LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Lutinus/Endometrin (Progesterone)

SE/H/836/01/DC

This module reflects the scientific discussion for the approval of Lutinus/Endometrin. The procedure was finalised at 20 November. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Ferring Läkemedel AB has applied for a marketing authorisation for Lutinus/Endometrin vaginal tablets 100 mg. The active substance is progesterone, a naturally occurring steroid hormone which is a member of the pharmacological class called progestogens. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Lutinus/Endometrin is presented in the form of vaginal tablets containing 100 mg of progesterone. The excipients are colloidal silicone dioxide, lactose monohydrate, pregelatinised starch, polyvinylpyrrolidone, adipic acid, sodium bicarbonate, sodium lauryl sulphate and magnesium stearate. The vaginal tablets are packed in aluminium/aluminium peel blisters.

II.2 Drug Substance

Progesterone has a monograph in the Ph Eur.

Progesterone is a white or almost white, crystalline powder or colourless crystals which is practically insoluble in water, freely soluble in ethanol, sparingly soluble in acetone and in fatty oils. The structure of progesterone has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on e.g. polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Lutinus/Endometrin vaginal tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility.
The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in the original container.

III. NON-CLINICAL ASPECTS

Since the active substance progesterone is well known, the pharmacodynamics, pharmacokinetics and toxicity of the active substance is referred to the published literature of progesterone, which was adequately covered in the Non-clinical Overview. To support the application of Lutinus vaginal tablets for the present indication, four toxicology studies were performed, which are summarised below.

The potential irritant and/or corrosive effects of Lutinus were evaluated in one dermal irritation study in rabbits. The results from that study revealed that the test article was non irritant to intact and abraded skin according to the primary irritation index, P.I.I (CPSC). There were no difference between the test article or the vehicle treated group.

Repeated dose local tolerance/toxicity studies with vaginal administration showed no systemic toxicity after 14 or 90 days of exposure in rabbits. The systemic exposure in rabbits in the highest dose group was up to 2 times the anticipated human systemic exposure at 100 mg Lutinus three times daily. The method for analysis of progesterone in plasma, including information of the method validation, was missing but was submitted with the day 106 response and found acceptable. Minimal vaginal mucosal irritation was seen in all groups including the vehicle with no effects in other parts of the reproductive tract. Histopathology of all other organs and tissues revealed no toxicological effects of treatment.

One skin sensitisation study (standard Buehler patch procedure) was conducted in guinea pigs using the test article and excipients. The interpretation of the incidence score and severity index indicated that Lutinus did not have potential to be a contact sensitizer based on the used test system.

A phase II environmental risk assessment was not deemed necessary for Lutinus, in the opinion of the RMS, based on the fact that progesterone is a known active substance and the amount progesterone derived from Endometrin/Lutinus will present a minor fraction as compared to the environmental load from the endogenous production of progesterone in fertile as well as in pregnant women. The present prescribed use in patients of Lutinus is not considered to increase the risk to the environment. However, during the procedure further studies were requested by one CMS. The applicant proposed to perform additional studies post-approval using a stepwise approach, and this was considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical development of Lutinus comprised a total of three studies including 1287 patients. These were two Phase 1 studies and one Phase 3 study.

IV.2 Pharmacokinetics

The pharmacokinetic (PK) documentation for Lutinus consists of two Phase I studies and one PK sub-study from the Phase 3 study. Progesterone is a naturally occurring steroid hormone,

present both during the normal menstrual cycle and during pregnancy. A midluteal phase serum progesterone level of 10 ng/ml (31.8 nmol/l) is seen with adequate corpus luteum function and results in an endometrium that is capable of maintaining a pregnancy. Since progesterone is a naturally occurring hormone and also available in other medicinal products, a complete characterisation of its PK properties (plasma protein binding, elimination, etc.) has not been performed in this application. No studies in special populations or interaction studies have been performed either. The lack of these data is deemed acceptable.

For the present application, pharmacokinetic data can be used to characterise the absorption and pharmacokinetic profile of progesterone in the Lutinus vaginal tablets. It is also of interest to gain knowledge about the progesterone plasma levels in comparison with available products for use on the same indication, e.g. Crinone gel. Demonstration of strict bioequivalence is not necessary, though, since clinical data are available to support efficacy and safety of Lutinus. It is, however, of importance that the progesterone plasma levels are above a certain level which is considered to be sufficiently high to achieve adequate luteal phase support, i.e. the levels produced with Lutinus should preferably not be lower compared with levels produced with Crinone. Factors that could influence the absorption of progesterone from this product are also of interest. In the pharmacokinetic studies, progesterone was analysed in plasma samples by immunological assays.

