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Evans et al.

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(45) **Date of Patent: *Dec. 11, 2012**

(54) **FORMULATION**

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(73) Assignee: **AstraZeneca AB**, Södertälje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 338 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 10/872,784, filed on Jun. 22, 2004, now Pat. No. 7,456,160.

(30) **Foreign Application Priority Data**

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A61K 31/56 (2006.01)

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(58) **Field of Classification Search** 514/177, 514/178

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,822,316 A 2/1958 Richter et al.
2,983,649 A 5/1961 Ercoli et al.
3,164,520 A 1/1965 Huber
3,541,209 A 11/1970 Neumann et al.
RE28,690 E 1/1976 Lehmann et al.
4,048,309 A 9/1977 Chen et al.
4,048,310 A 9/1977 Chen et al.
4,212,863 A 7/1980 Cornelius
4,388,307 A 6/1983 Cavanak
4,659,516 A 4/1987 Bowler et al.
4,888,331 A 12/1989 Elger et al.
5,095,129 A 3/1992 Ottow et al.
5,183,814 A 2/1993 Dukes
5,484,801 A 1/1996 Al-Razzak et al.
5,733,902 A 3/1998 Schneider
5,929,030 A 7/1999 Hamied et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP 0138504 4/1985

(Continued)

OTHER PUBLICATIONS

The abstract of Wakeling et al., The Journal of Steroid Biochemistry and Molecular Biology, 1992;43:1-3:173-177.*

(Continued)

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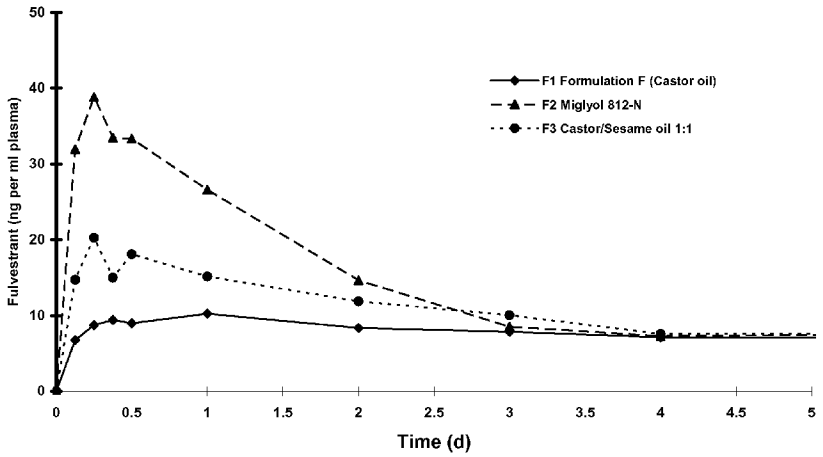
(57) **ABSTRACT**

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3, 17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

20 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

2001/0006963 A1 7/2001 Lachnit-Fixson et al.

FOREIGN PATENT DOCUMENTS

EP	0310542	A1	4/1989
EP	0346014		12/1989
EP	0819431		3/1999
EP	0905143		3/1999
FR	6241		9/1968
GB	817241		7/1959
GB	1126892		9/1968
GB	1207571		10/1970
GB	1569286		6/1980
JP	43-27327		11/1992
JP	09-208496		12/1997
JP	10-203982		4/1998
JP	10-152438		6/1998
JP	11-501649		2/1999
JP	11-158200		6/1999
SU	549118		3/1977
SU	676284		7/1979
WO	WO 95/12383		5/1995
WO	WO 96/19997		7/1996
WO	WO 97/21440		6/1997
WO	WO 97/37653		10/1997
WO	WO 97/40823		11/1997
WO	WO 98/11902		3/1998
WO	WO 99/27906		6/1999
WO	WO 03/006064		1/2003
WO	WO 2011/012885		2/2011
ZA	681014		2/1968
ZA	682530		4/1968

OTHER PUBLICATIONS

Anschel, "Lösungsmittel und Lösungsvermittler in Injektionen", Pharm, Ind., 1965, vol. 27 (11a), pp. 781-787.

