EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 September 2012
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Patient Health Protection

Assessment report for Mifepristone Linepharma and associated names

Pursuant to Article 29(4) of Directive 2001/83/EC

International Non-proprietary Name of the active substance: mifepristone

Procedure no: EMEA/H/A-29/1331

Referral under Article 29(4) of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Mutual recognition procedure (MRP) and CMD(h) 60 day procedure

Linepharma France submitted an application for mutual recognition of Mifepristone Linepharma and associated names, 200mg tablets on the basis of the marketing authorisation granted by Sweden on 28 January 2011.

The application for Mifepristone Linepharma 200 mg tablets is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The reference product is Mifegyne 200 mg tablet. The application was submitted through a repeat use procedure to the reference Member State (RMS), Sweden, and the concerned Member States (CMS): France and United Kingdom. The first marketing authorisation was approved through the Decentralised Procedure with Sweden acting as RMS and Denmark, Finland, Iceland and Norway as CMS.

The mutual recognition procedure SE/H/986/01/E01 started on 07 September 2011.

The names and MAHs of this medicinal product currently authorised following previous Decentralised Procedure are listed in Annex I.

On day 90, major issues on safety, efficacy and bioequivalence, raised by France, remained unsolved; hence the procedure was referred to CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by Sweden on 08 December 2011. The CMD(h) 60 day procedure was initiated on 26 December 2011.

Day 60 of the CMD(h) procedure was on 23 February 2012, and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by Sweden on 23 February 2012. France raised public health objections as a positive benefit-risk balance for the proposed indications has not been proven based on clinical data (lack of efficacy/safety data with 200 mg Mifepristone Linepharma associated with gemeprost and the lack of demonstrated bioequivalence with the reference product in EU- Mifegyne).

2. Scientific discussion during the referral procedure

2.1. Introduction

The approved indication for Mifepristone Linepharma through the initial Mutual Recognition Procedure is *"Medical termination of a developing intra-uterine pregnancy in sequential combination with a prostaglandin analogue up to 63 days of amenorrhea".* The approved posology is 200 mg of mifepristone in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.

The application for Mifepristone Linepharma 200 mg tablets is a hybrid application made according to Article 10(3) of Directive 2001/83/EC, with Mifegyne 200 mg tablet as reference product. The posology of Mifepristone Linepharma is not the same as for the reference product Mifegyne. Compared to Mifegyne, which could be administered either at a high dose of 600 mg or a lower dose of 200 mg,

only the lower dose of 200 mg is approved for Mifepristone Linepharma. The product is currently approved in Sweden, Denmark, Finland, Iceland and Norway.

The current SmPC for the reference product mifepristone recommends mifepristone at the dose of 600 mg followed 36 to 48 hours later by 400 µg misoprostol orally or gemeprost 1 mg per vaginam for pregnancy termination up to 49 days of amenorrhea. An alternative of 200 mg of mifepristone was also approved to be used as a single dose, provided that this dose is followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam. The reason for this alternative was the fact that the combination of 200 mg mifepristone with oral misoprostol was associated with a potentially higher risk of continuing pregnancy, whereas 1mg gemeprost vaginally had been demonstrated in many studies to provide a strong prostaglandin action also in combination with a lower dose of mifepristone.

During the repeat use procedure potential serious risk to public health was raised by the France as bioequivalence with the reference product had not been demonstrated for Cmax. During the following CMDh-referral procedure no consensus was reached and the CMDh referred the matter to the CHMP through an article 29(4) referral procedure.

The clinical documentation submitted by the MAH to support this article 10(3) application includes clinical data and supportive pharmacokinetic data in the form of two bioequivalence studies.

2.2. Critical evaluation

The marketing authorisation holder has provided clinical efficacy and safety data from 2 studies, performed both with Mifepristone Linepharma in Mexico and Australia respectively. The clinical trials have been performed in co-operation with two organisations which have administered the medicinal product to a large number of women.

