Clinical Study 9238IL/0037.

19. A "Confidentiality and Proprietary Rights Agreement" was entered into by each Investigator prior to his involvement in Clinical Study 9238IL/0037, in which the Investigator acknowledged that "he will have access to and obtain knowledge of certain proprietary and confidential Information of Zeneca and that as a condition of receiving such information" the parties agreed, in part as here relevant:

"1. 'Confidential Information' shall mean all information (a) disclosed by Zeneca to Investigator, either orally or in writing or (b) obtained by the Investigator from a third party or any other source, regarding the protocol entitled 'An Open-label, Treatment-use Protocol of 250 mg of FASLODEX™ (Long-acting ICI 182,780) in Postmenopausal Women With Advanced Breast Cancer, Study No. 9238IL/0037' ('Study')

"Confidential Information shall not include information that: (i) was already in the possession of Investigator before disclosure thereof by Zeneca to Investigator as evidenced by Investigator's written records (ii) is independently developed by Investigator as evidenced by Investigator's written records, (iii) is or becomes publicly available through no fault of Investigator, or (iv) is obtained by Investigator from a third party under no obligation not to disclose same.

"Nothing herein shall prevent Investigator from complying with a legal obligation to disclose Confidential Information so long as Investigator (i) provides Zeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) takes reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) affords Zeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator has sought to resist disclosure) or obtain protection for the Information disclosed.

"2. The purpose of the disclosure of Confidential Information is to allow Investigator to participate in the Treatment-use Protocol.

"3. Investigator agrees to maintain in strictest confidence and to take all reasonable steps to maintain the confidentiality of the Confidential Information. Investigator also agrees not to disclose Confidential Information to any third party, and to use Confidential Information only for the purposes stated in paragraph 2 of this Agreement.

"4. Investigator recognizes that all documents and records received by Investigator from Zeneca and all copies of such records and documents shall be Zeneca's property exclusively. The Investigator shall at all times keep all such documents, records and copies of documents and records in Investigator's custody and subject to Investigator's control and shall surrender the same upon request by Zeneca.

"5. Investigator shall not disclose any Confidential Information to any of its employees, except employees of Investigator who have a need to know the Confidential Information for the purposes stated in paragraph 2 of this Agreement and who have assumed an obligation to maintain Zeneca's Confidential Information in confidence at least to the extent that Investigator is bound hereunder. Investigator shall advise each such employee of the confidential nature of the Confidential Information received from Zeneca and the existence and importance of the confidentiality provisions of this Agreement and shall be responsible for ensuring that such employees maintain the Confidential Information in confidence in accordance with the terms of this Agreement.

"6. Because of the unique nature of the Confidential Information, Investigator understands and agrees that Zeneca will suffer irreparable harm in the event that Investigator fails to comply with any of its obligations contained hereinabove and that monetary damages will be inadequate to compensate Zeneca for such breach. Accordingly, Investigator agrees that Zeneca shall have the right to seek immediate injunctive relief to enforce the confidentiality obligations contained herein.

"7. All rights to all data, inventions or discoveries Investigator may make or conceive in the course of Investigator participation in the Study will be the property of Zeneca and will be assigned to Zeneca, and Investigator will assist Zeneca, at Zeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries. Investigator agrees to make no claim which will restrict the rights of Zeneca to use and disclose to others any information, knowledge, and ideas which are disclosed to Zeneca by Investigator in the course of performance of the Study.

"8. Subject to the provisions of confidentiality set forth herein, Zeneca agrees to grant Investigator the right to publish his findings in the scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored by Investigator or by anyone in his research group and which are based in whole or in part on research conducted pursuant to this Study. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator agrees to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which Zeneca receives such final draft manuscripts. Investigator agrees to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator agrees to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

20. The Protocols referenced with respect to the above-noted Studies No. 9238IL/0021, No. 9238IL/0025 and No. 9238IL/0037 provided details of, *inter alia*, the:

- criteria for the selection and screening for eligibility of subjects for entry into the trial, as well as exclusion criteria;

- route, dose and regimen for administration of the respective drugs to individual subjects;
- procedures for drug accountability, including maintenance of accurate records on receipt and disposition of investigational materials, and return or destruction of any unused drug;
- frequency and procedures for clinical and laboratory evaluations;
- regular recordation of data on case report forms, record retention and submission of records to AstraZeneca; and
- trial monitoring and data verification by representatives of AstraZeneca.

21. These Protocols furthermore required that each subject be given appropriate information on the treatment prior to its commencement, including the experimental aspects of the treatment and the risks involved, and sign an informed consent form approved by AstraZeneca, and conforming to the requirements of 21 C.F.R. 50.20 *et seq.* , which requires as a basic element of informed consent, that each subject be provided with, *inter alia*, a "statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental." 21 C.F.R. 50.25(a)(1).

In evaluating the above circumstances in context of 35 U.S.C. § 102(b), the Examiner's attention is called to MPEP ¶ 2133.03 "Rejections Based on 'Public Use' or 'On Sale', and particularly MPEP ¶ 2133.03(a) "Public Use", section *B.* headed "*Use by Third*

Parties Deriving the Invention from Applicant." It is respectfully submitted that the above circumstances *do not* constitute a "public use" of the presently claimed invention under the criteria set forth in the MPEP, and as established by decisions of the Federal Circuit, because of the strict confidentiality and control imposed and maintained by AstraZeneca throughout the relevant trial periods. MPEP ¶ 2133.03(a)*B*. provides:

> **An Invention Is in Public Use If the Inventor Allows Another To Use the Invention Without Restriction or Obligation of Secrecy**
>
> "Public use" of a claimed invention under 35 U.S.C. 102(b) occurs when the inventor allows another person to use the invention without limitation, restriction or obligation of secrecy to the inventor." *In re Smith*, 714 F.2d 1127, 1134, 218 USPQ 976, 983 (Fed. Cir. 1983). The presence or absence of a confidentiality agreement is not itself determinative of the public use issue, but is one factor to be considered along with the time, place, and circumstances of the use which show the amount of control the inventor retained over the invention. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1265, 229 USPQ 805, 809 (Fed. Cir. 1986). See *Ex parte C*, 27 USPQ2d 1492, 1499 (Bd. Pat. App. & Inter. 1992) (Inventor sold inventive soybean seeds to growers who contracted and were paid to plant the seeds to increase stock for later sale. The commercial nature of the use of the seed coupled with the "on-sale" aspects of the contract and apparent lack of confidentiality requirements rose to the level of a "public use" bar.); *Egbert v. Lippmann*, 104 U.S. 333, 336 (1881) (Public use found where inventor allowed another to use inventive corset insert, though hidden from view during use, because he did not impose an obligation of secrecy or restrictions on its use.).

The samples of fulvestrant formulation provided under the SOPI forms was not for human use, and therefore outside of the scope of the present method of use claims. Nevertheless, the tests conducted on these samples by the third party Investigators did not constitute a "public use". Through the SOPI forms, AstraZeneca maintained strict confidentiality over the samples and tests conducted therewith, maintained control over the use and disposition of the samples, and was entitled to all data developed in the course of the

tests. (¶¶ 10-13, *supra*). Moreover, AstraZeneca received no payment or other commercial benefit from providing these samples

Similarly, the three clinical trials or studies conducted in human subjects did not constitute a "public use" under the definition thereof set out in the MPEP as developed by the courts. Prior to the release of any materials or formulations on which to carry out these studies, the institutions and/or investigators involved were required to sign an agreement whereunder strict confidentiality was required, and all information provided to or developed by the institution/investigator during the course of such studies remained or became the property of AstraZeneca. (¶¶ 16, 17 and 19, *supra*). Through the Clinical Study Agreements, and the Protocols under which all three studies were conducted, AstraZeneca maintained full control over the use and disposition of the study materials or formulation that it provided to the institutions/investigators throughout the course of these studies, and the right to receive the data and records that were produced. (¶¶ 16, 17 and 20, *supra*). Moreover, each subject of these studies was fully informed of the experimental nature of the formulation and its use, as acknowledged in signed informed consent forms, and clearly did not have any basis to believe that the formulation or its use in the treatments was in the public domain or otherwise freely available. (¶ 21, *supra*). Again, AstraZeneca received no payment for the formulation used in these studies, and these studies did not constitute a commercial exploitation of the formulation.

Therefore, under the case law as developed by the courts, and its application by the Patent and Trademark Office as set out in the above-quoted paragraph from the MPEP, it is

respectfully submitted that the foregoing circumstances do not constitute a "public use" under 35 U.S.C. § 102(b).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

September 13, 2002 By: _____

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PATENT

ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	
	)	Group Art Unit: 1617
EVANS et al.	)	
	)	Examiner: Hui, San Ming R.
Appln. No.: 09/756,291	)	
	)	
Filed: January 9, 2001	)	
	)	
FOR: FORMULATION	)	

Commissioner of Patents
Washington, D.C. 20231

Date: September 13, 2002

Sir:

THIRD INFORMATION DISCLOSURE STATEMENT

09/16/2002 DABRAHA1 00000047 500310 09756291

04 FC:1126 180.00 CH

Attached is a Form PTO-1449 listing the enclosed documents.