Davis et al., "17-Alpha-Hydroxyprogesterone-Caproate: . . . with Chemically Pure Progesterone", J. Clin. Endocrinol. and Metabolism, 1955, vol. 15, pp. 923-930.

Dukes et al., "Antiuterotrophic effects of pure antioestrogen. ICI 182,780, . . . the uterus in ovariectomized monkeys", J. Endocrinology, 1992, vol. 135, pp. 239-247.

Dukes et al., "Antiuterotrophic effects of the pure antioestrogen ICI 182, 780 . . . quantitative magnetic resonance imaging"; J. Endocrinology, 1992, vol. 138, pp. 203-209.

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.

Howell et al., "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer", The Lancet, Jan. 7, 1995, pp. 29-30.

Mackey et al, "Tolerability of intramuscular injections of testosterone ester in oil vehicle", Human Reproduction, vol. 10, No. 4, pp, 869-865, 1995.

Martindale, 32nd Ed., "Alcohol", Pharmaceutical Press, 1999, pp. 1099-1101.

Martindale, 32nd Ed., "Benzoates" and "Benzyl Alcohol"; Pharmaceutical Press, 1999, pp. 1102-1104.

Martindale, 32nd Ed., "Caster Oil"; 32nd Ed., Pharmaceutical Press, 1999, p. 1560.

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.

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.

Pellegrino, "Use of 17 α Hydroxyprogesterone Caproate in Threatened Abortion", Current Therapeutic Research, vol. 4, No. 6, Jun. 1962, pp. 301-305.

Piver et al., "Medroxyprogesterone Acetate (Depo-Provera) vs . . . Women with Metastatic Endometrial Adenocarcinoma", Cancer, vol. 45, American Cancer Society, 1980, pp. 268-272.

Remington's Pharmaceutical Sciences, 18th ed., 1990, p. 219.

Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, vol. 53, No. 8, Aug. 1964, pp. 891-895.

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 tamoxifen 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.

Sawada et al., "Estrogen Receptor Antagonist ICII82,780 Exacerbates Ischemic Injury in Female Mouse", Journal of Cerebral Blood Flow and Metabolism, vol. 20. No. 1, 2000, pp. 112-118.

Vidal, Le Dictionnaire, "Benzo-Gynoestryl Retard", 1998 p. 201.

Vidal, Le Dictionnaire, "Gravibinan", 1995, pp. 660-661.

Vidal, Le Dictionnaire, "Parabolan", 1997, p. 1245.

Vidal, Le Dictionnaire, "Trophobolene", 1997, pp. 1706-1707.

Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential", Cancer Research, 1991, vol. 51, pp. 3867-3873.

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.

"Pharmaceutical dosage forms: Parenteral medications, vol. 1", 2nd edition, edited by Avis, Lieberman and Lachman, 1992.

The Merck Index, 12th Ed., Merck & Co., Inc., pp. xiv, 189-190, 641-642 and 1715 (1996).

Guerrini, et al., "Pharmacokinetics of probenecid in sheep", J Vet Pharmacol Ther., 128-135 (1985).

Lavy, et al., "Pharmacokinetics of clindamycin HCI administered intravenously, intramuscularly and subcutaneously to dogs", J Vet Pharmacol Ther., 22(4):261-265 (1999).

Ismail, "Disposition kinetics of difloxacin after intravenous, intramuscular and subcutaneous administration in calves", Vet Res Commun., 31(4):467-476 (2007).

Documents from the prosecution of European Application No. 01900186.6 (EP 1 250 138) from Aug. 27, 2009 to Dec. 15, 2011.

Documents from the prosecution of European Application No. 10180667.7 (EP 2 266 573) from Nov. 23, 2010 to Dec. 19, 2011.

Documents from the prosecution of European Application No. 10180661.0 (EP 2 286 818) from Jan. 19, 2011 to Dec. 19, 2011.

Declaration Under 35 U.S.C § 1.132 of Dr. Paul Gellert filed in Aug. 2008 in U.S. Appl. No. 10/872,784.