- The organisation Gynuity Health Projects performed a GCP-compliant study in Mexico in 1000 women (open-label, non-comparative, prospective multi-site study of mifepristone 200 mg followed 24-48 hours later by buccal misoprostol 800 mcg for termination of pregnancy through 63 days). The MAH provided the synopsis and abstract of this study. The success rate is of 97.3%, comparable to studies reported in published literature. No serious unexpected events were related to the regimen studied.

- The second organisation (Marie Stopes International Australia) has set up a pre-launch training program in Australia under Therapeutic Goods Administration (TGA) Authorised Prescriber Program. A preliminary publication in 1343 women has been provided by the MAH. This program is on-going and overall from 01 September 2009 to 30 June 2011, 12,830 women have been exposed. Women were entitled to be treated with 200 mg of Mifepristone Linepharma orally followed by 800 µg of misoprostol if their pregnancy age was 63 days of amenorrhea or less. 1,913 (14.9%) of them had a pregnancy age above 49 DA. In the whole population, efficacy rate (complete termination, no need for additional surgical procedure) was 96.7%. For the 12,830 women who have received this treatment via the program, the efficacy and safety of the method was as expected from clinical studies reported in the literature.

The table I below indicates the outcome of pregnancy observed in this population. Efficacy decreased only minimally in women with pregnancy age >49 DA.

Table I: Main clinical findings after pregnancy termination using Mifepristone Linepharma followed by buccal administration of misoprostol (800 µg)

Main clinical findings after pregnancy termination using Mifepristone Linepharma followed by buccal administration of misoprostol (800 µg)

	Overall population		Population with pregnancy age > 49 DA	
N treated	12,830	100%	1,913	100%
N with complete success (no need for surgical intervention)	12,413	96.7%	1,775	92.8%
Retained products requiring surgical intervention	337	2.6%	120	6.3%
Ongoing pregnancy requiring surgical intervention	80	0.6%	18	0.9%

For the 12,830 women who have received this treatment via the program, the efficacy and safety of the method was as expected from clinical studies reported in literature. Safety data are presented in the table II below.

Table II: Main safety findings after pregnancy termination using Mifepristone Linepharma followed by buccal administration of misoprostol (800 µg)

Main safety findings after pregnancy termination using Mifepristone Linepharma followed by buccal administration of misoprostol (800 mcgg)

	Overall population		Population with pregnancy age > 49 DA	
N treated	12,830	100%	1,913	100%
Infection	8	0.06%	0	0.0%
Ongoing bleeding requiring transfusion	11	0.09%	0	0.0%
Ongoing bleeding not requiring transfusion	4	0.03%	0	0.0%

These Australian data indicate that medical termination using Mifepristone Linepharma 200 mg tablet yields efficacy and safety data as expected from literature review.

The results of these trials show a very high success rate and no unexpected adverse events. The fact that buccal misoprostol and not vaginal gemeprost (as proposed in the current application) was used as follow up treatment would, if anything, lower the success rates and therefore is reassuring to the CHMP.

In addition, the MAH provided supportive pharmacokinetic data in the form of two bioequivalence studies. The two bioequivalence studies were performed against Mifegyne (approved in EEA) and Mifeprex (approved in the USA).

Bioequivalence with the reference product (Mifegyne) was demonstrated for AUC while the Cmax was slightly above the conventional acceptance range of 80-125% (the Cmax ratio (90% CI) was 114.4 (103.33-126.66)). Based on the results of the 2 clinical studies and taking into consideration that Mifepristone Linepharma is only given once and as a single dose, the CHMP was of the opinion that the higher Cmax would not affect safety or efficacy of Mifepristone Linepharma.

In addition, the CHMP noted that the study with Mifeprex demonstrates bioequivalence for both AUC and Cmax.

Based on the above, in view of the slightly increased Cmax, the CHMP is of the opinion that a higher dose than 200mg of Mifepristone Linepharma should not be administered and that this should be

clearly indicated in the Product Information and a prospective observational study aiming to evaluate the prescription recommendations of Mifepristone Linepharma for early pregnancy termination should be performed.

