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(54) **Title:** FORMULATIONS FOR THE PREPARATION OF IMMEDIATE-RELEASE TABLETS FOR ORAL ADMINISTRATION CONTAINING LOW-DOSE MIFEPRISTONE, TABLETS THUS OBTAINED AND THEIR PREPARATION PROCESS

(57) **Abstract:** Formulations for the preparation of immediate-release tablets for oral administration containing low-dose mifepristone, the tablets thus obtained and their preparation process, are described.



FORMULATIONS FOR THE PREPARATION OF IMMEDIATE-RELEASE TABLETS FOR ORAL ADMINISTRATION CONTAINING LOW-DOSE MIFEPRISTONE, TABLETS THUS OBTAINED AND THEIR PREPARATION PROCESS

5 Field of the invention

The present invention relates to the field of tablets for oral administration in particular tablets containing low doses of active ingredient.

Background of the invention

Mifepristone, also known as RU486 with chemical formula 11β -[4-(N,N-Dimethylamino)-phenyl-17 β -hydroxy-17 α -(1-propynyl)-estra-4,9-dien-3-one], is a selective progesterone antagonist at receptor level without progestogenic, oestrogenic, androgenic and anti-oestrogenic activity. This molecule's ability to bind with the progesterone receptor at endometrial level is 5 times higher with respect to that of the progesterone itself. It can be quickly absorbed following oral administration with the appearance of a peak at blood level after just 1 and half hours. It has a long half-life time of around 20 hours (much longer than that of many glucocorticoid agonists), which makes its in vivo clearance very slow. It too is naturally subject to the first passage effect and the blood level of its metabolites after 1-2 hours from oral administration is greater with respect to the original compound. The use of high-dose mifepristone has proved effective as emergency post-coital contraceptive treatment for hospital use in combination with misoprostol by oral route or prostaglandin E₁ by vaginal route. There are prior art studies that have demonstrated the efficacy of mifepristone for the treatment of other diseases such as leiomyoma, myoma, uterine fibrosis, endometriosis, adenomyosis and related disorders.

Eisinger et al (2003) have demonstrated that the daily oral administration of a low-dose of Mifepristone (5 mg) for a period of 6 months has effects comparable with those of higher doses of Mifepristone in the treatment of uterine fibroma with reduction of the related side effects.

30 Intravaginal tablet formulations that offer the same advantages as the oral formulations but with a lower dose and thus a reduction of the possible

appearance of side effects are described in patents US 2011/0208118 A1, WO 2009/037704 A1 and EP 2 197 415 A0.

Other studies have demonstrated the efficacy of this medicinal product in the treatment of Amyotrophic Lateral Sclerosis (patent US 2011/0166115 A1, WO 2010/002901 and EP 2 306 830 A0) and of Cushing's syndrome in combination with an inhibitor of cortisone synthesis such as Metyrapone or mitotane (US 2010/0261693 A1, WO 2009/050136 A2 and EP 2 211 845 A0).

It should also be borne in mind that mifepristone, being equipped with a high activity, requires special conditions for the safe processing thereof, which must take place in suitable premises and with equipment capable of allowing processing in containment conditions.

It is thus evident, from what has been said above, how useful it would be to have low-dose mifepristone formulations in the form of immediate-release tablets for oral administration.

Summary of the invention

The present invention relates to formulations containing a low dose of mifepristone for the preparation of immediate-release tablets to be used in the treatment of uterine fibroma in particular.

Detailed description of the invention

The present invention allows the above-mentioned problems to be resolved thanks to a formulation and to a production process that does not require special procedures, allows the problems due to the handling of the mifepristone to be reduced and thus allows immediate-release tablets for oral administration containing a low dose of the active ingredient, to be effectively made available.

According to the invention, the formulations for the preparation of tablets for oral administration contain mifepristone in an amount between 3 and 10% w/w (preferably 6% w/w) in combination with suitable diluents, binders, disintegrants, lubricants and glidants.

According to the invention, diluent means microcrystalline cellulose

Glidant means anhydrous colloidal silica

Disintegrant means croscarmellose sodium

Binder means polyvinylpyrrolidone

Lubricant means magnesium stearate

Diluents are preferably used (in particular microcrystalline cellulose) containing moisture, water, between 1 - 10 weight %, which indeed allows the formation of the necessary microgranulate premix, this granulation makes the mixture smooth-flowing and easily compressible and reduces the segregation of the individual components of the mixture and this allows tablets with an excellent uniformity of content to be obtained.