This Information Disclosure Statement is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited, along with additional time under Rule 97(f), to enable Applicant to fully comply.

Please charge the Rule 17(p) official fee required by Rule 97(c) to our Deposit Account No. 50-0310 under Order No. 056291-5004.

Consideration of the foregoing and enclosures plus the return of a copy of the herewith filed Form PTO-1449 with the Examiner's initials in the left column per MPEP 609 along with an early action on the merits of this application are earnestly solicited.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this

application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** -in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: September 13, 2002 By: _____

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Morgan Lewis
COUNSELORS AT LAW

FAX MESSAGE

Send To:

Name:	Examiner San Ming R. Hui	FAX Number:	703-746-3123
Firm:	Group 1617 U.S. Patent and Trademark Office	Telephone Number:	703-305-1002

From:

Name	Donald J. Bird	Floor:	Operator Sending:
Telephone Number:	202-739-5320	Time Sent:	Date Sent: November 21, 2002

Number of Pages (INCLUDING COVER PAGE): 5

Note:

Comments: **Re: U.S. Application of EVANS et al.**
U.S. Application No. 09/756,291
Filed: January 9, 2001
Entitled: FORMULATION

Dear Examiner Hui:

Pursuant to your telephone request this afternoon, I am faxing herewith a copy of the claims as filed (and as currently pending) in related Application Serial No. 10/169,777.

With b st r gards,
D nald J. Bird

Received from < > at 11/21/02 7:01:22 PM [Eastern Standard Time]

Claims

1. A pharmaceutical formulation comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

2. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

3. A pharmaceutical formulation as claimed in claim 1 or 2 wherein the blood plasma fulvestrant concentration attained is at least $2.5ngml^{-1}$ for at least 2 weeks..

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7 A pharmaceutical formulation as claimed in claim 5 which contains 15-25% w/v of a pharmaceutically acceptable alcohol.

8 A pharmaceutical formulation as claimed in claim 5 which contains 17-23% w/v of a pharmaceutically acceptable alcohol.

9. A pharmaceutical formulation as claimed in any claim from 1 to 8 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 9 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

11. A pharmaceutical formulation as claimed in claim 9 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 9 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 9 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in claim 9 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

15. A pharmaceutical formulation as claimed in claim 9 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

16 A pharmaceutical formulation as claimed in claim 9 which contains 10-25% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

17 A pharmaceutical formulation as claimed in claim 9 which contains 12-18% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

18 A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

19 A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

20. A pharmaceutical formulation as claimed in any claim from 1 to 19 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

21. A pharmaceutical formulation as claimed in any claim from 1 to 20 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

22. A pharmaceutical formulation as claimed in any claim from 1 to 21 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

23 A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of benzyl benzoate in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

24 A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of benzylbenzoate in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

25 A pharmaceutical formulation according to claim 23 or 24 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

26 A pharmaceutical formulation according to claim 25 wherein the ethanol and benzyl alcohol are present at about equal % weight per volume of formulation.

27. A pharmaceutical formulation as claimed in any claim from 1 to 26 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

28. A pharmaceutical formulation as claimed in any claim from 1 to 27 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

29. A pharmaceutical formulation as claimed in claim 28 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

30. A pharmaceutical formulation as claimed in any of claims 1-29 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation, and the formulation contains 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

31. A pharmaceutical formulation adapted for intramuscular injection, as defined in any claim from 1 to 30, for use in medical therapy.

32. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any claim from 1 to 30, for the treatment of a benign or malignant disease of the breast or reproductive tract.

33. A syringe or vial containing a pharmaceutical formulation as defined in claim 30.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

9629 7590 12/03/2002

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/756,291	Applicant(s) EVANS ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendments filed September 13, 2002 have been entered. The cancellation of claims 1-23 in the amendments filed September 13, 2002 is acknowledged. The addition of claims 24-50 in the amendments filed September 13, 2002 is acknowledged.

Claims 24 – 50 are drawn to a method of treating benign or malignant disease of the breast or reproductive tract.

The outstanding objection is withdrawn in view of the cancellation of the claims.

The IDS received September 13, 2002 ahs been considered.

Claim Objections

Claim 32 is objected to because of the following informalities: no period at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cancer and certain hormonal-dependent benign diseases of the breast and endometrial lining, does not reasonably provide enablement for other non-hormonal dependent conditions of the breast and the reproductive tract. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define "benign disease of the breast and reproductive tract". In the instant case, only a limited number of "disease of the breast and reproductive tract" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the type or kind of disease treated. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant

claims read on all "disease of the breast and reproductive tract" which including non-hormonal-dependent medical conditions, such as yeast vaginitis, bacterial vaginitis, genitial herpes, viral vaginitis, and sexual transmitted diseases, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is not understood because it is an incomplete claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 24-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dukes (EP 0 346 014 from the IDS received February 1, 2002) in view of Lehmann et al. (US Patent Re. 28,690), GB 1 569 286 from the IDS received February 1, 2002 (herein after referred as '286), and Remington (Remington's Pharmaceutical Sciences, 18th ed., 1990, page 219).

Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, line 20-24).

Dukes does not expressly teach the dosage of fulvestrant to be 45mg. Dukes does not expressly teach the employment of benzyl benzoate, in the percent amount of 60% w/v or less, or 50% w/v or less, or 45% w/v or less, 40% w/v or less, or 35% w/v or less, or 30% w/v or less, 25% w/v or less, or 10-25% w/v, or 12-18% w/v, as part of the vehicle herein. Dukes does not expressly teach the total amount of the fulvestrant-containing composition administered. Dukes does not expressly teach weight amount

of castor oil and benzyl alcohol. Dukes does not expressly teach the employment of ethanol as part of the vehicle herein. Dukes does not expressly teach the dosage of fulvestrant to be 250mg. Dukes does not expressly teach the plasma concentration of fulvestrant herein.

Lehmann et al. teaches that benzyl benzoate and castor oil are well-known solvent useful as conventional carriers for steroids (See col. 1, line 21-26).

'286 teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in a ratio of 6:4 (See page 1, line 17).

Remington teaches that ethanol is one of the most commonly used solvents in pharmaceutical industry (See page 219).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy in the vagina.

One of ordinary skill in the art would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant, in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy because fulvestrant is known to be useful in treating urogenital atrophy, a benign disease of the female reproductive tract in the vagina. Castor oil and benzyl alcohol are known to be effective as vehicle for fulvestrant. Ethanol is a commonly used pharmaceutical solvent. Benzyl benozate is known to be effective as solvent for steroidal compounds. Since fulvestrant is a

estrogen derivative, benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant. Therefore, combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expected to be useful in formulating a pharmaceutical composition. Furthermore, employing such fulvestrant-containing composition to treat urogenital atrophy in vagina would be reasonably expected to be effective. Moreover, the optimization of result effect parameters (e.g., amount of excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan.

One of ordinary skill in the art would have been motivated to maintain the plasma concentration of fulvestrant herein because maintaining the therapeutic plasma level of the active compounds would be considered obvious as being within the purview of the skilled artisan.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
December 2, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER

12/2/02

SREENI PADMANABHAN
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 09/756,291	Applicant(s)/Patent Under Reexamination EVANS ET AL.	
	Examiner San-ming Hui	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-Re. 28,690	01-1976	Lehmann et al.	
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Remington's Pharmaceutical Sciences, 18th ed., 1990, page 219
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

1/21/02

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office

Atty. Dkt. No.	M#	Client Ref.
	056291-5004	Z70636/US

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

RECEIVED
SEP 17 2002
TECH CENTER 1600/2900

Applicant: Evans et al.

Appln. No.: 09/756,291

Filing Date: January 9, 2001

Date: September 13, 2002 Page 1 of 1

Examiner: Hui, San Ming R. Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						

OIPE JC34 SEP 13 2002 PATENT & TRADEMARK OFFICE

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	JR									
	KR									
	LR									
	MR									
	NR									
	OR									
	PR									
	QR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

SM	RR	Howell et al., "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer", The Lancet, Jan. 7, 1995, pp. 29-30
SM	SR	Osborne et al., "Comparison of the Effects of a Pure Steroidal Antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer", Journal of the National Cancer, May 1995, Vol. 87, No. 10, pp. 746-750
SM	TR	Robertson et al., "A PARTIALLY-BLIND, RANDOMISED, MULTICENTRE STUDY COMPARING THE ANTI-TUMOR EFFECTS OF SINGLE DOSES (50, 125 AND 250MG) OF LONG-ACTING (LA) 'FASLODEX' (ICI 182,780 WITH TAMOXIFIN IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER PRIOR TO SURGERY"; Abstract 28, 22nd Annual San Antonio Breast Cancer Symposium: Dec. 8-11, 1999, San Antonio, Breast Cancer Research and Treatment 1999; 57 (1; special issue); p. 31
	UR	

Examiner [signature] Date Considered: 11/21/02

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

1-WA/1862334.1

1617

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#14
6/10/03

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San Ming R.