The vaginal absorption of progesterone from Lutinus vaginal tablets was investigated in two studies. The first study was a Phase I/II, randomized, open-label, pharmacokinetic, pharmacodynamic and tolerability study of Lutinus vaginal tablets in healthy pre-menopausal females between 18 and 40 years of age with an intact uterus. The subjects were down-regulated with leuprolide acetate to suppress endogenous hormonal production and estradiol was administered via transdermal patches. Forty-eight subjects were randomly assigned to receive one of five different Lutinus treatments: Lutinus 50 mg, 100 mg and 200 mg QD, Lutinus 100 mg and 200 mg BID and 10 subjects were randomly assigned to receive Progesterone IM injection 50 mg QD for 10 days.

Progesterone was absorbed from the Lutinus vaginal tablets with maximum concentrations appearing after 8-12 hours after the first application. The concentrations were lower compared with IM administration of progesterone. Vaginal tablets had a systemic bioavailability of approximately 4% to 8% compared to IM injection, based on AUC_{0-t} comparisons. The exposure to progesterone increased in a less than dose proportional manner. Steady-state appears to have been reached within 24 hours using vaginal tablets and within 48 hours using IM injections.

The other study was a randomized, open-label, pharmacokinetic study in 18 pre-menopausal female subjects between 18 and 40 years of age, with an intact uterus. The study consisted of screening, a single day of dosing, a washout period and a multiple dose (5-day) phase. Six subjects each were randomly assigned to treatments with Lutinus 100 mg BID, Lutinus 100 mg TID or Crinone 8% gel (90 mg QD). Blood samples for PK analyses were collected over a 48-hour period during the both the Single-day Phase and on Day 5 of the Multiple-dosing Phase. The PK results are shown below:

Table PK1. Mean (±SEM) Serum Progesterone Pharmacokinetic Parameters in Study 2005-08

	ENDOMETRIN 100 mg BID (N=6) Mean ± SEM	ENDOMETRIN 100 mg TID (N=6) Mean ± SEM	Crinone 90 mg QD (N=6) Mean ± SEM
Single Day of Dosing			
C_{max} (ng/mL)	17.0 ± 2.7	19.8 ± 2.9	6.82 ± 1.69
T_{max} (hr)	24.0 ± 0.0	17.3 ± 3.0	13.3 ± 2.5
AUC_{0-t} (ng•hr/mL)	88.4 ± 21.1	41.7 ± 15.5	80.9 ± 17.0
AUC_{0-24} (ng•hr/mL)	217 ± 46	284 ± 58	80.9 ± 17.0
Day 5 of Multiple Days of Dosing			
C_{max} (ng/mL)	18.5 ± 2.3	24.1 ± 2.3	14.3 ± 2.3
T_{max} (hr)	18.0 ± 3.8	18.0 ± 3.8	12.3 ± 5.2
C_{min} (ng/mL)	8.90 ± 1.85	10.9 ± 2.7	7.40 ± 1.43
T_{min} (hr)	10.7 ± 2.8	3.67 ± 1.09	6.67 ± 3.96
AUC_{0-t} (ng•hr/mL)	167 ± 24	127 ± 14	264 ± 46
AUC_{0-24} (ng•hr/mL)	327 ± 52	436 ± 43	264 ± 46
Cl/F (L/hr)	657 ± 87	846 ± 112	417 ± 95
Fluctuation Index (ratio)	0.769 ± 0.106	0.783 ± 0.137	0.701 ± 0.149
C_{min}/C_{max} (ratio)	0.464 ± 0.045	0.425 ± 0.084	0.504 ± 0.060

C_{max} and AUC_{0-24h} on the single day of dosing were higher for both Lutinus regimens (100 mg BID and TID) vs. Crinone gel 90 mg. Also after repeated dosing for 5 days, C_{max}, C_{min} and AUC_{0-24h} were higher for Lutinus in comparison with Crinone. Hence, with the recommended dose regimen (100 mg TID for Lutinus and 90 mg QD with Crinone gel) the progesterone plasma levels will be somewhat higher compared with a product already used in this indication. It is noted, though, that the progesterone daily dose needed to produce the somewhat higher levels is two- or three-fold higher for Lutinus compared with Crinone (200 or 300 mg/day vs. 90 mg/day). Reasons for the apparent difference in bioavailability between Lutinus and Crinone are unknown, but could be due to a loss of active substance from the vagina before absorption has occurred, which could be more prominent for the Lutinus vaginal tablets compared with Crinone gel. Crinone is developed with a release system which is intended to stick to the mucous membrane and release progesterone over several days. The fluctuation in plasma progesterone levels over the day was similar or slightly higher for Lutinus BID and TID compared with Crinone gel QD. The inter-individual variability in pharmacokinetic parameters was somewhat lower for Lutinus vs. Crinone.