McLeskey et al., "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and two aromatase inhibitors," Clin. Cancer Res., 4:697-711 (1998).

JRF Robertson, et al., "Fulvestrant: pharmacokinetics and pharmacology," British Journal of Cancer, 90(1):S7-S10 (2004).

John F. R. Robertson, "Fulvestrant (Faslodex®)—how to make a good drug better," The Oncologist, 12:774-784 (2007).

Search Report for European Patent Application No. 10180667.7 dated Nov. 23, 2010.

Search Report for European Patent Application No. 10180661.0 dated Jan. 19, 2011.

Documents from the Opposition against European Patent Application No. 01900186.6 from Apr. 21, 2009 to Sep. 7, 2009.

P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development: Techniques to Reduce Pain and Irritation*. Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999).

P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* 6:724-733 (1972).

S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* 51:166-71 (1997).

Physicians' Desk Reference (*27th edition*). 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973).

M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* 52:238-311 [pp. 238-255 provided] (1998).

R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999)—Part I. *PDA J Pharm. Sci. Technol*. 53:324-349 (1999).
R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999)—Part II *PDA J Pharm. Sci. Technol*. 54:69-96 (2000).
R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999)—Part III. *PDA J Pharm. Sci. Technol*. 54:152-169 (2000).
Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J Parenteral Drug Assoc*. 34:452-462 (1980).
U.S. Appl. No. 13/387,584, filed Jan. 27, 2012, Dimery et al.
Buzdar, A. U., "Fulvestrant—A novel estrogen receptor antagonist for the treatment of advanced breast cancer," *Drugs of Today*, 44(9):679-692 (2008).
"Comparison of fulvestrant (faslodex) 250 mg and 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer progressing or relapsing after previous endocrine therapy," Clinicaltrials.gov (May 20, 2009) retrieved Jan. 24, 2012.
Di Leo A., et al., "Confirm: a phase III, randomized, parallel-group trial comparing fulvestrant 250 mg vs fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer," Cancer Res., 69(24) Supp. 3, (2009).
International Search Report for PCT Application No. PCT/GB10/51228 (WO 2011/012885) mailed Dec. 20, 2012.
International Preliminary Report on Patentability for PCT Application No. PCT/GB10/51228 (WO 2011/012885) mailed Dec. 20, 2012.
Documents from the prosecution of European Application No. 01900186.6 (EP 1 250 138) dated Dec. 15, 2011.
Documents from the prosecution of European Application No. 01900186.6 (EP 1 250 138) dated Feb. 27, 2012.