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: June 3, 2003

Sir:

AMENDMENT TRANSMITTAL FORM

1. Transmitted herewith is an Amendment responding to the Office Action dated December 3, 2002.

2. Additional papers enclosed:

- ☒ Information Disclosure Statement
- ☒ Form PTO-1449, 1 reference included
- ☐ Citations
- ☐ Declaration of Biological Deposit
- ☐ Submission of "Sequence Listing", computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
- ☐ Drawings: ☐ Formal ☐ Informal (Correction)

06/04/2003 HGUTEMA1 00000060 500310 09756291
01 FC:1253 930.00 CH

1-WA/1979119.1

3. Extension of Time

The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136(a) apply.

☐ Applicant believes that no extension of time is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

☐ Applicant petitions for an extension of time, the fees for which are set out in 37 C.F.R. § 1.17(a), for the total number of months checked below:

Total Months Requested	Fee for Extension	Small Entity Fee
☐ one month	$ 110.00	$ 55.00
☐ two months	410.00	205.00
☒ three months	930.00	465.00
☐ four months	1,450.00	725.00
☐ five months	1,970.00	985.00

If an additional extension of time is required, please consider this a Petition therefor.

☐ An extension for _____months has already been secured and the fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension of time fee due with this request: $930.00

4. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

5. Fee Calculation (37 C.F.R. §1.16)

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		Highest No. Previously Paid	Present Extra	at Rate of	Total Fees
Total Claims (37 C.F.R. §1.16(c))	47	minus	47	0	x $18.00 each=	$ 0.00
Independent Claims (37 C.F.R.§1.16(b))	4	minus	4	0	x $84 each=	$ 0.00
☐ First presentation of Multiple dependent claim(s)					$280.00	$ 0.00
SUB-TOTAL =						$ 0.00
Fee for _2_ Month Extension of Time						$ 930.00
Fee for Information Disclosure Statement						$ 180.00
Reduction by ½ for filing by a small entity						$ 0.00
TOTAL FEE =						$ **1,110.00**

6. Fee Payment

☒ The Commissioner is hereby authorized to charge **$1,110.00** to Deposit Account No. 50-0310 for Three Month Extension of Time Fee ($930.00) and Information Disclosure Statement Fee ($180.00).

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 3, 2003 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
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Tel. No.: 202-739-3000
DJB:mk

ATTORNEY DOCKET NO.: 056291-3064

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#15/B
MP
6/10/03

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San Ming R

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: June 3, 2003

Sir:

AMENDMENT AND RESPONSE

This is in response to the Office Action dated December 3, 2002, the time for responding to which has been extended to and including June 3, 2003, by the petition and authorization for fee payment submitted herewith. Please amend the above-identified application as follows:

IN THE CLAIMS:

Claims 1-23 (cancelled)

24. (currently amended) A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ is attained for at least 2 weeks after injection.

25. (previously added) The method as claimed in claim 24 wherein the benign or malignant disease is breast cancer.

26. (previously added) The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

27. (previously added) The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

28. (currently amended) A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle whereby the formulation comprises at least $45mgml^{-1}$ of fulvestrant.

29. (previously added) The method as claimed in claim 24 or 28 wherein the pharmaceutical formulation contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

30. (previously added) The method as claimed in claim 29 wherein the pharmaceutical formulation contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

31. (previously added) The method as claimed in claim 29 wherein the pharmaceutical formulation contains 15-25% w/v of a pharmaceutically acceptable alcohol.

32. (currently amended) The method as claimed in claim 29 wherein the pharmaceutical formulation contains 17-23% w/v of a pharmaceutically acceptable alcohol.

33. (previously added) The method as claimed in claim 24 or 28 wherein the pharmaceutical formulation contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

34. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

35. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

36. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

37. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

38. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

39. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

40. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 10-25% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

41. (previously added) The method as claimed in claim 33 wherein the pharmaceutical formulation contains 12-18% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

42. (previously added) The method as claimed in claim 24 or 28 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

43. (previously added) The method as claimed in claim 24 or 28 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

44. (previously added) The method as claimed in claim 43 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

45. (previously added) The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$.

46. (previously added) The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

47. (previously added) The method as claimed in claim 46 wherein the total volume of the formulation is from 5 to 5.25ml, the total amount of fulvestrant in said volume of formulation is 250mg.

48. (previously added) The method as claimed in claim 24 or 28 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

49. (currently amended) A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

50. (currently amended) A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of a pharmaceutically-acceptable non-aqueous ester solvent

miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Independent claims 24, 28, 49 and 50 are currently amended above to clarify that the claimed invention is directed toward a method of treating "hormonal dependent benign or malignant disease of the breast or reproductive tract" pursuant to the Examiner's suggestion at page 2 of the Action. Support for this amendment is found throughout the specification, *e.g.*, at page 2, lines 9-18 and page 16, lines 4-5.

Claim 32 is currently amended above to clarify that the 17-23% refers to "w/v of a pharmaceutically acceptable alcohol." The need for this correction and the nature thereof is readily apparent from claim 29, upon which claim 32 is dependent.

No new matter is added by the above amendments, and entry thereof is believed to be in order and is respectfully requested. Following entry of these amendments, claims 24-50 remain pending in this application.

Claim Objections

The informality objection to claim 32 as lacking a period has been corrected and overcome by the above amendment to claim 32.

Claim Rejections – 35 USC § 112

Claims 24-50 have been rejected under 35 USC § 112, first paragraph, as lacking enablement. Specifically, the Examiner notes that the specification, "while being enabling for cancer and certain hormonal-dependent benign diseases of the breast and endometrial lining, does not reasonably provide enablement for other non-hormonal dependent conditions of the breast and the reproductive tract." This ground for rejection has been specifically addressed and overcome by amending each dependent claims (and therefore each claim dependent thereon) to specifically recite that the method of treatment applies to "hormonal dependent benign or malignant disease of the breast or reproductive tract." Withdrawal of this ground for rejection is therefore respectfully requested.

Claim Rejections – 35 USC § 103

Claims 24-50 have been rejected under 35 USC § 103(a) as being unpatentable over Dukes, EP 0 346 014 (hereinafter "Dukes") in view of Lehmann *et al*, US Patent Re 28,690 (hereinafter "Lehmann") , GB 1 569 286 (hereinafter "GB '286), and Remington's Pharmaceutical Sciences (hereinafter "Remington").

In applying the primary Dukes reference, the Examiner notes:

> Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, 20-24).

(Action at page 5). The Examiner acknowledges in the following paragraph, however, that Dukes does not expressly teach the dosage of fulvestrant, the formulation and/or plasma concentration of fulvestrant as recited in the present claims. The Examiner attempts to fill the

acknowledged gaps in the Dukes disclosure with the secondary references, specifically noting:

> Lehman et al. teaches that benzyl benzoate and caster oil are well-known solvent useful as conventional carriers for steroids (See col. 1, line 21-26).
> '286 teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in the ratio of 6:4 (See page 1, line 17).
> Remington teaches that ethanol is one of the most commonly used solvents in pharmaceutical industry (See page 219).

(Action page 6). From a combination of these references, the Examiner concludes:

> Therefore, combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expect to be useful in formulating a pharmaceutical composition. Furthermore, employing such fulvestrant-containing composition to treat urogenital atrophy in vagina would be reasonably expected to be effective. Moreover, the optimization of result effect parameters (e.g., amount of excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan.
> One of ordinary skill in the art would have been motivated to maintain the plasma concentration of fulvestrant herein because maintaining the therapeutic plasma level of the active compounds would be considered obvious as being within the purview of the skilled artisan.

(Action page. 7).

Applicants respectfully disagree.

Applicants recognize in their specification at page 3 and in Table I that sustained release injectable steroidal formulations are known (and commercialized) using various oils to solubilize the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol. However, as also noted at page 3, lines 4-7, fulvestrant (to which the presently claimed invention is specifically directed) is a *particularly* lipophilic molecule, even when compared with other steroidal compounds, and has an *extremely* low aqueous solubility of

around 10 $ngml^{-1}$.[1] In their quest for an appropriate injection vehicle for fulvestrant, applicants found that fulvestrant is significantly more soluble in castor oil than any of the other oils tested, as noted at page 6 of the specification and in Table 2. They acknowledge that the greater solvating ability of castor oil for steroidal compounds is known, and is attributed to the high number of hydroxyl groups of ricinoleic acid present in castor oil, citing Riffkin (1964).[2] Nevertheless, applicants found that it was not possible to dissolve fulvestrant in castor oil alone so as to achieve a high enough concentration to dose a patient in an acceptably low volume injection and still achieve a therapeutically significant release rate (specification pages 6-7). Even with the prior art disclosures of additionally using various alcohols and esters, applicants were faced with a particularly difficult problem resulting from the very low solubility of fulvestrant that was not specifically addressed by the prior art.

