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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

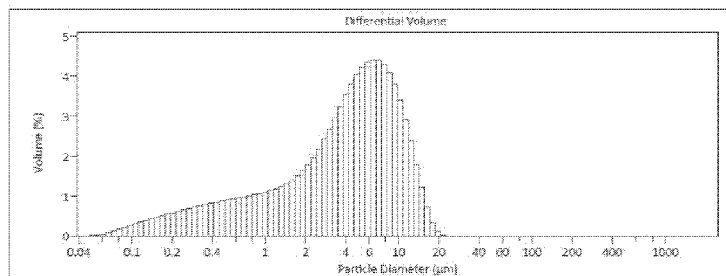


FIG. 4

(57) Abstract: Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/66406

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/48; A61K 9/66; A61K 31/565; A61K 31/57 (2013.01)
USPC - 424/451, 424/455, 424/457, 424/489, 514/177, 514/1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8)- A61K 9/48; A61K 9/66; A61K 31/565; A61K 31/57 (2013.01);
USPC- 424/451, 424/455, 424/457, 424/489, 514/177, 514/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/177, 514/182, 424/489, 424/451, 424/455, 424/457;
Patents and NPL (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest, PatBase (USPTO, EPO, JPO, WIPO), GoogleScholar (PL, NPL), FreePatentsOnline (USPTO, EPO, JPO, WIPO, NPL);
search terms: progesterone, estradiol, micronize, solubilise, x50, x90, d50, d90, capsule, intra, inter, patient, variability, PROMETRIUM, MIGLOYL, GELUCIRE, butylated, hydroxytoluene

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,900,734 A (MAXSON et al.) 13 February 1990 (13.02.1990), col 4, ln 61-68; col 5, ln 6-12; co. 7, ln 19-40; col 8, ln 29-31	1, 5, 9, 17-23,25,26,38-40 ----- 2-4, 6-8, 10-16, 24, 27-37, 41-46
X	US 6,077,531 A (SALIN-DROUIN) 20 June 2000 (20.06.2000), col 1, ln 56-62	1, 9
Y	US 2010/0316724 A1 (WHITFIELD et al.) 16 December 2010 (16.12.2010), para [0090], [0091], [0146], [0159]-[0162], [0170], [0174], [0194], [0227]	2-4, 6-8, 24, 29
Y	US 2003/0077297 A1 (CHEN et al.) 24 April 2003 (24.04.2004), Figs. 10, 11A, 11B, para [0011], [0051], [0217], [0312], [0336], [0360], [0368], [0370]	10-16, 37
Y	US 2003/0124182 A1 (SHOJAEI et al.) 03 July 2003 (03.07.2003), Tables 1-3; para [0006], [0014], [0016], [0022], [0026], [0029], [0031], [0033], [0038]-[0041], [0050]	30-37, 41-46
Y	US 2011/0262494 A1 (ACHLEITNER et al.) 27 October 2011 (27.10.2011), para [0018], [0047], [0063], [0081]	27
Y	US 2010/0137271 A1 (CHEN et al.) 03 June 2010 (03.06.2010), para [0004], [0031], [0034], [0052]	28
Y	US 2011/0182997 A1 (LEWIS et al.) 28 July 2011 (28.07.2011), para [0025]-[0165]	1-46
Y	US 2008/0299220 A1 (TAMARKIN et al.) 04 December 2008 (04.12.2008), para [0012]-[1020]	1-46

Further documents are listed in the continuation of Box C.

* 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 application or patent 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 04 January 2013 (04.01.2013)	Date of mailing of the international search report 24 JAN 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/66406

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

- 1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claims Nos.: 47-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.