HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

16 October 2013

MIFFEE 200 mg, tablet

B/1 (CIP: 34009 267 678 2 2)
B/30 (CIP: 34009 583 774 8 8)

Applicant: Linepharma

INN	mifepristone
ATC code (year):	G03XB01 (progesterone receptor modulator)
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"The prescription and administration of MIFFEE 200 mg, tablet and prostaglandins for the termination of pregnancy must be performed in accordance with current legislation.** **Medical termination of developing intrauterine pregnancy, in sequential combination with a prostaglandin analogue, up to 63 days of amenorrhoea."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**MIFFEE offers no improvement in actual benefit (IAB V, nonexistent) in the treatment regimen for medical voluntary termination of pregnancy.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	29 March 2013, (mutual recognition procedure, reference member state: Sweden) Medicinal product registered under a hybrid procedure (Article 10(3) of Directive 2001/83/EC)
Prescribing and dispensing conditions / special status	List 1 For professional use only

ATC Classification	2012	
	G	Genito-urinary system and sex hormones
	G03	Sex hormones and modulators of the genital system
	G03X	Other sex hormones and modulators of the genital system
	G03XB	Progesterone receptor modulators
	G03XB01	Mifepristone

02 BACKGROUND

This is an application for inclusion of a new proprietary mifepristone medicinal product in boxes of 1 and 30 tablets.

A bioequivalence study versus MIFEGYNE 200 mg concluded that MIFFEE 200 mg was bioequivalent in AUC, but not in Cmax, for which the upper limit of the 90% confidence interval was in excess of the predefined range of 80%-125%.
As a result, only the administration of a single dose of 200 mg, in combination with gemeprost (and not with misoprostol) per vaginam, was authorised in the Marketing Authorisation.

03 THERAPEUTIC INDICATIONS

“The prescription and administration of MIFFEE 200 mg, tablet and prostaglandins for the termination of pregnancy must be in accordance with current legislation.
Medical termination of developing intrauterine pregnancy, in sequential combination with a prostaglandin analogue, up to 63 days of amenorrhoea.”

04 DOSAGE

“Medical termination of developing intrauterine pregnancy, up to 63 days of amenorrhoea.
The treatment regimen is a single oral dose of 200 mg of mifepristone, followed 36 to 48 hours later by administration of a dose of 1 mg of the prostaglandin analogue gemeprost per vaginam.
The dose of 200 mg must not be exceeded.

There are no available data in women under 18 years.”

05 THERAPEUTIC NEED

There is at present only one available mifepristone proprietary medicinal product, MIFEGYNE, in unit doses of 200 mg and marketed in boxes of 3 tablets. Mifepristone must be used in combination with a prostaglandin analogue.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

MIFEGYNE (mifepristone):
- Manufacturer: Nordic Pharma SAS
- Opinion of 18 July 2007: Substantial AB
- Reimbursement on the list of products for hospital use only

06.2 Other health technologies

Uterine aspiration.
Dilatation and curettage.

◗ Conclusion

MIFEGYNE is the clinically relevant comparator.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation overseas:
This medicinal product has Marketing Authorisation in the indication of the European Marketing Authorisation in the following countries:
Iceland, Denmark, Sweden, Norway, Finland, United Kingdom, Kenya.
This medicinal product has Marketing Authorisation in Australia in the indications:
- Medical termination of developing intrauterine pregnancy, in combination with a prostaglandin analogue, up to 49 days of pregnancy
- Preparation for the action of registered prostaglandin analogues indicated in the termination of pregnancy for medical reasons after the first trimester

Hospital use of this medicinal product is reimbursed overseas in the following countries:
Iceland, Denmark, Sweden, Norway, Finland, United Kingdom.

08 ANALYSIS OF AVAILABLE DATA

08.1 Bioequivalence study

The applicant has submitted one bioequivalence study versus MIFEGYNE 200 mg. This study concluded that MIFEGYNE and MIFFEE 200 mg were bioequivalent in AUC, but not in Cmax, for which the upper limit of the 90% confidence interval was in excess of the permitted range of 80%-125% (Cmax ratio = 114.4, 90% CI: [103.33; 126.66]). This is the reason for its use in a single dose of 200 mg.

08.2 Efficacy

The applicant has submitted 26 published studies and one study report. There have been no studies of the effect of MIFFEE in combination with gemeprost in the treatment regimen in the Marketing Authorisation.

Of these publications, 21 concerned the proprietary medicinal product MIFEGYNE.