Again, it should be borne in mind that the claims are drawn to the *single pharmaceutical agent, fulvestrant*. In this regard, the Examiner cites Dukes as the primary reference as teaching that antiestrogen agents, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol. However, Dukes lists an enormous number of possible formulations, including tablets and capsules for oral administration, aqueous suspensions of the active ingredient in finely powdered form, oily suspensions, dispersible powders, oil-in-water emulsions, injectable aqueous or oily suspensions, including in the form of a depot of the active ingredients at the injection site to

[1] This solubility had to be estimated from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute (specification at page 3, lines 6-7.

[2] Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, pp. 891-895; cited at specification page 6, lines 14-15, and as Reference NR on page 3 of the form PTO-1449 submitted with the Information Disclosure Statement filed herein on February 1, 2002.

provide the sustained release thereof, suppository formulations and topical formulations; see the text from page 4, line 28 to page 5, line 36. Dukes does not suggest that there are any problems with fulvestrant in these formulations. Example 3 of Dukes discloses a castor oil formulation for intramuscular injection consisting of fulvestrant 50mg/ml, benzyl alcohol (40 %) administered at 2 weekly intervals. Again, Dukes does not suggest that there are any problems with this formulation. Example 2 of Dukes uses a propylene glycol based intramuscular injection of fulvestrant, and again Dukes does not suggest that there are any problems with this formulation.

Therefore Dukes does not suggest that there would be any problem using fulvestrant in any of these formulations, and does not even express a preference for castor oil based intramuscular formulations over other injectable formulations of fulvestrant in general, let alone the particular castor oil based formulations having the features of the presently claimed invention. Accordingly, there is no motivation to move on from Dukes.

In particular, persons skilled in the art would have no motivation to combine Dukes with the disclosures of Lehmann or GB '286, as asserted by the Examiner. Fulvestrant is a very different pharmaceutical agent from the agents described in Lehmann and GB '286 patent for the following reasons.

These citations all relate to formulated *prodrugs* (not drugs *per se*) in the form of drug esters. Fulvestrant is not a prodrug and a skilled person working with fulvestrant drug would not turn to such citations for teaching relevant to fulvestrant *per se,* which is not amenable to such prodrug formulation.

Esterification of readily soluble base drugs with lipophilic fatty acids forms a prodrug ester whose hydrophobic side chains partition preferentially into the oil vehicle.

Prolongation of prodrug release is provided by rate limiting diffusion of prodrug into extracellular fluid where various esterases liberate active drug. As explained in Mackey (1995),[3] a copy of which is included with the further Information Disclosure Statement submitted herewith:

> Depot formulations are widely used to enhance therapeutic compliance and convenience by prolonging the duration of drug action. Among the most widely used depot formulations are drug esters administered in an oil vehicle. Esterification of base drugs with appropriate lipophilic fatty acids forms a pro-drug ester whose hydrophobic side-chains partition preferentially into the oil vehicle. Prolongation of the pro-drug release is provided by the rate-limiting retarded diffusion of the pro-drug ester into the extracellular fluid where ubiquitous non-specific esterases hydrolyse the ester bond to liberate active drug. In addition to forming a hydrophobic depot, the oil vehicle limits local chemical irritation and cytotoxicity caused by some drugs (Svendsen and 'Blom, 1984). This oil-based formulation has been widely and successfully used for sex steroids including androgens, oestrogens and progestins as well as psychotrophic drugs such as fluphenazine, haloperidol and related major tranquilizers (Gilman *et al.*, 1990). Oils derived from vegetable sources such as castor or sesame seeds or peanuts (*Arachis*) have been widely used whereas mineral oils are too irritating (Symmers, 1955).

(Mackey at pages 863-864 under "Discussion"; emphasis added)

Mackey continues at the top of page 863, "(t)estosterone esters in an oil vehicle have been for decades the most widely used modality of delivering androgen replacement therapy in male hypogonadism" (emphasis added). Similarly, steroidal ester prodrugs in an oil vehicle are disclosed in Lehmann (diesters of nortestosterone in a variety of vegetable oils including caster oil, as well as various synthetic solvents including benzyl benzoate) and GB '286 ((norethisterone oenanthate in a mixture of castor oil/benzyl benzoate). See, also, Riffkin (1964), *supra*, disclosing 17-hydroxyprogesterone caproate and estradiol valerate in

[3] Mackey *et al.*, "Tolerability of intramuscular injections of testosterone ester in oil vehicle," Human Reproduction, 1995, vol. 10 no. 4, pp. 862-895.

various oil vehicles (including caster oil) with various cosolvents (including benzyl alcohol and benzyl benzoate).

As well as not being amenable to the prodrug approach, fulvestrant has very different chemical properties in terms of its markedly lower water solubility compared with the drugs disclosed in these references. Even if formulated in oils, water solubility is one of the principal factors governing release and bioavailability from any formulation.

For example, the drugs of Lehmann and GB '286 are suitable for oral administration and are converted into a *less hydrophilic* prodrug form to allow formulation in a oily depot. Given the already low water solubility of fulvestrant, it would simply not make sense for a skilled person to make it into an even less water soluble prodrug.

Lehmann states that the relevant prodrug compounds are "readily soluble" (col 1, line 21) and refers to their "considerable solubility" (col 1, line 27). These prodrug compounds are said to be readily soluble in a wide range of vegetable oils and synthetic solvents (col 1, lines 23-26). In contrast, fulvestrant is significantly more soluble in castor oil (20 mg/ml) compared with other oils tested (see Table 2 of the specification). Lehman lists benzyl benzoate as a synthetic solvent in which the prodrugs are "readily soluble" whereas the solubility of fulvestrant in benzyl benzoate is only 6.15 mg/ml (again see Table 2 of the specification).

A specific example in the '286 patent uses 200 mg of prodrug (norethisterone oenanthate) in as little as 0.6 ml of castor oil/ benzyl benzoate (6:4) – see page 1, lines 27-29. This formulation would simply not work for fulvestrant.

Therefore a skilled person starting from Dukes would not turn to the injectable vehicles of Lehmann or GB '286 patent, or Riffkin, to improve upon the formulations disclosed in Dukes with respect to fulvestrant.

Finally, Remington simply teaches in the abstract, and unrelated to injectable oil vehicles for steroidal compounds, that "*(e)thanol*, as a solvent, is next in importance to water." This reference provides no teaching specifically relevant to formulation of fulvestrant, and does not overcome the shortcomings of the combination of the other references as discussed above.

As discussed above, the primary Dukes references teaches antiestrogen agents, including fulvestrant, in a great variety of modes of administration and vehicles, including in a vehicle comprising caster oil and benzyl alcohol. However, as the Examiner notes at page 5 of the Action, Dukes does not teach the inclusion of benzyl benzoate in such vehicle. In fact, Dukes does not teach the inclusion of any "pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle" in context of fulvestrant. Although other references cited by the Examiner and/or noted above teach various combinations of oil, alcohol and/or ester, these references would not suggest to persons skilled in the art the modification of the Dukes teaching by addition of such a "pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle" in formulations of fulvestrant, for the reasons detailed above. In particular, there is no motivation in Dukes to modify the formulation of Example 3 by including an ester solvent, particularly as fulvestrant is less soluble in esters than in alcohols.

A person of ordinary skill would always measure solubility of fulvestrant in a vehicle component before using it. Example 3 of Dukes discloses a castor oil formulation for

intramuscular injection consisting of fulvestrant 50mg/ml, benzyl alcohol (40 %). Looking at Table 2 in the specification, the solubility of fulvestrant in benzyl alcohol is over 200mg/ml. A non-aqueous ester solvent such as benzyl benzoate gives a solubility of fulvestrant of only 6.15 mg/ml. Upon making such a determination, the observed low solubility of the ester would teach a person of ordinary skill not to use it further in the formulation. However, when the inventors included ester solvent in lieu of part of the alcohol component, they observed the following:

> We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$ - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

(Specification page 7, lines 13-18).

In other words, looking at Table 3 of the specification and comparing the data in column pairs across the page, it is evident that inclusion of ester (benzyl benzoate) increases the solubility of fulvestrant in the formulation. For example, looking at columns 1 and 2, the addition of ester to the formulation increases the solubility of fulvestrant from 27 mg/ml to 36 mg/ml. This is unexpected because Table 2 shows us that non-aqueous ester solvent such as benzyl benzoate gives a solubility of fulvestrant of only 6.15 mg/ml.