Preferably, the above-mentioned components of the formulation are present in the following amounts, expressed by weight on the total weight:

10	Diluents	76 - 94%
	Glidants	0 – 1 %
	Disintegrants	1 – 5 % (preferably 3%)
	Binders	2 – 6 % (preferably 4%)
	Lubricants	0 – 2%

15 According to a particularly preferred embodiment, a tablet according to the invention, obtained with a formulation as previously described, has the following composition expressed by weight on the total weight:

	Mifepristone	6 %
	Microcrystalline Cellulose	85.7 %
20	Polyvinylpyrrolidone	4 %
	Croscarmellose Sodium	3 %
	Magnesium Stearate	1 %
	Anhydrous Colloidal Silica	0.3 %

25 According to the invention, the tablets are produced by the formation of a premix wherein the active ingredient comes to be mixed with an equal amount of microcrystalline cellulose and is sieved.

In the meantime, the remaining microcrystalline cellulose, binder and disintegrant are sieved and mixed together. To this mixture is added and mixed the premix containing the active ingredient. Lastly, the lubricants and glidants are added and such a mixture is compressed.

Using the above-described components and process, it is possible to obtain immediate-release, low-dose Mifepristone tablets for oral administration that

guarantee the uniformity of content requirements with excellent uniformity of content.

It is thus possible to easily obtain, and with fewer risks, low-dose mifepristone tablets that guarantee therapeutic efficacy in the treatment of uterine fibroma with fewer side effects.

Example

Formulation of low-dose, immediate-release mifepristone tablets with excellent uniformity of content.

For a batch of 1,000,000 tablets 5 kg of raw material 71.417 kg of microcrystalline cellulose, 3.333 kg of polyvinylpyrrolidone, 2.5 kg of croscarmellose sodium, 0.833 kg of magnesium stearate and 0.250 kg of anhydrous colloidal silica were used.

a) Preparation of the Premix

The mifepristone and the microcrystalline cellulose are mixed together and the mixture is sieved.

b) Mixing of the excipients

The remaining microcrystalline cellulose, polyvinyl pyrrolidone and croscarmellose sodium are mixed together.

c) Mixing of the excipients with the active premix

To the excipient mixture is added the premix containing the active ingredient and mixed in BIN for 10 minutes at 8 rpm.

d) Addition of lubricants and glidants

The magnesium stearate and microcrystalline silica are sieved and added to the BIN to be mixed with the remaining components.

e) Compression of the mixture.

The mixture is compressed to obtain tablets having a 6mm diameter and average weight of 80 mg with active ingredient content equal to 5 mg/TBL.

CLAIMS

1. Formulations for the preparation of immediate-release tablets for oral administration, wherein said formulations contain mifepristone in an amount
 5 between 3 and 10% w/w in combination with suitable diluents, binders, disintegrants, lubricants and glidants and wherein said diluents have a moisture, water content of 1 – 10 weight %.
2. Formulation according to claim 1, wherein the diluent is microcrystalline cellulose, the glidant is anhydrous colloidal silica, the disintegrant is
 10 croscarmellose sodium, the binder is polyvinylpyrrolidone and the lubricant is magnesium stearate.
3. Formulations according to claim 2, wherein said components are present in the following amounts:

Diluents	76 – 94%
15 Glidants	0 – 1 %
Disintegrants	1 – 5 %
Binders	2 – 6 %
Lubricants	0 – 2 %
4. A process for the preparation of immediate-release tablets for oral
 20 administration comprising a direct compression step of a formulation according to claims 1 – 3.
5. Process according to claim 5, wherein:
 - a) a premix is prepared by mixing the active ingredient with an equal amount of microcrystalline cellulose and sieved;
 - 25 b) the remaining microcrystalline cellulose, the binder and disintegrant are sieved and mixed together
 - c) the mixture prepared in point (b) is added to the premix containing the active ingredient and, lastly, the lubricants and glidants are added
 - d) the aforementioned mixture is compressed into tablets.
- 30 6. Immediate-release tablets for oral administration consisting of:

Mifepristone	6 %
Microcrystalline Cellulose	85.7 %
Polyvinylpyrrolidone	4 %

Croscarmellose Sodium	3 %
Magnesium Stearate	1 %
Anhydrous Colloidal Silica	0.3 %

7. Tablets according to claim 6 for the treatment of uterine fibroma.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/567
ADD.

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)
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 practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, INSPEC, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 210 585 A1 (EXELGYN [FR]) 28 July 2010 (2010-07-28) paragraphs [0043], [0083] -----	1-7
A	EP 1 987 814 A1 (EXELGYN [FR]) 5 November 2008 (2008-11-05) example 1 -----	1-7
A	CN 101 455 671 A (HUBEI GEDIAN HUMANWELL PHARMAC [CN]) 17 June 2009 (2009-06-17) example 4 -----	1-7



Further documents are listed in the continuation of Box C.



See patent family 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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"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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			EP	2387388 A1		23-11-2011
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