Summary of Risk Management Plan for Esmya (ulipristal acetate)

This is a summary of the risk management plan (RMP) for Esmya. The RMP details important risks of Esmya, how these risks can be minimised, and how more information will be obtained about Esmya's risks and uncertainties (missing information).

Esmya's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Esmya should be used.

Important new concerns or changes to the current ones will be included in updates of Esmya's RMP.

I. The medicine and what it is used for

Esmya is authorised for intermittent treatment of moderate to severe symptoms of uterine fibroids in women for whom surgical procedures are contraindicated or have already failed (see Product Information for the full indication). It contains ulipristal acetate as the active substance and it is given by oral route, 5 mg tablet.

Further information about the evaluation of Esmya's benefits can be found in Esmya's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002041/human_med_001542.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Esmya, together with measures to minimise such risks and the proposed studies for learning more about Esmya's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size, the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status, the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Esmya, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Esmya is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Esmya are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is

sufficient proof of a link with the use of Esmya. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Inappropriate management of endometrium thickening (unnecessary interventions or treatments) Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia) Drug Induced Liver Injury
Important potential risks	Acute uterine bleeding requiring immediate intervention Treatment course beyond three months
Missing information	Long-term effects of prolonged treatment of the endometrium (including possible malignant changes) Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma Impact on surgery Use in patients with moderate to severe hepatic impairment Use in patients with severe renal impairment

II.B Summary of important risks

Important identified risk **Inappropriate management of endometrium thickening (unnecessary interventions or treatments)**	
Evidence for linking the risk to the medicine	Clinical trials data and literature.
Risk factors and risk groups	The phase III studies did not reveal a specific patient profile or an ulipristal acetate dose more susceptible to induce endometrium thickening.
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Warnings and precautions section - Pharmacodynamic safety Additional risk minimisation measures: - Educational material to prescribers
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Important identified risk **Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)**	
Evidence for linking the risk to the medicine	Clinical trials data and literature.
Risk factors and risk groups	The phase III data did not reveal a specific patient profile or ulipristal acetate dose more prone to the development of Progesterone Receptor Modulator Associated Endometrial Changes (PAEC).
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Warnings and precautions section - Pharmacodynamic safety Additional risk minimisation measures: - Educational material to prescribers - Educational material to pathologists
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Important identified risk **Drug Induced Liver Injury**	
Evidence for linking the risk to the medicine	Literature, press release and post-marketing experience.
Risk factors and risk groups	Patients with underlying hepatic disorder.
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Contraindications - Special warnings and precautions for use - Recommendation for liver function monitoring - Pharmacokinetic properties Additional risk minimisation measures: - Educational material to prescribers - Patient alert card
Additional pharmacovigilance activities	- Study PGL18-002, retrospective, cohort study in multinational databases - Observational study using EU registries with biomarker data e.g. Pro-EURO DILI registry and Spanish registry - Genetic analysis (HLA) study using data from EU registries with

Important identified risk **Drug Induced Liver Injury**	
	biomarker data in patients with severe DILI in registries such as Spanish registry and the Pro-EURO DILI registry. - Study PGL18-001, retrospective drug utilisation study through a chart review across four major EU countries

Important potential risk **Acute uterine bleeding requiring immediate intervention**	
Evidence for linking the risk to the medicine	Literature and press release.
Risk factors and risk groups	The small number of cases in the clinical trial programme does not allow identification of any additional risk group or risk factor (beyond the presence of fibroids). In particular, these cases did not display especially large myomas nor marked endometrium thickening during treatment. The administration of repeated intermittent treatment courses has not shown to increase that risk.
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Warnings and precautions section - Undesirable effect Additional risk minimisation measures: - No risk minimisation measures
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Important potential risk **Treatment course beyond three months**	
Evidence for linking the risk to the medicine	Few occurrences reported spontaneously during post-marketing.
Risk factors and risk groups	Patients treated with Esmya.
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Posology - Warnings and precautions section

Important potential risk **Treatment course beyond three months**	
	- Pharmacodynamic safety section Additional risk minimisation measures: - Educational material to prescribers
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Missing information **Long-term effects of prolonged treatment of the endometrium (including possible malignant changes)**	
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Posology - Warnings and precautions section Additional risk minimisation measures: - No risk minimisation measures
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Missing information **Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma**	
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Warnings and precautions section Additional risk minimisation measures: - Educational material to prescribers - Educational material to pathologists
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Missing information **Impact on surgery**	
Risk minimisation measures	Impact of Esmya may be beneficial and/or adverse effect on the subsequent fibroid surgery.

Missing information **Impact on surgery**	
	Routine risk minimisation measures: - No risk minimisation measures Additional risk minimisation measures: - No risk minimisation measures
Additional pharmacovigilance activities	PREMIUM (PGL14-001) a prospective, non-interventional study

Missing information **Use in patients with moderate to severe hepatic impairment**	
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Contraindications - Warnings and precautions section - Pharmacokinetic properties Additional risk minimisation measures: - No risk minimisation measures

Missing information **Use in patients with severe renal impairment**	
Risk minimisation measures	Routine risk minimisation measures: Information for healthcare professionals: - Posology - Warnings and precautions section Additional risk minimisation measures: - No risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Not applicable.

II.C.2 Other studies in post-authorisation development plan

- Study PGL18-002, retrospective, cohort study in multinational databases, an updated feasibility report.

Purpose of the study: to estimate the absolute and relative risk of liver injury with Esmya treatment and compare with patients with uterine fibroids not taking Esmya. The feasibility assessment of various EU national databases is ongoing, e.g. in United Kingdom (Clinical Practice Research Datalink (CPRD)). Based on the feasibility assessment result, the study will be conducted or cancelled due to lack of statistical power.

- Observational study using EU registries with biomarker data e.g. Pro-EURO DILI registry and Spanish registry.

  Purpose of the study:

  - to describe trends in biomarkers for hepatic injury following exposure to Esmya,
  - to estimate the proportion of patients exposed to Esmya that develop clinically relevant increases in biomarkers for hepatic injury,
  - to describe adherence to monitoring of biomarkers for hepatic injury,
  - to identify risk factors for DILI.

- Genetic analysis (HLA) study using data from EU registries with biomarker data in patients with severe DILI in registries such as Spanish registry and the Pro-EURO DILI registry.

  Purpose of the study: to identify patients at risk of DILI.

- PREMIUM (PGL14-001), a prospective, non-interventional study to evaluate the long-term safety of Esmya, in particular the endometrial safety, and the current prescription and management patterns of Esmya in a long-term treatment setting.

  Purpose of the study: to investigate Esmya use in a 'real world' practice.

- Study PGL18-001, retrospective drug utilisation study through a chart review across four major EU countries.

  Purpose of the study: to measure effectiveness of monitoring of liver parameters in patients treated with Esmya in regular clinical practice, also an effectiveness of adherence to modified indication and the new contraindication of underlying hepatic disorder.