Thus, persons of ordinary skill in this art, starting from the Dukes disclosure with respect to fulvestrant, would not be motivated to draw from the teachings of the secondary references, which teach or strongly favor the use of ester prodrugs of the steroidal compounds they employ, which are significantly more water soluble than fulvestrant. The particularly lipophilic fulvestrant is not amenable to such prodrug formulation, as discussed

above. Moreover, even if such skilled person were to explore the possibility of substituting an ester such as benzyl benzoate for a portion of the alcohol component of Dukes, they would have been put off from doing so when they appreciated the very low solubility of fulvestrant in such ester. Applicants' discovery of the surprising synergistic effect from the introduction of such a non-aqueous ester solvent which is miscible in the caster oil and an alcohol on easing the solubilization of fulvestrant in castor oil further heightens the unobviousness of the present claims.

Information Disclosure Statement

A further Information Disclosure Statement is submitted herewith, together with a form PTO-1449 formally citing the Mackey *et al.* article noted above and a copy of the cited article. Also, for clarification, it is assumed that the Examiner's statement at page 2 of the action that "the IDS received September 13, 2002 [has] been considered" refers to both Information Disclosure Statements submitted (received) on September 13, 2002, in that both are specifically referred to on page 6 of the Amendment and Response filed September 13, 2002, and a search of the PAIR database confirms that both were separately received and entered into the file by the US Patent and Trademark office on that date.

Conclusion

In view of the above amendments and the foregoing remarks, it is believed that all grounds for rejection have been addressed and overcome. Therefore, withdrawal of the rejections and allowance of all claims are believed to be in order and are respectfully requested.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 3, 2003 By: _____

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#16
6/10/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	Group Art Unit: 1617
EVANS et al.	Examiner: Hui, San Ming R.
Appln. No.: 09/756,291	
Filed: January 9, 2001	
FOR: FORMULATION	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop** _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: June 3, 2003

Sir:

FOURTH INFORMATION DISCLOSURE STATEMENT

Attached is a Form PTO-1449 listing the enclosed document.

This Information Disclosure Statement is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited, along with additional time under Rule 97(f), to enable Applicant to fully comply.

Please charge the Rule 17(p) official fee ($180.00) required by Rule 97(c) to our Deposit Account No. 50-0310 under Order No. 056291-5004.

Consideration of the foregoing and enclosure plus the return of a copy of the herewith filed Form PTO-1449 with the Examiner's initials in the left column per MPEP 609 along with an early action on the merits of this application are earnestly solicited.

1-WA/2001089.1

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** -in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
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Date: June 3, 2003 By: _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

9629 7590 08/27/2003

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EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	17

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/756,291	Applicant(s) EVANS ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-47,49 and 50* is/are rejected.

7)☒ Claim(s) *48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendments filed June 3, 2003 have been entered.

The outstanding rejections under 35 USC 112, first and second paragraph are withdrawn in view of the amendments filed June 3, 2003.

The outstanding objection of claim 32 is withdrawn in view of the amendments filed June 3, 2003.

Claims 24-50 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 24-47, and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dukes (EP 0 346 014 from the IDS received February 1, 2002) in view of Lehmann et al. (US Patent Re. 28,690), GB 1 569 286 from the IDS received

February 1, 2002 (herein after referred as '286), and Remington (Remington's Pharmaceutical Sciences, 18th ed., 1990, page 219).

Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, line 20-24).

Dukes does not expressly teach the dosage of fulvestrant to be 45mg. Dukes does not expressly teach the employment of benzyl benzoate, in the percent amount of 60% w/v or less, or 50% w/v or less, or 45% w/v or less, 40% w/v or less, or 35% w/v or less, or 30% w/v or less, 25% w/v or less, or 10-25% w/v, or 12-18% w/v, as part of the vehicle herein. Dukes does not expressly teach the total amount of the fulvestrant-containing composition administered. Dukes does not expressly teach weight amount of castor oil and benzyl alcohol. Dukes does not expressly teach the employment of ethanol as part of the vehicle herein. Dukes does not expressly teach the dosage of fulvestrant to be 250mg. Dukes does not expressly teach the plasma concentration of fulvestrant herein.

Lehmann et al. teaches that benzyl benzoate and castor oil are well-known solvent useful as conventional carriers for steroids (See col. 1, line 21-26).

'286 teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in a ratio of 6:4 (See page 1, line 17).

Remington teaches that ethanol is one of the most commonly used solvents in pharmaceutical industry (See page 219).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy in the vagina.

One of ordinary skill in the art would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant, in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy because fulvestrant is known to be useful in treating urogenital atrophy, a benign disease of the female reproductive tract in the vagina. Castor oil and benzyl alcohol are known to be effective as vehicle for fulvestrant. Ethanol is a commonly used pharmaceutical solvent. Benzyl benozate is known to be effective as solvent for steroidal compounds. Since fulvestrant is a estrogen derivative, benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant. Therefore, combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expected to be useful in formulating a pharmaceutical composition. Furthermore, employing such fulvestrant-containing composition to treat urogenital atrophy in vagina would be reasonably expected to be effective. Moreover, the optimization of result effect parameters (e.g., amount of

excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary.

One of ordinary skill in the art would have been motivated to maintain the plasma concentration of fulvestrant herein because maintaining the therapeutic plasma level of the active compounds would be considered obvious as being within the purview of the skilled artisan, absent evidence to the contrary.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, unexpected increase of solubility of fulvestrant by adding 15% of benzyl benzoate into the composition with ethanol, benzyl alcohol, and castor oil as carrier is seen (See Table 3). However, the unexpected result is not commensurate of the scope of the broadest claim herein.

Response to Arguments

Applicant's arguments filed June 3, 2003 averring the enhanced and superior solubility achieved by the herein claimed formulation have been fully considered but they are not persuasive. In Dukes, fulvestrant is an exemplified antiestrogen compound.

As the matter of fact, it is the preferred compound (See Dukes, pages 8 and 9, example 2-3). Furthermore, castor oil and benzyl alcohol are the preferred carriers (See page 7, 20-23). Especially in example 3, the concentration of fulvestrant in a benzyl alcohol/castor oil carrier is 50mg/ml (See page 9, lines 40-42).

Applicant's arguments filed June 3, 2003 with regard to Lehmann, '286, and Remington have been fully considered but they are not persuasive. These two references merely point out that benzyl benzoate, ethanol, castor oil, and benzyl alcohol as commonly used solvent for steroidal compounds. Employing these solvents together for formulating an steroidal composition containing fulvestrant (a steroidal compound) would have been reasonably expected to be useful, absent evidence to the contrary.

Applicant's arguments filed June 3, 2003 with regard to Mackey have been considered, but are not found persuasive. As discussed above, Dukes clearly teaches fulvestrant, which is not a prodrug, as useful in combining with castor oil/benzyl alcohol, incorporating other commonly used solvent would be obvious as being within the skill of artisan, absent evidence to the contrary. No such evidence is present herein.

Applicant's arguments filed June 3, 2003 with regard to the addition of benzyl benzoate should reduce the solubility of fulvestrant have been considered, but are not found persuasive (See the discussion above).

Allowable Subject Matter

Unexpected increase of solubility of fulvestrant by adding 15% of benzyl benzoate into the composition with ethanol, benzyl alcohol, and castor oil as carrier is

seen (See Table 3). Therefore, the composition with the specific disclosed ratio of the solvents recited in claim 48 is allowable.

Claim 48 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax

phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

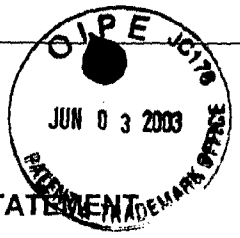
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
August 22, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

8/25/03

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
Patent and Trademark Office



Atty. Dkt. No.	M#	Client Ref.
	056291-5004	Z70635/US

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: Evans et al.

Appln. No.: 09/756,291

Filing Date: January 9, 2001

Date: June 3, 2003 Page 1 of 1

Examiner: Hui, San Ming R. Group Art Unit: 1617

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclose	No
	JR									
	KR									
	LR									
	MR									
	NR									
	OR									
	PR									
	QR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

SM	RR	Mackey et al, "Tolerability of intramuscular injections of testosterone ester in oil vehicle", Human Reproduction, vol. 10, no. 4, pp, 869-865, 1995
	SR	
	TR	
	UR	

Examiner [signature] Date Considered: 8/22/03

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

-WA/2001086 1

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	
EVANS et al.	Group Art Unit: 1617
Appln. No.: 09/756,291	Examiner: Hui, San Ming R.
Filed: January 9, 2001	
FOR: FORMULATION	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop AF**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: December 29, 2003
Dec. 27, 2003 = Saturday

Sir:

AMENDMENT AND RESPONSE AFTER FINAL

This is in response to the Final Office Action dated August 27, 2003, the time for responding to which has been extended to and including December 29, 2003 (December 27 being a Saturday), by the petition and authorization for fee payment submitted herewith.

Please amend the above-identified application as set forth below:

IN THE CLAIMS:

Claims 1-23 (cancelled)

Claim 24 (currently amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation ~~30% or less weight of a pharmaceutically acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation~~ and a sufficient amount of a castor oil ~~ricinoleate~~ vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks after injection.