- Seventeen of them[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17] examined methods of administration of MIFEGYNE that did not correspond to the one in the Marketing Authorisation for MIFFEE:

1 McKinley C. Thong KJ. Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. Human Reprod 1993, 8, 1502-5

2 WHO Task Force on Post-ovulatory Methods of Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: A randomised trial. Br J ObstetrGynecol 2000, 107, 524-30

3 Bartley J. Brown A. Elton R. Baird DT. Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation. Human Reprod 2001, 16, 2098-102

4 Baird DT. Sukcharoen N. Thong KJ. Randomized trial of misoprostol and cervagem in combination with a reduced dose of mifepristone for induction of abortion. Human Reprod 1995, 10, 1521-7

5 Coyaji K. Krishna U. Ambardekar S. Bracken H. Raote V. Mandlekar A. Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? Br J ObstetrGynecol 2007, 114, 271-8

6 Sang GW. Weng LJ. Shao QX. Du MK. Wu XZ. Lu YL. Cheng LN. Termination of early pregnancy by two regimens of mifepristone with misoprostol and mifepristone with PG05-a multicentre randomized clinical trial in China. Contraception 1994, 50, 501-10

7 Schaff EA. Fielding SL. Westhoff C. Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy.[erratum in Contraception. 2002 Dec;66(6):481.] Contraception 2002, 66, 247-50

8 Schaff EA. Fielding SL. Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. Contraception 2001, 64, 81-5

9 Shannon C. Wiebe E. Jacot F. Guilbert E. Dunn S. Sheldon WR. Winikoff B. Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. Br J ObstetrGynecol 2006, 113, 621-8

10 Shannon CS. Winikoff B. Hausknecht R. Schaff E. Blumenthal PD. Oyer D. Sankey H. Wolff J. Goldberg R. Multicenter trial of a simplified mifepristone medical abortion regimen. ObstetrGynecol 2005, 105, 345-51

11 Von Hertzen H. Honkanen H. Piaggio G. Bartfai G. Erdenetungalag R. Gemzell-Danielsson K. Gopalan S. Horga M. Jerve F. Mittal S. Ngoc NT. Peregoudov A. Prasad RN. Pretnar-Darovec A. Shah RS. Song S. Tang OS. Wu SC. WHO Research Group on Post-Ovulatory Methods for Fertility Regulation. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. Br J ObstetrGynecol 2003, 110, 808-18

12 Bhattacharya M, Das SK, Gopalakrishnan K, Kodkany BS, Mukherjee GG, Kukherjee K, Pal MN, Shrotri AN, Shanmugapriya KN, Takkar D, Datey S, Gupta NK, Mittal R, Roy M, Shekhar C, Kumar S, Vishwanath P, Saxena BN. A multicentre randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE2 gel (meteneprost) or 600 mcg oral PGE1 (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. Contraception, 2000, 62, 125-30

13 El-Refaey H. Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure. Br J ObstetrGynecol 1994, 101, 792-6

14 Elul B. Hajri S. Ngoc N.T.N. Ellertson C. Slama C.B. Pearlman E. Winikoff B. Can women in less-developed countries use a simplified medical abortion regimen? Lancet 2001, 357, 1402-5

15 Middleton T. Schaff E. Fielding SL. Scahill M. Shannon C. Westheimer E. Wilkinson T. Winikoff B. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005, 72, 328-32

doses other than 200 mg of mifepristone, in combination with a dose of gemeprost lower than the one in the Marketing Authorisation for MIFFEE or with another orally or vaginally administered prostaglandin. These were not taken into account.

- Two publications concerned the proprietary medicinal product MIFFEE in combination with oral misoprostol[18,19], which does not correspond to the treatment regimen in the Marketing Authorisation. These will therefore not be discussed below.

- Four publications[20,21,22,23] studied the efficacy of 200 mg of MIFEGYNE in combination with 1 mg of gemeprost. For information purposes, the percentage of complete abortion was between 92.4% and 96%, depending on the publication.

The SPC for MIFFEE states that “the non-negligible risk of failure of the method, of the order of 11.7% of cases, makes the control visit mandatory in order to check that expulsion has been completed”.

08.3 Safety/Adverse effects

Clinical studies using MIFFEE according to a treatment regimen that did not correspond to the one in the Marketing Authorisation (combination with oral misoprostol)

The most common adverse events reported in the Mexican clinical study[18] were episodes of diarrhoea (59.5%), fever/chills (45.3%), nausea (34.2%) vomiting (26.4%), weakness (20.9%), headache (13.9%) and dizziness (13.1%).
Ten patients were hospitalised for curettage after heavy bleeding and one patient was hospitalised for an infection and treated with antibiotics.

The adverse events reported in the published Australian clinical study[19] were haemorrhage (0.1%, n = 16, with transfusion in 11 cases) and infection, both diagnosed (0.03%, n = 4) and suspected (0.2%, n = 21). One death due to an infection occurred 9 days after taking mifepristone.