* cited by examiner

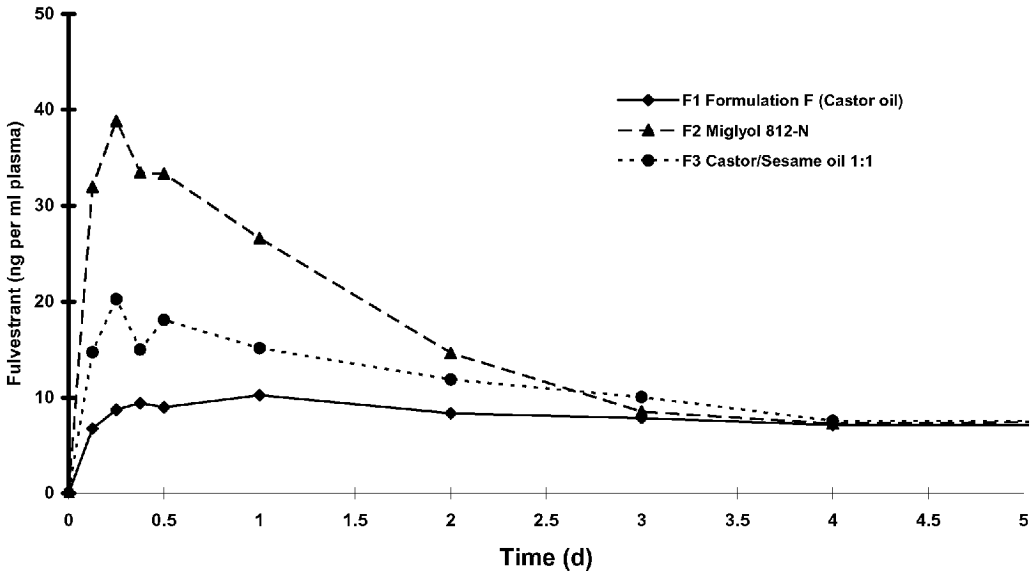


Figure 1

FLOW DIAGRAM OF MANUFACTURING

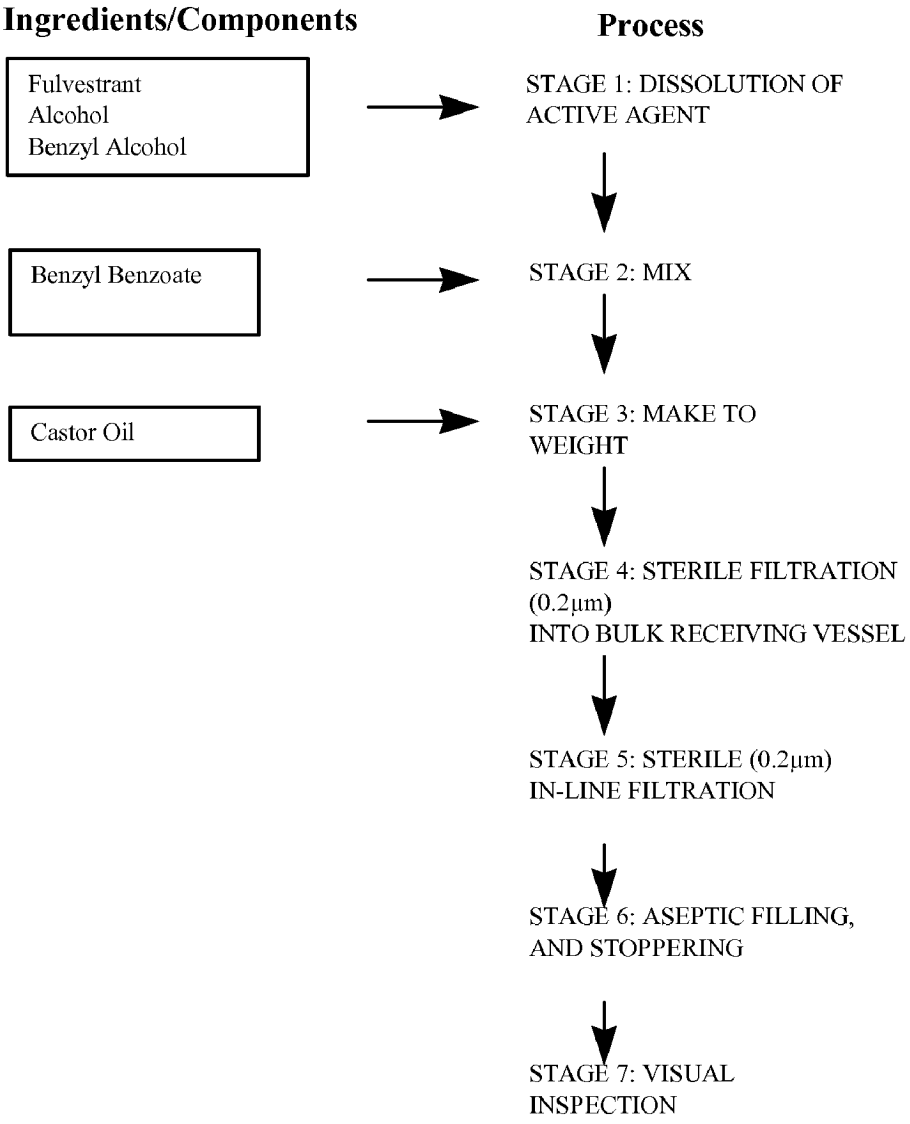


Figure 2

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