Lutinus is only available in one strength (100 mg). Some data are available concerning dose proportionality, though, and results from both PK studies show dose dependent absorption of progesterone from Lutinus with less than dose proportional increases in exposure with increasing dose. Except for limited data from the Phase 3 study, no pharmacokinetic data beyond 10 days are available for Lutinus. The inter-individual variability in the pharmacokinetic parameters is in the range 20-40% after repeated administration of Lutinus and the variability is somewhat lower with Lutinus compared with the marketed product Crinone vaginal gel. No data on the intra-individual variability for Lutinus were presented in the dossier.

Pharmacokinetic data in the target population were available from a sub-study in the Phase 3 IVF study. The subjects received either Lutinus 100 mg BID (N=7), Lutinus 100 mg TID (N=8) or Crinone 8% gel 90 mg QD (N=12). The number of females included in each group was very small and after further division into categories of females becoming pregnant or not, only 2-4 subjects in each group were left. Thus, the results should be interpreted cautiously and were of limited value for the overall pharmacokinetic assessment. The Day 16 results in non-

pregnant subjects were fairly consistent with those in women without ovarian stimulation in Study 2005-08, though, with Lutinus TID providing the highest circulating progesterone levels and Crinone QD the lowest levels.

No studies in special populations have been performed with Lutinus. Progesterone is an endogenously produced hormone, and hence, conventional studies of the pharmacokinetics in renal impairment or hepatic impairment are not necessary.

In conclusion, even if the relative bioavailability of progesterone from the Lutinus tablet seems to be somewhat lower compared with Crinone gel, based on a comparison of daily doses (200 or 300 mg/day vs. 90 mg/day), the plasma progesterone concentrations achieved with Lutinus are higher compared with Crinone, in particular for the TID dosage. Furthermore, the fluctuation in plasma progesterone levels over the day was similar or only slightly higher for Lutinus BID and TID compared with Crinone gel QD and the inter-individual variability in PK parameters was somewhat lower for Lutinus vs. Crinone. Thus, the Lutinus tablet seems to offer an adequate way to deliver progesterone for achievement of adequate plasma levels for ART.

IV.3 Pharmacodynamics

The pharmacodynamic actions of progesterone are well-known. A dose response study with different strengths of Lutinus is discussed below.

IV.4 Clinical efficacy

The clinical efficacy part of the assessment includes one pivotal clinical trial and the pharmacodynamic part with regard to effects on the endometrium from the Phase I study discussed above.

The results of the Phase I study with regard to endometrial effects suggest that Lutinus 100 mg or 200 mg BID provide histologically typical progesterone effects in slightly fewer women than seen with 50 mg IM progesterone after down-regulation with GnRH and priming with exogenous oestrogen. Too few patients were, however, included for conclusive results. Neither do studies on endometrial progesterone concentration or progesterone/oestrogen receptor analyses contribute to the clinical evaluation of Lutinus, which is better demonstrated in the comparative clinical trials, in which pregnancy rate is the main outcome.

The main efficacy and safety data come from the pivotal study 2004-02, which was open-label, assessor-blinded and randomized and performed at 25 IVF sites in the USA. The primary objective of the study was to determine the efficacy of Lutinus administered vaginally in terms of ongoing pregnancy rates in women undergoing IVF. Ongoing pregnancy rate was defined as identification of foetal heart movements at approximately 6 weeks of gestation.

Patients undergoing IVF were randomized to a treatment group on the day of or day following oocyte retrieval. The ITT population included all women who had received at least one dose of study drug, some of whom did eventually not have an embryo transfer whereas those having had an embryo transfer were included in the efficacy population.