16 Ngoc NT. Nhan VQ. Blum J. Mai TT. Durocher JM. Winikoff B. Is home-based administration of prostaglandin safe and feasible for medical abortion? Results from a multisite study in Vietnam. Br J ObstetrGynecol 2004, 111, 814-9
17 Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion. A Randomized Controlled Trial. ObstetrGynecol 2008, 112, 1303-10
18 Mifepristone and misoprostol for abortion in pregnancies up to 63 days of gestation. Clinical study report, 2011
19 Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: a large Australian observational study. MJA 2012; 197:282-286 doi: 10.5694/mja12.10297
20 WHO Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. Br Med J 1993, 307, 532-7
21 WHO Task Force on Post-ovulatory Methods of Fertility Regulation. Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost. A randomized controlled trial. Acta ObstetrGynecol Scand 2001, 80, 447-51
22 Prasad RN. Choolani M. Termination of early human pregnancy with either 50 mg or 200 mg single oral dose of mifepristone (RU486) in combination with either 0.5 mg or 1.0 mg vaginal gemeprost. Austr NZ J ObstetrGynaecol 1996, 36, 20-3
23 Lowering the doses of mifepristone and gemeprost for early abortion: a randomised controlled trial. World Health Organization Task Force on Post-ovulatory Methods for Fertility Regulation. Br J ObstetrGynecol 2001, 108, 738-42

SPC for MIFFEE

The SPC for MIFFEE mentions in particular the possible occurrence of prolonged, sometimes profuse metrorrhagia (on average 10 to 16 days after taking MIFFEE). Metrorrhagia occurs in almost all cases and does not constitute any proof whatsoever of complete expulsion.
A follow-up visit must take place 14 to 21 days after the administration of MIFFEE, to check that expulsion was complete and that metrorrhagia has ceased.
The persistence of metrorrhagia at this follow-up visit could indicate incomplete abortion or an undetected extrauterine pregnancy, and must result in the appropriate treatment.
Given the possibility of severe metrorrhagia necessitating haemostatic curettage in 5% of cases of medical termination of pregnancy, caution is advisable in patients with haemostasis disorders associated with hypocoagulability or anaemia.

The SPC for MIFFEE also states that “Very rare cases of fatal toxic shock due to Clostridium sordellii endometritis, without fever or other obvious symptoms, have been reported after taking 200 mg mifepristone followed by off-label vaginal administration of misoprostol tablets intended for oral use.”

The other very common (≥ 1/10) adverse events mentioned in the SPC for MIFFEE are nausea, vomiting, diarrhoea, dizziness, gastric disorders, abdominal cramps, headache, uterine contractions, fatigue and chills/fever.

08.4 Summary & discussion

The applicant has submitted a dossier based primarily on literature data that for the most part involve the proprietary medicinal product MIFEGYNE, which has the same active ingredient as the proprietary medicinal product MIFFEE, but has not been shown to be bioequivalent. In four of these studies, in which 200 mg of MIFEGYNE was used in combination with 1 mg of gemeprost, i.e. the same dosage regimen as that of MIFFEE, the percentage of complete abortions was between 92.4% and 96%, depending on the publication.
The most common adverse events mentioned in the SPC for MIFFEE are nausea, vomiting, diarrhoea, dizziness, gastric disorders, abdominal cramps, headache, uterine contractions, fatigue and chills/fever.
Metrorrhagia occurs in almost all cases and may necessitate haemostatic curettage in 5% of cases.

08.5 Planned studies

Since the administered dose must not exceed 200 mg, the CHMP requested the performance of a prospective observational study with the aim of collecting, within three months after Marketing Authorisation or by the 1000th reported case, postmarketing prescribing information on MIFFEE 200 mg (administered dose) and on the associated prostaglandin (type, administered dose and route of administration).

09 THERAPEUTIC USE

09.1 Therapeutic strategy[24]

In all cases or wherever possible, women must be allowed to choose the method of voluntary termination of pregnancy (medical or surgical) and must be given detailed information[25].
In France, the medical method is currently based on the combination of an antiprogestogen, mifepristone, and a prostaglandin. It is possible up to 9 weeks of amenorrhoea (WA).

The efficacy of the medical method is evaluated according to two criteria: the success rate (defined as obtaining complete abortion without the need for surgical intervention, irrespective of the indication) and the rate of developing or persisting pregnancy.

For pregnancies of less than 7 WA (i.e. not more than 49 days of amenorrhoea), the treatment regimens currently recommended in the Marketing Authorisation for MIFEGYNE and MIFFEE (proprietary medicinal product for which the dose of 200 mg must not be exceeded) are:
- a single oral dose of 600 mg of mifepristone (MIFEGYNE), followed 36 to 48 h later by oral administration of a prostaglandin analogue: 400 µg of misoprostol;
- or a single oral dose of 200 mg of mifepristone (MIFEGYNE or MIFFEE), followed 36 to 48 h later by vaginal administration of a prostaglandin analogue: 1 mg of gemeprost.