Claim 25 (previously added): The method as claimed in claim 24 wherein the benign or malignant disease is breast cancer.

Claim 26 (previously added): The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

Claim 27 (previously added): The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

Claim 28 (currently amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation ~~30% or less weight of a pharmaceutically acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically acceptable non-aqueous ester solvent~~

~~miscible in a ricinoleate vehicle per volume of formulation~~ and a sufficient amount of a ~~ricinoleate~~ castor oil vehicle whereby the formulation comprises at least $45mgml^{-1}$ of fulvestrant.

Claims 29 – 44 (cancelled).

Claim 45 (previously added): The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$.

Claim 46 (previously added): The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

Claim 47 (currently amended): The method as claimed in claim 46 wherein the total volume of the formulation is from 5 to 5.25ml, and the total amount of fulvestrant in said volume of formulation is 250mg.

Claim 48 – 50 (cancelled).

REMARKS

All claims have been finally rejected except for claim 48, which the Examiner has noted would be allowable if put in independent form. In order to expedite the allowance of this application, now under Final Rejection, Applicants have put claim 48 in independent form as suggested by the Examiner, by inserting the limitations thereof into independent claims 24 and 28 upon which claim 48 was dependent. Amended claims 24 and 28 are therefore believed to now be in allowable form. Claims 25-27 and 45-49 are dependent on amended claims 24 and 28, and therefore should be allowable as well. [1] Rejected claims 29-44 and 48-50 have been cancelled.

Entry of the above amendments after Final Rejection is believed to be in order, in that they place this application in condition for allowance in the manner suggested by the Examiner. Following entry of these amendments, claims 24-28 and 45-47 remaining pending in this application.

Applicants remain of the belief that the previously claimed subject matter deleted by the above amendments is patentably distinct from the cited references. Therefore, these amendments are being made without abandonment or prejudice to Applicants' right to prosecute any subject matter thereby deleted in one or more continuing applications.

Conclusion

In view of the above amendments and the foregoing remarks, it is believed that this application and all claims are now in condition for allowance, and a Notice to that effect is respectfully requested.

---

[1] Dependent claim 47 has also been amended to correct a minor typographical error.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: December 29, 2003 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

ATTORNEY DOCKET NO.: 05629.C5004 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	Group Art Unit: 1617
EVANS et al.	Examiner: Hui, San Ming R.
Appln. No.: 09/756,291	
Filed: January 9, 2001	
FOR: FORMULATION	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop AF**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: December 29, 2003
Dec. 27, 2003 = Saturday

Sir:

AMENDMENT (FEE) TRANSMITTAL FORM

1. Transmitted herewith is an Amendment responding to the Office Action dated August 27, 2003

2. Additional papers enclosed:

- ☐ Information Disclosure Statement
- ☐ Form PTO-1449, copies of ___ references
- ☐ Citations
- ☐ Declaration of Biological Deposit
- ☐ Submission of "Sequence Listing", computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
- ☐ Drawings: ☐ Formal ☐ Informal (Correction)

01/05/2004 KBETEMA1 00000024 500310 09756291
01 FC:1251 110.00 DA

3. Extension of Time

The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136(a) apply.

☐ Applicant believes that no extension of time is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

☒ Applicant petitions for an extension of time, the fees for which are set out in 37 C.F.R. § 1.17(a), for the total number of months checked below:

Total Months Requested	Fee for Extension	[Fee for Small Entity]
☒ one month	**$ 110.00**	$ 55.00
☐ two months	$ 420.00	$210.00
☐ three months	$ 950.00	$475.00
☐ four months	$1,480.00	$740.00
☐ five months	$2,010.00	$1,005.00

If an additional extension of time is required, please consider this a Petition therefor.

☐ An extension for _____months has already been secured and the fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension of time fee due with this request: $110.00

4. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

5. Fee Calculation (37 C.F.R. §1.16)

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		Highest No. Previously Paid	Present Extra	at Rate of	Total Fees
Total Claims (37 C.F.R. §1.16(c))	11	minus	47	0	x $18/$9 each=	$ 0.00
Independent Claims (37 C.F.R.§1.16(b))	2	minus	4	0	x $86/$43 each=	$ 0.00
First presentation of Multiple dependent claim(s): previously paid					$290/$145	$ 0.00
SUB-TOTAL =						$ 0.00
Fee for _1_ Month Extension of Time						$ 110.00
TOTAL FEE =						$ **110.00**

6. Fee Payment

☒ The Commissioner is hereby authorized to charge **$110.00** to Deposit Account No. 50-0310 for One-Month Extension of Time Fee.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: December 29, 2003 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

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Morgan Lewis
COUNSELORS AT LAW

FAX MESSAGE

Send To:

1.	Name:	**Examiner San Ming R. Hui Group 1617**	FAX Number:	**703-872-9306**
	Firm:	**U.S. Patent and Trademark Office**	Telephone Number:	703-305-1002

From:

Name	Donald J. Bird	Floor:	Operator Sending:
Telephone Number:	202-739-5320	Time Sent:	Date Sent: January 30, 2004

Number of Pages (INCLUDING COVER PAGE): 9

Note:

Re: **U.S. Patent Application of Evans et al.**
U.S. Serial No. 09/756,291
Filed: January 9, 2001
For: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San Ming. R.

Attached:
1. **AMENDMENT TRANSMITTAL FORM with authorization to charge $840.00 to Deposit Account No. 50-0310 for Second and Third Month Extension of Time Fee (1st month already paid)**
2. **SUPPLEMENTAL AMENDMENT AFTER FINAL**

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San Ming R.

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop AF**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: January 30, 2004

FILED VIA FACSIMILE

Sir:

AMENDMENT (FEE) TRANSMITTAL FORM

1. Transmitted herewith is an Amendment responding to the Office Action dated August 27, 2003.

2. Additional papers enclosed:

- ☐ Information Disclosure Statement
- ☐ Form PTO-1449, copies of ___ references
- ☐ Citations
- ☐ Declaration of Biological Deposit
- ☐ Submission of "Sequence Listing", computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
- ☐ Drawings: ☐ Formal ☐ Informal (Correction)

3. Extension of Time

The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136(a) apply.

☐ Applicant believes that no extension of time is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

☒ Applicant petitions for an extension of time, the fees for which are set out in 37 C.F.R. § 1.17(a), for the total number of months checked below:

Total Months Requested	Fee for Extension	[Fee for Small Entity]
☐ one month	$ 110.00	$ 55.00
☐ two months	$ 420.00	$210.00
☒ three months	$ 950.00	$475.00
☐ four months	$1,480.00	$740.00
☐ five months	$2,010.00	$1,005.00

If an additional extension of time is required, please consider this a Petition therefor.

☐ An extension for 1 month has already been secured and the fee paid therefor of $110.00 is deducted from the total fee due for the total months of extension now requested.

Extension of time fee due with this request: $840.00

4. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

5. Fee Calculation (37 C.F.R. §1.16)

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		Highest No. Previously Paid	Present Extra	at Rate of	Total Fees
Total Claims (37 C.F.R. §1.16(c))	12	minus	47	0	x $18/$9 each=	$ 0.00
Independent Claims (37 C.F.R.§1.16(b))	2	minus	4	0	x $86/$43 each=	$ 0.00
First presentation of Multiple dependent claim(s): previously paid					$290/$145	$ 0.00
SUB-TOTAL =						$ 0.00
Fee for 3 Month Extension of Time minus fee previously paid ($110.00)						$ 840.00
TOTAL FEE =						$ **840.00**

6. Fee Payment

☒ The Commissioner is hereby authorized to charge **$840.00** to Deposit Account No. 50-0310 for Second Month Extension of Time Fee.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: January 30, 2004 By: _____
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San Ming R.

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop AF**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: January 30, 2004

FILED VIA FACSIMILE

Sir:

SUPPLEMENTAL AMENDMENT AFTER FINAL

Supplemental to the Amendment and Response After Final filed on December 29, 2003, it is respectfully requested that the following further amendment be entered. This amendment adds new dependent claim 51, which is identical to existing claim 25 except dependent upon existing claim 28. As discussed in the Remarks below, the conditions of 37 CFR 1.116(c) and MPEP ¶ 714.13 have been met, and entry of claim 51 requires only a cursory review by the Examiner. Therefore, entry of this Supplemental Amendment After Final is believed to be in order and is respectfully requested.

Amendments to the Claims are reflected in the claim listing which begins at page 2.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in this application:

Listing of Claims:

Claims 1-23 (cancelled)

Claim 24 (previously amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ is attained for at least 2 weeks after injection.

Claim 25 (previously added): The method as claimed in claim 24 wherein the benign or malignant disease is breast cancer.

Claim 26 (previously added): The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

Claim 27 (previously added): The method as claimed in claim 24 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

Claim 28 (previously amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle whereby the formulation comprises at least $45mgml^{-1}$ of fulvestrant.

Claims 29 – 44 (cancelled).