A serum pregnancy test was performed 14 days post embryo transfer to document biochemical pregnancy. If positive, a repeat pregnancy test was performed 2 days later. Approximately 14 days after the second positive serum pregnancy test, a transvaginal ultrasound (TVU) was performed by a blinded assessor to confirm clinical pregnancy, defined as presence of gestational sac. If clinical pregnancy was noted without foetal heart motion, the subject

continued on the study drug and a second blinded TVU was performed at approximately 6 weeks' gestation to identify foetal heart motion and thereby ongoing pregnancy.

To declare non-inferiority, the lower bound of the confidence interval was to exclude a difference greater than 10% in favour of the comparator. To adjust for multiple comparisons, Lutinus 100 mg TID versus Crinone was considered the primary comparison.

Clinical outcome
The main results in the whole efficacy population are shown in table 1.

Table 1. Ongoing, Biochemical, and Clinical Pregnancy Rates – Efficacy Population

Outcomes	**Lutinus 100mg** BID N=392	**Lutinus 100mg** TID N=390	**Crinone 8% gel** QD N=393
Ongoing Pregnancy Rate %	40	44	43
95% CI	34,9, 44,8	38,9, 48,9	38,3, 48,3
Difference between E and C	-3,5	0,6	
95% lower bound for difference	-10,4	-6,4	
Biochemical Pregnancy Rate	51	58	54
95% CI	45,4, 55,6	52,6, 62,6	48,9, 59,0
Difference between E and C	-3,4	3,7	
95% lower bound for difference	-10,4	-6,4	
Clinical Pregnancy Rate	42	47	44
95% CI	36,7, 46,6	41,9, 52,0	39,3, 49,3
Difference between E and C	-2,7	2,6	
95% lower bound for difference	-9,6	-4,3	

In table 2, the subgroup of women older than 35 or having an FSH of 10-15 IU/l is shown.

Table 2. Ongoing pregnancy rates in the subgroup women >35 and in women with FSH 10-15 IU/l – ITT population.

	Lutinus 100 mg BID	**Lutinus 100 mg TID**	**Crinone 8% gel QD**	**Difference to Crinone (95% CI lower bound for difference)**
Women >35 years of age (N)	157	157	160	Not assessed for whole age group >35
- Ongoing pregnancy N (%)	46 (29)	54 (34)	62 (39)	
Women with FSH 10-15 IU/l (N)	46	51	49	BID: -12.2% (-31.8)
- Ongoing pregnancy N (%)	16 (35)	20 (39)	23 (47)	TID: -7.7% (-27.1)

In table 3, pregnancy rates for the subgroup of subjects aged ≤ 40 year are shown. In this analysis, the data excluding the subpopulation of 36 patients aged >40 years (Lutinus 100 mg BID 12 patients, Lutinus 100 mg TID 17 patients and Crinone 7 patients) are shown. For the ongoing, biochemical and clinical pregnancy rate, these data indicate that slightly lower efficacy in patients >35 years was mainly driven by the sub-group of patients >40 years. The lower bound of the 95% CI for ongoing, biochemical, and clinical pregnancy rates in both Lutinus groups met the non-inferiority criteria of 10% in this analysis.

Table 3. Pregnancy rates for the subgroup of subjects aged ≤ 40 year – Efficacy population

Pregnancy rates	**AGE ≤40 years**		
	LUTINUS 100 mg BID	**LUTINUS 100 mg TID**	**CRINONE 8% gel QD**
Efficacy population	**(N=380)**	**(N=373)**	**(N=386)**
Ongoing pregnancy rate	41%	45%	43%
95% CI	[35.6, 45.7]	[39.4, 49.7]	[37.8 , 47.9]
Difference	-2.2%	1.8%	
95%CI LL diff	[-9.2]	[-5.3]	
Biochemical pregnancy rate	51%	58%	53%
95% CI	[45.9, 56.2]	[53.0, 63.2]	[48.3 , 58.4]
Difference	-2.3%	4.8%	
95% CI LL of diff	[-9.4]	[-2.3]	
Clinical pregnancy rate	42%	48%	44%
95% CI	[37.1, 47.3]	[42.6, 52.9]	[38.8 , 48.9]
Difference	-1.7%	3.9%	
95% CI LL of diff	[-8.7]	[-3.2]	

LL = Lower Limit (non-inferiority margin = -10%)

The conduct of the study and the choice of outcome variables are acceptable. As the non-inferiority limit was defined, the results with regard to Lutinus TID fulfilled that limit. The BID dose, however, did not quite fulfil the definition of non-inferiority with regard to the primary endpoint ongoing pregnancy. Therefore, only the TID dosage is included as a recommended dosage in the product information.