For pregnancies of 7 to 9 WA (50 to 63 days of amenorrhoea),
- a single oral dose of 600 mg of mifepristone (MIFEGYNE), followed 36 to 48 h later by vaginal administration of a prostaglandin analogue: 1 mg of gemeprost.
- or a single oral dose of 200 mg of mifepristone (MIFEGYNE or MIFFEE), followed 36 to 48 h later by vaginal administration of a prostaglandin analogue: 1 mg of gemeprost.

The clinician must inform the patient of the possible risk of continuation of pregnancy, of the need in such cases to use a surgical method if termination of pregnancy is still desired, and of the absolute necessity of thefollow-up visit after two weeks provided for by French regulation.

09.2 Role in the therapeutic strategy

MIFFEE, as a single dose of 200 mg and only in combination with gemeprost, can be used as a first-line option for the voluntary termination of developing intrauterine pregnancy.

24 HAS guidelines on voluntary termination of pregnancy by the medical method, December 2010.
25 An information guide to VTP for adult and under-age women is published by the French Ministry of Health.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

- Voluntary termination of pregnancy (VTP) is a regulated procedure requiring rigorous follow-up.
- MIFFEE is a preventive treatment.
- The efficacy/adverse effects ratio of MIFFEE is high.
- Pharmacological and non-pharmacological alternatives exist.
- MIFFEE is a first-line proprietary medicinal product.

- In France, one in three pregnancies is unwanted[26] and the number of voluntary terminations of pregnancy (VTPs) carried out in 2011 is estimated at 222,000, of which 55% were medical[27].
  On this basis and taking into consideration the associated psychological consequences and social repercussions, the public health burden of unwanted pregnancies and VTP can be considered substantial.
  Ensuring access to suitable contraception, emergency contraception and VTP for all women who choose to make use of it and preventing unwanted pregnancy are public health needs that are an established priority (objective 97 of the Law of 9 August 2004 relating to public health policy, Law No. 2001-588 of 4 July 2001). In France, despite the widespread use of medical methods of contraception[28] and the increased use of emergency contraception[29], the number of VTPs carried out has remained relatively stable since 2006, including among minors and in 18-19 year-olds[2]. The public health need therefore remains[30]. However, the response to this need is primarily preventive in approach and based on better information about available methods of contraception, their use and their efficacy.
  On the basis of the available data and taking into consideration the existing drug treatments, this proprietary medicinal product is not expected to achieve higher success rates in voluntary terminations of pregnancy or better safety.
  Consequently, the proprietary medicinal product MIFFEE is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of MIFFEE is substantial in the treatment regimen for the medical termination of developing intrauterine pregnancy, in sequential combination with a prostaglandin analogue, up to 63 days of amenorrhoea.

[26] Bajos N, Leridon H, Goulard H, Oustry P, Job-Spira N; COCON Group. Contraception: from accessibility to efficiency. Hum Reprod. 2003;18:994-9.
[27] Vilain A, Mouquet MC, Gonzalez L, de Riccardis N. Voluntary terminations of pregnancy in 2011 - Studies and results – 843 – June 2013 - DREES.
[28] First results of the 2010 Health Barometer, cited in M-C. Naves, S. Sauneron. "How can access to contraception for young people be improved? An international comparison" Analysis No. 226 of the Centre for strategic analysis, June 2011
[29] Public health guidelines: Emergency contraception. Prescription and supply in advance. Haute Autorité de santé. April 2013
[30] Aubin C, Jourdain Menninger D, Chambaud L. Evaluation of the politics of preventing unwanted pregnancy and managing voluntary termination of pregnancy pursuant to the Law of 4 July 2001. Inspectorate General of [Social] Affairs. October 2009.

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

MIFFEE offers no improvement in actual benefit (IAB V, nonexistent) in the treatment regimen for medical voluntary termination of pregnancy.

010.3 Target population

In 2011, 222,500 VTPs were carried out in France, of which 55% were medical[27]. Given that MIFFEE may be used only in combination with gemeprost, for which the conditions of use are less straightforward than those of misoprostol, the estimated target population is, on this basis, overstated.

The target population of MIFFEE will therefore be no more than 122,300 women.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions according to the indication, dosage and treatment duration.

◗ Request for data

The Committee would like to be sent the results of the prospective observational study requested by the EMA with the aim of collecting, in the three months following Marketing Authorisation or until the 1.000th reported case, postmarketing prescribing information on MIFFEE 200 mg (administered dose) and on the associated prostaglandin (type, administered dose and route of administration).