Claim 45 (previously added): The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least $45mgml^{-1}$.

Claim 46 (previously added): The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

Claim 47 (previously amended): The method as claimed in claim 46 wherein the total volume of the formulation is from 5 to 5.25ml, and the total amount of fulvestrant in said volume of formulation is 250mg.

Claim 48 – 50 (cancelled).

Claim 51 **(new)**: The method as claimed in claim 28 wherein the benign or malignant disease is breast cancer.

REMARKS

The Amendment and Response After Final filed on December 29, 2003, inserted the limitations of 48 into independent method claims 24 and 28. Inasmuch as the Examiner had stated that claim 48 would be allowable if placed in independent form, it is believed that the December 29, 2003 Amendment placed claims 24 and 28 in condition for allowance. Since all other claims are dependent on claims 24 and 28, it is understood that the December 29, 2003 Amendment and Response placed all claims in condition for allowance.

Independent claims 24 and 28 are directed toward a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract. Existing dependent claim 25 provides that the benign or malignant disease of independent claim 24 is breast cancer. However, upon a further review of the claims pending the anticipated allowance, applicant has just noted (and brought to the attention of the undersigned) that there is no parallel claim dependent on independent method claim 28. New dependent claim 51 added herein is intended to remedy this inadvertent oversight.

Specifically, newly added dependent claim 51 provides that the benign or malignant disease of independent claim 28 is breast cancer, in the same manner that existing claim 25 provides that the benign or malignant disease of existing independent claim 24 is breast cancer. Newly added claim 51 is clearly within the scope of claim 28, and support is found in the specification, *inter alia*, at page 16, lines 4-5, and in original claim 22.

Therefore, new dependent claim 51 is clearly within the scope of claim 28 upon which it is dependent, finds support in the original specification and claims, and entry of this amendment requires only a cursory review by the Examiner. While it is recognized that entry of this amendment after Final is not a matter of right, it is believed that the above showings

meet all conditions of 37 CFR 1.116(c) and MPEP ¶ 714.13. Accordingly, entry of this amendment is believed to be in order and is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: January 30, 2004 By: _____
Donald J. Bird
Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
Fax No.: (202) 739-3001
DJB:

Image 1617 AF

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	
	)	Group Art Unit: 1617
EVANS et al.	)	
	)	Examiner: Hui, San Ming R.
Appln. No.: 09/756,291	)	
	)	
Filed: January 9, 2001	)	
	)	
FOR: FORMULATION	)	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop AF**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: February 24, 2004

Sir:

NOTICE OF APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated August 27, 2003 of the Primary Examiner finally rejecting claims of the above-identified application.

The item(s) checked below are appropriate:

1. ☒ A timely response to the final rejection was filed on December 29, 2003 and January 30, 2004.
2. ☒ Notice of Appeal Fee is enclosed: $ 330.00
3. ☒ An extension for 3 months has already been secured and the fee paid therefor of $950.00 is deducted from the total fee due for the total months of extension now requested.

   Extension of time fee due with this request: $ 0.00
4. ☒ Total Fees Due **$ 330.00**

02/26/2004 CNGUYEN 00000147 500310 09756291
01 FC:1401 330.00 DA

1-WA/2143778.1

5. ☒ The Commissioner is hereby authorized to charge **$330.00** to Deposit Account No. 50-0310 for Notice of Appeal Fee.

The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: February 24, 2004 By: _____

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

PTO/SB/17 (01-03)
Approved for use through 04/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant Claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 330.00

Complete if Known	
Application Number	09/750,619
Filing Date	November 30, 2000
First Named Inventor	Afana
Examiner Name	Nguyen, D.
Art Unit	2643
Attorney Docket No.	09710-1144

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account

Deposit Account Number: 13-2491

Deposit Account Name: WorldCom, Inc.

The Commissioner is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☐ Credit any overpayments

☐ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below		Fee Paid
Total Claims	-20**=		X		=	
Independent Claims	- 3**=		X		=	
Multiple Dependent					=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	**Reissue independent claims over original patent
1205	18	2205	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

** or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet	
1053	130	1053		Non-English specification	
1812	2,520	1812		For filing a request for *ex parte* reexamination	
1804	920*	1804		Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805		Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	330.00
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451		Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460		Petitions to the Commissioner	
1807	50	1807		Processing fee under 37 CFR 1.17(q)	
1806	180	1806		Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802		Request for expedited examination of a design application	
				Other fee (specify)	

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** **($)330.00**

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Phouphanomketh Ditthavong	*Registration No. (Attorney/Agent)*	44658	*Telephone*	(703) 425-8508
Signature				*Date*	February 23, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 37 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, Washington, DC 20231.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 09/756,291

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	minus 20=	*
INDEPENDENT CLAIMS	minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

01-30-04

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 12	Minus	** 45	= —
Independent	* 2	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

09/756,291

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
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21						
22						
23						
24			1		1	
25				1		1
26				1		1
27				1		1
28			1		1	
29						
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45				2		2
46				2		2
47				2		2
48						
49						
50						
TOTAL IND.			2		2	
TOTAL DEP.			9		10	

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						1
52						
53						
54						
55						
56						
57						
58						
59						
60						
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89						
90						
91						
92						
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP.						

PATENT
ATTORNEY DOCKET NO.: 056291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	
EVANS et al.	Group Art Unit: 1617
Appln. No.: 09/756,291	Examiner: Hui, San Ming R.
Filed: January 9, 2001	
FOR: FORMULATION	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, **Mail Stop AF**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: February 24, 2004

Sir:

NOTICE OF APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated August 27, 2003 of the Primary Examiner finally rejecting claims of the above-identified application.

The item(s) checked below are appropriate:

1. ☒ A timely response to the final rejection was filed on December 29, 2003 and January 30, 2004.
2. ☒ Notice of Appeal Fee is enclosed: $ 330.00
3. ☒ An extension for 3 months has already been secured and the fee paid therefor of $950.00 is deducted from the total fee due for the total months of extension now requested.
   Extension of time fee due with this request: $ 0.00
4. ☒ Total Fees Due **$ 330.00**

02/26/2004 CNGUYEN 00000147 500310 09756291
01 FC:1401 330.00 DA

1-WA/2143778.1

5. ☒ The Commissioner is hereby authorized to charge **$330.00** to Deposit Account No. 50-0310 for Notice of Appeal Fee.

The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: February 24, 2004 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

09629 7590 03/24/2004

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 03/24/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

TITLE OF INVENTION: FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$300	$1630	06/24/2004

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

09629 7590 05/24/2004

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

TITLE OF INVENTION: FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$300	$1630	06/24/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
HUI, SAN MING R	1617	514-177000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent); ❑ individual ❑ corporation or other private group entity ❑ government

4a. The following fee(s) are enclosed:

❑ Issue Fee
❑ Publication Fee
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE; The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

09629 7590 03/24/2004

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 03/24/2004

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

Notice of Allowability	Application No.	Applicant(s)	
	09/756,291	EVANS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *24-28,45-47 and 51*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: Applicant's amendments filed January 30, 2004 have been entered. The addition of claim 51 is acknowledged. The amendments limit the claims to the specific ratio of ethanol, benzyl alcohol, and benzyl benzoate. The herein recited ratio of ethanol, benzyl alcohol, and benzyl benzoate is demonstrated to have unexpected increase of solubility of fluvestrant. Therefore, the rejection under 35 USC 103 is withdrawn.

Claims 24-28, 45-47, and 51 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Issue Classification	Application No.	Applicant(s)	
	09/756,291	EVANS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

ISSUE CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)
514	177	514	178

INTERNATIONAL CLASSIFICATION

A	6	1	K	31/56
				/
				/
				/
				/

3/15/04
(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER
(Primary Examiner) (Date)

Total Claims Allowed: 9

O.G. Print Claim(s)	O.G. Print Fig.
1	1

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
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	12		42		72		102		132		162		192
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	14		44		74		104		134		164		194
	15	6	45		75		105		135		165		195
	16	7	46		76		106		136		166		196
	17	8	47		77		107		137		167		197
	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
	20		50		80		110		140		170		200
	21	9	51		81		111		141		171		201
	22		52		82		112		142		172		202
	23		53		83		113		143		173		203
1	24		54		84		114		144		174		204
2	25		55		85		115		145		175		205
3	26		56		86		116		146		176		206
4	27		57		87		117		147		177		207
5	28		58		88		118		148		178		208
	29		59		89		119		149		179		209
	30		60		90		120		150		180		210

Search Notes

Application No.	Applicant(s)	
09/756,291	EVANS ET AL.	
Examiner	**Art Unit**	
San-ming Hui	1617	

SEARCHED			
Class	Subclass	Date	Examiner
514	177	3/15/2004	SH
514	178	3/15/2004	SH

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**177**	**3/15/2004**	**SH**
514	178	3/15/2004	SH

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Medline, Biosis, USPatfull	3/15/2004	SH
Inventor search	3/15/2004	SH

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in this application:

Listing of Claims:

Claims 1-23 (cancelled)

11 Claim ~~24~~ (previously amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks after injection.

2 Claim ~~25~~ (previously added): The method as claimed in claim ~~24~~ 11 wherein the benign or malignant disease is breast cancer.