The chosen non-inferiority limit of 10% was considered slightly large. The applicant argued that a gigantic sample size (around n=6000) would have been required in order to meet, for example, a 5% NI margin and that this is a pragmatic justification of settling for a 10% NI margin. The focus should be on the results, rather than the chosen non-inferiority level, and the results for the TID dose shows a difference clearly below the 10% level. It could also be argued that the treatment with Lutinus vaginal tablets (or Crinone) is to support the possibly inadequate endogenous progesterone production and a relevant factor is that Lutinus treatment will provide adequate progesterone levels, comparable to those of other products established for luteal support, in this case Crinone. In the PK study, progesterone levels were higher with the TID dose compared to those of Crinone.

No apparent difference between test products could be seen in the group of patients in whom the prognosis for a positive outcome was greatest, i.e. in the younger age group and among women with an adequate ovarian reserve. However, the data for the subgroups aged >35 gave a visual impression that Lutinus is inferior to Crinone. In particular, the ongoing pregnancy rate with the lower (BID) dose of Lutinus appears inferior to that of Crinone.

It is well established that age is the important predictor of success in natural cycles as well as in ART and poorer outcomes are expected with increasing age. The Applicant argues that the appearance of lower efficacy in the subgroup over 35-40 and in women with low ovarian reserve is a chance finding and appears to be caused by a poorer outcome in women over 40 years. This is illustrated by the results shown in Table 3, i.e. the pregnancy rates for the subgroup of subjects aged ≤ 40 year. The fact that the PK studies did not show lower progesterone levels in women treated with Lutinus vaginal tablets as compared to those treated with Crinone, supports the finding of clinical non-inferiority across all age groups. Even if no subgroup analysis of PK data with respect to age or FSH levels has been possible to perform on available data, it is not likely that the absorption would differ to a relevant extent in these subgroups compared with the overall population.

It is acknowledged that the studies were powered to show non-inferiority for the whole group rather than in each individual subgroup. For the whole group, including age range up to 42 years, non-inferiority was demonstrated for the TID dose, which is therefore the recommended dose.

The most adequate duration of luteal support in ART still remains to be established. Emerging evidence suggests that luteal support in ART is justified until about the time of diagnosis of pregnancy, which usually occurs around 2 weeks after embryo transfer, but probably no longer as longer duration of luteal support has not been shown to improve pregnancy rate. However, it has long been common practice among many clinicians to continue luteal support beyond the detection of a foetal heart beat or even to gestational week 10 - 12, presumably to be sure that the placenta by then will provide sufficient progesterone.

Even if most data supporting a concern about an increased risk of hypospadia in male foetuses come from studies with synthetic progestogens, the duration of progesterone treatment should be as short as possible. It is proposed that the duration recommendation for Lutinus follows that of Crinone, which is used for the same indication and provides plasma progesterone levels in the same range as Lutinus. Crinone is recommended for a total duration of 30 days. In the pivotal clinical trial, treatment with both Lutinus and Crinone continued for 10-12 weeks. Therefore, Lutinus has not been tested for shorter duration. However, it seems acceptable that either treatment is given to provide luteal support with progesterone and there is little evidence of a clinically significant difference between the products in the provision of progesterone. Since the PK data support a similar, or even higher, exposure to progesterone for Lutinus, there is no reason to doubt that there would be any concerns with a 30-day treatment with Lutinus, although this was not actually used in the pivotal study.

IV.5 Clinical safety

Progesterone supplementation is a necessary part of an ART programme, in which the normal ovarian function is inhibited. The progesterone administration, which tries to copy the normal corpus luteum function, does not infer any particular risks or safety concerns.

A total of 31 subjects experienced serious adverse events, all of which were considered by the Investigator to be not related to study drug. Although 7 of the 9 subjects who discontinued study drug due to adverse events had used Lutinus TID, most discontinuations were classified as unrelated. There were no differences between groups in any of the laboratory parameters investigated.

Apart from more withdrawals for AEs in the Lutinus TID group, there was little apparent difference between groups. Few of the reported AEs were considered related to the test products. A variety of vulvovaginal symptoms were considered related to treatment. The number of such AEs was low and there was no apparent difference between groups, although Crinone was administered QD in contrast to Lutinus which was given BID or TID.

