Annex II

Scientific conclusions and grounds for positive opinion subject to condition to the marketing authorisation and amendment of the summary of product characteristics and package leaflet presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Mifepristone Linepharma and associated names (see Annex I)

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.

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. 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 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.

The marketing authorisation holder was in agreement with the amendments of the section 4.2 of the SmPC and section 3 of the Package Leaflet as proposed by the CHMP.

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 some remaining concerns with regards to the required investigations on the potential risk of off label use of mifepristone, either using a higher dose or a combination with another prostaglandin analogue than gemeprost per vaginam. Some other specific methodological comments were also raised by the CHMP such as representativity of prescribers, sample size and inclusion criteria. 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.

Conclusion

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.

Grounds for positive opinion subject to condition to the marketing authorisation and amendment of the summary of product characteristics and package leaflet

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 as set out in Annex IV and for which the amended sections of the summary of product characteristics and package leaflet are set out in Annex III for Mifepristone Linepharma and associated names (see Annex I).