3 Claim ~~26~~ (previously added): The method as claimed in claim ~~24~~ 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

4 Claim ~~27~~ (previously added): The method as claimed in claim ~~24~~ 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

5 Claim ~~28~~ (previously amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle whereby the formulation comprises at least 45mgml^{-1} of fulvestrant.

Claims 29 – 44 (cancelled).

Claim 45 (previously added): The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least 45mgml^{-1}.

Claim 46 (previously added): The method as claimed in claim 24 or 28 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

Claim 47 (previously amended): The method as claimed in claim 46 wherein the total volume of the formulation is from 5 to 5.25ml, and the total amount of fulvestrant in said volume of formulation is 250mg.

Claim 48 – 50 (cancelled).

Claim 51 (new): The method as claimed in claim 28 wherein the benign or malignant disease is breast cancer.

Index of Claims

Application No.	Applicant(s)	
09/756,291	EVANS ET AL.	
Examiner	**Art Unit**	
San-ming Hui	1617	

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
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Claim		Date
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Claim		Date
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

09629 7590 03/24/2004

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,291	01/09/2001	John R. Evans	PM 275507 PHM70635/US	5974

TITLE OF INVENTION: FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$300	$1630	06/24/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
HUI, SAN MING R	1617	514-177000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 MORGAN, LEWIS &
2 BOCKIUS LLP
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: AstraZeneca AB

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Sodertalje, Sweden

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☒ Issue Fee
☒ Publication Fee
☒ Advance Order - # of Copies -4-

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 50-0310 (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above. Any deficiencies

(Authorized Signature) (Date)
Donald J. Bird Reg. No. 25,323 June 22, 2004

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

06/25/2004 HBERHE1 00000035 500310 09756291

01 FC:1501 1330.00 DA
02 FC:1504 300.00 DA
03 FC:8001 12.00 DA

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
09/756,291	6774122	1617	04B0

Change of Address/Power of Attorney

The following fields have been set to Customer Number 09629 on

- Correspondence Address
- Maintenance Fee Address

The address of record for Customer Number 09629 is:
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

The Practitioners of record for Customer Number 09629 are:

PTO INSTRUCTIONS:

Please take the following action when the correspondence address has been changed to a customer number:
1) Add 'ADDRESS CHANGE TO CUSTOMER NUMBER' on the next available content line of the File Jacket.
2) Put a line through the old address on the File Jacket and enter the Customer Number as the new address.
3) File this Notice in the File Jacket.

Please take the following action when the correspondence address has NOT been changed:
1) File this Notice in the File Jacket

CJC

PATENT
ATTORNEY DOCKET NO.: 056291-**5004**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.	**6,774,122**	) Confirmation No.	**5974**
Granted:	**August 10, 2004**	)	
Patentees:	**John R. Evans *et al.***	)	
Application No.	**09/756,291**	)	
Filed:	**January 9, 2001**	)	
FOR:	**FORMULATION**	)	

Attention Certificate of Corrections Branch
Commissioner for Patents,
P.O. Box 1450,
Alexandria, VA 22313-1450

Date **August 6, 2007**

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR § 1.322

This is a request for the issuance of a Certificate of Correction under 37 C.F.R. 1.322 in the above-referenced patent. Two (2) copies of form PTO-1050 are enclosed. The complete Certificate of Correction involves one (1) page.

It is requested that the above patent be corrected as shown in the attached proposed Certificate of Correction to correct printing errors that occur in claims 5 and 6. In claim 5, line 2 (column 13, line 8) "brass" should be corrected to read --breast--; and in claim 5, line 10 (column 13, line 16) "mgml" should be corrected to read --$mgml^{-1}$--. In claim 6, line 4 (column 14, line 4) "mgm^{-1}" should be corrected to read --$mgml^{-1}$--.

These errors in claims 5 and 6 occurred in the printing of the patent. This is clear from a comparison of claims 28 and 45 presented with the Supplemental Amendment After Final filed January 30, 2004, against corresponding granted patent claims 5 and 6. A copy of the claims from this Supplemental Amendment from PAIR (showing the corresponding patent numbers) is attached for the Examiner's convenience.

As the errors identified in the above-referenced U.S. Patent occurred through the fault of the U.S. Patent and Trademark Office, correction under 37 C.F.R. 1.322 is respectfully corrected, and no fee is enclosed. However, if there are any additional fees due in connection with the

filing of this Request, the Commissioner is hereby authorized to charge any fees due to Deposit Account No. 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: August 6, 2007 By: _____

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in this application:

Listing of Claims:

Claims 1-23 (cancelled)

11 Claim ~~24~~ (previously amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5ngml^{-1} is attained for at least 2 weeks after injection.

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3 Claim ~~26~~ (previously added): The method as claimed in claim ~~24~~ 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks after injection.

4 Claim ~~27~~ (previously added): The method as claimed in claim ~~24~~ 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks after injection.

5 Claim ~~28~~ (previously amended): A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle whereby the formulation comprises at least 45mgml^{-1} of fulvestrant.

Claims 29 – 44 (cancelled).

16 Claim ~~45~~ (previously added): The method as claimed in claim ~~24~~ 1 or ~~28~~ 5 wherein the total volume of the formulation administered to said human is 6ml or less, and the concentration of fulvestrant in said formulation is at least 45mgml^{-1}.

17 Claim ~~46~~ (previously added): The method as claimed in claim ~~24~~ 1 or ~~28~~ 5 wherein the total volume of the formulation administered to said human is 6ml or less, and the total amount of fulvestrant in said volume of formulation is 250mg or more.

18 Claim ~~47~~ (previously amended): The method as claimed in claim ~~46~~ 7 wherein the total volume of the formulation is from 5 to 5.25ml, and the total amount of fulvestrant in said volume of formulation is 250mg.

Claim 48 – 50 (cancelled).

19 Claim ~~51~~ (new): The method as claimed in claim ~~28~~ 5 wherein the benign or malignant disease is breast cancer.

PTO/SB/44 (08-07)
Approved for use through 08/31/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,774,122

APPLICATION NO. : 09/756,291

ISSUE DATE : August 10, 2004

INVENTOR(S) : John R Evans, Rosalind U. Grundy

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, line 8, "brass" should read --breast--; and line 16, "mgml" should read --$mgml^{-1}$--.

Column 14, line 4, "mgm^{-1} " should read --$mgml^{-1}$--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004

PTO/SB/44 (08-07)
Approved for use through 08/31/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,774,122

APPLICATION NO. : 09/756,291

ISSUE DATE : August 10, 2004

INVENTOR(S) : John R Evans, Rosalind U. Grundy

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, line 8, "brass" should read --breast--; and line 16, "mgml" should read --$mgml^{-1}$--.

Column 14, line 4, "mgm^{-1} " should read --$mgml^{-1}$--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004

AUG 8 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,774,122 B2
APPLICATION NO. : 09/756291
DATED : August 10, 2004
INVENTOR(S) : John R. Evans and Rosalind U. Grundy

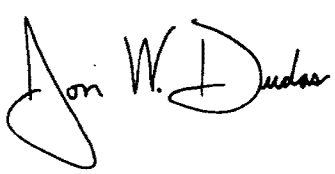
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, line 8, "brass" should read --breast--; and line 16, "mgml" should read --$mgml^{-1}$--.

Column 14, line 4, "mgm^{-1}" should read --$mgml^{-1}$--.

Signed and Sealed this

Sixteenth Day of October, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or ☐ Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
10cv18	1/7/2010	DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
AstraZeneca Pharmaceuticals LP, et al	Teva Parenteral Medicines, Inc., et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,774,122 B2	8/10/2004	AstraZeneca AB
2	7,456,160 B2	11/25/2008	AstraZeneca AB
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
PETER T. DALLEO, CLERK OF COURT		11/8/2010

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or ☐ Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
10cv18	1/7/2010	DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
AstraZeneca Pharmaceuticals LP, et al	Teva Parenteral Medicines, Inc., et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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2	7,456,160 B2	11/25/2008	AstraZeneca AB
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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3		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Stipulation of Dismissal filed and So Ordered 6/15/2011.

CLERK	(BY) DEPUTY CLERK	DATE
PETER T. DALLEO, CLERK OF COURT		1~~1/8/2010~~ 6/16/2011

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–03547–FLW–LHG	6/3/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA PHARMACEUTICALS LP	SANDOZ INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,774,122 B2	August 10, 2004	AstraZeneca AB
2 US 7,456,160 B2	November 25, 2008	AstraZeneca AB
3 US 8,329,680 B2	December 11, 2012	AstraZeneca AB
4 US 8,466,139 B2	June 18, 2013	AstraZeneca AB
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
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5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	6/3/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy