US010258630B2

(12) **United States Patent**
Mirkin et al.

(10) **Patent No.: US 10,258,630 B2**
(45) **Date of Patent: *Apr. 16, 2019**

(54) **VAGINAL INSERTED ESTRADIOL PHARMACEUTICAL COMPOSITIONS AND METHODS**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(72) Inventors: **Sebastian Mirkin**, Boca Raton, FL (US); **Julia M. Amadio**, Boca Raton, FL (US); **Brian A. Bernick**, Boca Raton, FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/893,546**

(22) Filed: **Feb. 9, 2018**

(65) **Prior Publication Data**

US 2018/0161344 A1 Jun. 14, 2018

Related U.S. Application Data

(63) Continuation of application No. 15/372,385, filed on Dec. 7, 2016, which is a continuation-in-part of application No. 14/521,230, filed on Oct. 22, 2014.

(60) Provisional application No. 62/264,309, filed on Dec. 7, 2015, provisional application No. 62/296,552, filed on Feb. 17, 2016, provisional application No. 62/324,838, filed on Apr. 19, 2016, provisional application No. 62/329,940, filed on Apr. 29, 2016, provisional application No. 62/348,820, filed on Jun. 10, 2016.

(51) **Int. Cl.**

A61K 31/565	(2006.01)
A61K 9/00	(2006.01)
A61K 9/02	(2006.01)
A61K 9/48	(2006.01)
A61K 47/14	(2017.01)
A61K 31/57	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/565*** (2013.01); ***A61K 9/0034*** (2013.01); ***A61K 9/0036*** (2013.01); ***A61K 9/02*** (2013.01); ***A61K 9/4825*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 9/4866*** (2013.01); ***A61K 31/57*** (2013.01); ***A61K 47/14*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351	A	1/1934	Doisy
2,232,438	A	2/1941	Butenandt
2,379,832	A	7/1945	Serini et al.
2,649,399	A	8/1953	Beall et al.
3,198,707	A	8/1965	Nomine et al.
3,478,070	A	11/1969	Stein et al.
3,526,648	A	9/1970	Bertin et al.
3,710,795	A	1/1973	Higuchi et al.
3,729,560	A	4/1973	Hagerman
3,729,566	A	4/1973	Ericsson et al.
3,755,573	A	8/1973	Berman
3,755,575	A	8/1973	Lerner
3,903,880	A	9/1975	Higuchi et al.
3,916,898	A	11/1975	Robinson
3,916,899	A	11/1975	Theeuwes et al.
3,921,636	A	11/1975	Zaffaroni
3,923,997	A	12/1975	Meuly
3,948,254	A	4/1976	Zaffaroni
3,971,367	A	6/1976	Zaffaroni
3,977,404	A	8/1976	Theeuwes
3,993,072	A	11/1976	Zaffaroni
4,008,719	A	2/1977	Theeuwes et al.
4,012,496	A	3/1977	Schopflin et al.
4,014,334	A	3/1977	Theeuwes et al.
4,014,987	A	3/1977	Heller et al.
4,016,251	A	8/1977	Higuchi et al.
4,071,623	A	1/1978	van der Vies
4,093,709	A	6/1978	Choi et al.
4,154,820	A	5/1979	Simoons
4,155,991	A	5/1979	Schopflin et al.
4,196,188	A	4/1980	Besins
4,215,691	A	8/1980	Wong
4,237,885	A	12/1980	Wong et al.
4,310,510	A	1/1982	Sherman et al.
4,327,725	A	5/1982	Cortese et al.
4,372,951	A	2/1983	Vorys
4,384,096	A	5/1983	Sonnabend
4,393,871	A	7/1983	Vorhauer et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI1001367-9	A	7/2012
CA	2612380		12/2006

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)

Abbas et al., Regression of endometrial implants treated with vitamin D_3 in a rat model of endometriosis, European J of Pharma, 715 (2013) 72-75, Elsevier.

Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.

Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.

Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.

(Continued)

Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

In one aspect, compositions and methods for the treatment of vulvovaginal atrophy (VVA) are provided. In one embodiment, the method comprises administering an estrogen to a subject having VVA by inserting a dosage form comprising a liquid pharmaceutical composition.

9 Claims, 22 Drawing Sheets