Concerns were raised during the procedure due to the higher frequency of birth defects observed in the Lutinus TID group compared with the Crinone group. This issue was partly related to the higher systemic exposure of progesterone observed with administration of Lutinus TID in comparison with Crinone administered once daily. The rate of foetal abnormality was not higher than expected in the general population in any of the treatment arms and the observed difference may be a chance finding in a limited patient population. The applicant has, however, described the rate of birth defects in section 4.6 of the SmPC and included assessments of birth defects and pregnancy outcomes in the PSURs and in the Risk Management Plan.

IV.6 Discussion on the clinical aspects

Human pharmacokinetic data have shown that progesterone is absorbed after vaginal administration of Lutinus with steady state plasma concentrations of progesterone are reached within approximately 24 hours. With the proposed dose regimen (100 mg TID for Lutinus and 90 mg QD with the marketed product Crinone gel) the progesterone plasma levels produced with Lutinus were somewhat higher compared with a product already used in this indication. The fluctuation in plasma progesterone levels over the day was similar or only slightly higher for Lutinus TID compared with Crinone gel QD and the inter-individual variability in PK parameters was somewhat lower for Lutinus vs. Crinone. Thus, the Lutinus vaginal tablet seems to offer an adequate way to deliver progesterone for achievement of adequate plasma levels for ART.

The clinical efficacy and safety of Lutinus was supported by one phase 3 trial, with acceptable study design and choice of outcome variables. Lutinus BID and TID was compared with Crinone vaginal gel administered QD.

To declare non-inferiority, the lower bound of the confidence interval was to exclude a difference greater than 10% in favour of the comparator. A non-inferiority limit of 10% may be considered large. A gigantic sample size (around n=6000) would have been required in order to meet, for example, a 5% non-inferiority margin and that this is a pragmatic justification of settling for a 10% non-inferiority margin. Additionally, the focus should be on the results, rather than the chosen non-inferiority level, and the results for the TID dose show a difference clearly below the 10% level. As the non-inferiority limit was defined, the results with regard to Lutinus TID fulfilled that limit.

In the clinical studies, both products, Lutinus and Crinone, were given during a period of 10-12 weeks. As clinical practice with regard to duration of treatment is changing as a consequence of new data suggesting no improved outcome with luteal support beyond the time of a positive pregnancy test, it is proposed that the duration recommendation follows that of Crinone which is 30 days. Lutinus has not been tested for shorter duration. However, it seems acceptable that either treatment is given to provide luteal support with progesterone and there is little evidence of a clinically significant difference between the products in the provision of progesterone. Since the PK data support a similar, or even higher, exposure to progesterone for Lutinus, there is no reason to doubt that there would be any concerns with a 30-day treatment with Lutinus, although this was not actually used in the pivotal study. This is further justified by a concern that long exposure of progesterone to the foetus may increase the risk of teratogenicity.

From a clinical safety perspective, no major concerns have been identified. Progesterone supplementation is a necessary part of an ART programme, in which the normal ovarian function is inhibited. Compliance may be an issue for a product to be administered three times daily. However, since patients involved in ART are very motivated, compliance is not deemed to be of concern and specific post-authorisation surveillance was not considered necessary.

Some concerns were raised due to the higher frequency of birth defects observed in the Lutinus TID group compared with the Crinone group. The rate of foetal abnormality was not higher than expected in the general population in any of the treatment arms and the observed difference may be a chance finding in a limited patient population. The applicant has, however, described the rate of birth defects in section 4.6 of the SmPC and included assessments of birth defects and pregnancy outcomes in the PSURs and in the Risk Management Plan.

In conclusion, Lutinus 100 mg tablet given vaginally three times daily does not appear to be inferior in comparison with an available alternative product for progesterone administration with the same indication, Crinone vaginal gel given once daily. The duration of Lutinus

treatment should be the same as recommended for Crinone. Some patients may find the application of a vaginal gel bothersome and uncomfortable, and Lutinus is considered to constitute a valuable alternative for the administration of progesterone for luteal support in ART. Therefore, the benefit risk profile for Lutinus vaginal tablet 100 mg TID is considered positive.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Lutinus/Endometrin vaginal tablets 100 mg was recommended for approval.

Since additional data related to the environmental risk assessment for Lutinus/Endometrin were requested during the procedure, the applicant has agreed to perform additional studies as follow-up measures.

VI. APPROVAL

The Decentralised procedure for Lutinus/Endometrin vaginal tablets 100 mg was successfully finalised on 20 November 2009.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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