As proposed by the MAH at the time of the CMDh referral procedure, the protocol for the prospective observational study aimed to evaluate the prescription recommendations of Mifepristone Linepharma for early pregnancy termination was reviewed by the CHMP during the referral procedure. This protocol has been designed to provide further reassurance of the safety and efficacy of the product. However the CHMP expressed the following remaining concerns:

- The scope of the survey: the potential risk of off-label use with mifepristone LinePharma is linked to the differences in the regimens approved compared to the reference product Mifegyne. Compared to Mifegyne, which could be administered either at a high dose of 600 mg or a lower dose of 200 mg, only the lower dose of 200 mg is approved for Mifepristone Linepharma. The patterns of off-label use of the product could be thus either use of higher doses of Mifepristone and/or use of another prostaglandin analogue, which are expected to depend on current practices/protocols in each centre or country. Therefore, in order to improve relevance and interpretability of results the CHMP requests the MAH to broad the scope of the questionnaire to all mifepristone-containing products that could be used within a same centre. All relevant parts of the questionnaire should thus be revised: in order to reflect the the multiple possible situations (use of Mifepristone Linepharma, Mifegyne or other mifepristone-containing product).
- In order to minimise selection bias, particularly feared in such studies assessing off-label use, confidential responses should be preferred. Therefore, the CHMP considers that the marketing authorisation holder should propose alternative methods of data collection ensuring anonymous answers. Identifying questions on the first box of the questionnaire should thus be deleted.
- It should be indicated in the protocol that only one questionnaire by centre would be sufficient, except if prescribers within a same centre have different practices. In this case, one questionnaire by prescriber should be completed.
- The representativeness of prescribers participating in each country - The marketing authorisation holder should clarify the target of this questionnaire, in terms of type of practice (Private practice, hospital based, specialized pregnancy centres, etc) and medical specialty (GP, gynaecologist, others) and indicate the source/list of potential prescribers that will be used for random sampling. In order to verify representativeness a posteriori, the questionnaire should include relevant questions on the prescriber/centre, specialty of the prescriber, type of activity (hospital and/or private, specialised centre) and average number of medical abortions per year (and not per month), etc.
- The countries participating in the Drug Utilisation Study (DUS): given that the product is already marketed in Sweden, the marketing authorisation holder should discuss the possibility to also include this country in the DUS. Indeed, this would enable getting faster results, as the time needed for enough market penetration in UK and France is difficult to estimate.
- The study timelines and milestones: The marketing authorisation holder should provide information on the expected timelines for launch in France and UK, as well as expected dates by when market penetrations will enable study conduction. Clear timelines should be proposed accordingly.

- Inclusion and exclusion criteria: Given that the questionnaire will be addressed to prescribers, who will document general practices and not individual treatments/patients, the inclusion and exclusion criteria, notably based on product contraindications, are not deemed appropriate.
- The sample size: The marketing authorisation holder should further justify the proposed sample size of 1000 subjects (prescribers), especially considering the precision around estimates and the realistic estimations of non-response rates.
- The planned DHPC letter in case of off-label use greater than 5%: The need for minimisation tools, their content and diffusion modalities should be agreed between the marketing authorisation holder and the RMS/CMS, in function of the study results and may be different according to the participating countries. For example, in France, the threshold of 5% of off-label use is very likely to be exceeded, since the use in gemeprost is known to be low. Therefore the marketing authorisation holder should plan milestones for the submission of the results as soon as they are available (regarding the first 500 or 1000 questionnaires, depending on sample size considerations). The results should be submitted together with a discussion on the need for minimisation measures, broken down by country. If mitigation actions are deemed necessary, a second wave of the survey would be indeed suitable for evaluating their impact.
- Finally, the questionnaire includes questions regarding treatment efficacy and safety, which is actually not necessary for answering the study objectives. Moreover, getting accurate and interpretable data on such endpoints would require a totally different and more robust methodology than the one proposed for drug utilisation purposes. Therefore, question 5 should be deleted.

Hence the CHMP is of the opinion that a revised protocol should be submitted to the national competent authorities, for final agreement prior the start of the clinical trial, as a condition to the marketing authorisation.

2.3. Proposed changes to the SmPC

The marketing authorisation holder was in agreement with the amendments of the section 4.2 of the SmPC as proposed by the CHMP. The valid summary of product characteristics is the final version achieved during the Coordination group procedure with the following amendments (highlighted below in bold underlined) in the section 4.2:

4.2 Posology and method of administration

Medical termination of developing intra-uterine pregnancy up to 63 days of amenorrhea.

The method of administration is 200 mg of mifepristone in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.

The dose of 200 mg should not be exceeded.

Paediatric population

No data are available for women under 18 years.

The section 3 of the Package Leaflet was amended accordingly.

2.4. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities (condition to the marketing authorisations) are necessary for the safe and effective use of the medicinal product:

> *a prospective observational study aimed to evaluate the prescription recommendations of Mifepristone Linepharma for early pregnancy termination mentioned in the opinion should be performed. The submission of a revised protocol should take place within 10 days after the Commission Decision.*

The National Competent Authorities coordinated by the Reference Member State, shall ensure that the above condition is fulfilled by the MAH.

2.5. Recommendation

Mifepristone Linepharma is submitted as a hybrid application. The posology is different to the reference product Mifegyne. Compared to Mifegyne, which can be administered either at a high dose of 600 mg or a lower dose of 200 mg, only the lower dose of 200 mg was approved for Mifepristone Linepharma through the first wave of the Mutual Recognition Procedure and was also being proposed in the current MRP repeated procedure.

Taking into consideration that Mifepristone Linepharma is only given once and as a single dose of 200mg, the CHMP is of the opinion that the provided clinical data supports that the slightly higher Cmax would not affect efficacy and safety of Mifepristone Linepharma.

The CHMP considers however that a higher dose than 200mg of Mifepristone Linepharma should not be administered and that this should be clearly indicated in the Product Information. A prospective observational study aiming to evaluate the prescription recommendations of Mifepristone Linepharma for early pregnancy termination should be performed as a condition to the marketing authorisation. The CHMP is of the opinion that the marketing authorisation holder should submit a revised protocol to the national competent authorities, for final agreement prior the start of the clinical trial.

Based on the above, the CHMP considers that the overall efficacy and safety profile of the Mifepristone Linepharma has been sufficiently proven by the studies presented and therefore concluded that the benefit-risk balance for Mifepristone Linepharma in the applied indication *"Medical termination of a developing intra-uterine pregnancy in sequential combination with a prostaglandin analogue up to 63 days of amenorrhea"* is favourable.

The divergent positions are appended to this report.

2.6. Conclusions and benefit risk assessment

Whereas,

- The Committee considered the notification of the referral triggered by France under Article 29(4) of Council Directive 2001/83/EC;

- The Committee reviewed all available data submitted by the marketing authorisation holder to address the potential serious risk to public health, in particular the efficacy and safety in respect of the 200 mg Mifepristone Linepharma dosing regimen;
- The Committee considered that the overall efficacy and safety have been proven by the studies presented ;
- The CHMP is of the opinion that a dose higher than 200 mg should not be administered and that this should be clearly indicated in the Product Information. In addition, a prospective observational study aiming to evaluate the prescription recommendations of Mifepristone Linepharma for early pregnancy termination should be performed;
- Therefore the Committee concluded that the benefit-risk balance for Mifepristone Linepharma in the applied indications is favourable,

the CHMP has recommended the granting of the marketing authorisation subject to a recommended condition with regard to the safe and effective use of the medicinal product and for which the amended sections of the summary of product characteristics and package leaflet are amended for Mifepristone Linepharma and associated names.

Appendix I

Divergent Positions dated 21 June 2012

Article 29(4) referral of Council Directive 2001/83/EC, as amended

Procedure No: EMEA/H/A-29/1331

Mifepristone Linepharma and associated names (INN: mifepristone)

Divergent statement

Based on the presented clinical and bioequivalence evidence in their totality, the following member of CHMP did not agree with the CHMP's final Opinion taken on 21 June 2012 regarding Mifepristone Linepharma especially on the agreed indication.

The following CHMP member is of the opinion that the application is not approvable based on the following:

- The failed bioequivalence study is not acceptable as an hybrid application;
- The supporting clinical data obtained in a setting not available in many European countries (i.e. use with gemeprost) do not provide sufficient evidence on the efficacy and safety of Mifepristone Linepharma for the use with the other prostaglandin misoprostol only available in some Member States
- The trial was performed outside EU, with not known proportion of participants having similar internal characteristics and external circumstances e.g. lifestyle, diet… to EU population)

CHMP member expressing a divergent opinion:

Agnes Gyurasics (HU)	21 June 2012	Signature: …….....

Article 29(4) referral of Council Directive 2001/83/EC, as amended

Procedure No: EMEA/H/A-29/1331

Mifepristone Linepharma and associated names (INN: mifepristone)

Divergent statement

The following members of CHMP did not agree with the CHMP's final Opinion taken on 21 June 2012 regarding Mifepristone Linepharma especially on the agreed indication, based on the below rationale:

1. The posology of Mifepristone Linepharma is not the same as for the reference product Mifegyne. Compared to Mifegyne, which can be administered either at a high dose of 600 mg or a lower dose of 200 mg, only the lower dose of 200 mg is approved for Mifepristone Linepharma in the countries involved in the first wave Mutual Recognition Procedure.
2. The different posology is based on the results from bioequivalence studies. The bioequivalence with the EU-reference Mifegyne was demonstrated for AUC but not for Cmax which was slightly above the conventional acceptance range of 80-125%. For the lower dose (200 mg) proposed by the marketing authorisation holder for first trimester indication for Mifepristone Linepharma, the slight difference in bioequivalence was not considered a hinder for approval. Hence Mifepristone Linepharma is a hybrid and is not bioequivalent to Mifegyne.
3. There is a serious risk of off-label use because in the clinical practice it will not be known that bioequivalence is not proven. Instead, this product will be seen as a generic of the innovator Mifegyne. There is thus a clear risk that physicians will also use Mifepristone Linepharma in the dose of 600 mg.
4. Moreover, there are countries in which the prostaglandin gemeprost is not available. In that situation, there is the possibility that Mifepristone Linepharma will be combined with the prostaglandin analogue misoprostol orally. For this combination the mifepristone dose must be 3 times higher, i.e. mifepristone 600 mg + misoprostol 400 mcg.

CHMP members expressing a divergent opinion:

Daniela Melchiorri (IT)	21 June 2012	Signature: ……...
Nela Vilceanu (RO)	21 June 2012	Signature: ……...

Article 29(4) referral of Council Directive 2001/83/EC, as amended

Procedure No: EMEA/H/A-29/1331

Mifepristone Linepharma and associated names (INN: mifepristone)

Divergent statement

the following member of CHMP did not agree with the CHMP's final Opinion taken on 21 June 2012 regarding Mifepristone Linepharma especially on the agreed indication.

The reasons are:

1. Pregnancy normally cannot be considered a disease, and furthermore termination of pregnancy in a normal setting is not a therapeutic indication. It is a medical procedure only in distinct settings.

2. The medical termination of pregnancy involves the destruction and death of a human life. This falls under the definition contained in the *Guideline on the definition of a potential serious risk to public health*.

3. The benefit-risk of this product in the situations described above is therefore negative.

4. This procedure is in direct conflict with the responsibility of medicine to protect and promote life.

5. The use (indication) of the product does not fit the definition of a Medicinal product "*Any substance or combination of substances presented as having properties for treating or preventing disease in human beings*".

CHMP members expressing a divergent opinion:

John Joseph Borg (MT)	21 June 2012	Signature: …….....