COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dydrogesteron Adalvo 10 mg film-coated tablets (dydrogesterone)

NL/H/5824/001/DC

Date: 24 October 2025

This module reflects the scientific discussion for the approval of Dydrogesteron Adalvo 10 mg film-coated tablets. The procedure was finalised on 6 February 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dydrogesteron Adalvo 10 mg film-coated tablets, from Abbott B.V.

The product is indicated for:

- Irregular menstrual cycles
- Endometriosis
- Dysmenorrhoea
- Secondary amenorrhoea
- Dysfunctional uterine bleeding
- Infertility as a result of corpus luteum insufficiency
- Support of the luteal phase as part of an ART (Assisted Reproductive Technology) procedure
- Threatened miscarriage as a result of progesterone deficiency
- Habitual miscarriage as a result of progesterone deficiency

As a cyclical addition to oestrogen replacement therapy in postmenopausal women with an intact uterus for prevention of endometrial hyperplasia.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Duphaston 10 film-coated tablets 10 mg (formerly Dydrogesterone Lotus) which has been registered in the Netherlands via national procedure (NL RVG 05619) since 31 May 1968.

The concerned member states (CMS) involved in this procedure were Belgium, France, Germany, Ireland, Italy, Poland, Portugal and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Dydrogesteron Adalvo is a film-coated tablet. Each tablet contains as active substance 10mg dydrogesterone. The tablets are round, biconvex, white to off-white, debossed with "711" on one side and plain on another.

The excipients are:
Tablet composition: lactose monohydrate, pregelatinized maize starch, hypromellose 2910 (E464), colloidal anhydrous silica and magnesium stearate (E572)

Tablet coating: lactose monohydrate, hypromellose (E464), titanium dioxide (E171) and triacetin (E1518)

The film-coated tablets are packed in polyvinyl chloride/ polyvinylidene chloride – aluminium (PVC/PVDC-Alu) blisters.

II.2 Drug Substance

The active substance is dydrogesterone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is white or almost white, crystalline powder. It is practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96%). Dydrogesterone has only one polymorph, characteristic peaks and X-ray diffraction (XRD) spectra are provided. Its specific optical rotation is controlled.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEP, with additional requirements for particle size. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
The active substance is stable for 30 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions are explained.
A conventional wet granulation process was selected to ensure the uniform distribution of the drug. Hence, considering low dose and low particle size of the drug substance, a wet granulation was selected as the method of manufacture for generic product development.

Two pilot-scale bioequivalence (BE) studies were conducted with changes in the formulation to the ratio lactose monohydrate and pre-gelatinised starch. Based on the pilot BE-study outcomes the formulation and the manufacturing process were finalised. The final formulation was used in the bioequivalence study.
To support the results obtained in the BE-studies, the MAH has performed comparative dissolution studies. Also, study data are provided to support the proposed particle size for the active substance. These data are deemed sufficient.
Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the following steps: dry blending, wet granulation, drying, sieving, dry blending of granulate with extra granular excipients, final blending, compression and film-coating. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scale batches at the lower batch size. The product is manufactured using conventional manufacturing techniques. Process validation for upper limit of the full scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph. Eur. requirements. Most specifications are acceptable. Based on the data provided in the pharmaceutical development section, additional tests and limits have been adopted for magnesium stearate.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, water content, identification, assay, uniformity of dosage units, dissolution, related substances and microbial quality.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life tests and limits are identical.
An adequate nitrosamines risk evaluation report has been provided. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided on three batches of the proposed lower scale of the commercial scale, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three lower scale production batches stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months). in accordance with applicable European guidelines. No changes were observed at long term or accelerated conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.
On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: “Store below 25°C”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dydrogesteron Adalvo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dydrogesteron Adalvo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Duphaston 10 which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dydrogesterone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides two pivotal bioequivalence studies (C1B02339, n=56 and C1B00662, n=60) and one pilot study C1B00805, n=16), which are

discussed below. The MAH also provided pooling data of the three studies as a supportive additional sensitivity analysis.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Dydrogesteron Adalvo 10 mg film-coated tablets (Abbott B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Duphaston 10 film-coated tablets 10 mg (Abbott B.V., the Netherlands).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution study results and composition. Dissolution profiles were performed in 0.1N HCL, in acetate buffer at pH 4.5 and in phosphate buffer at pH 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies
Study 1: (C1B02339), pivotal, n=56
Design
A single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate, crossover bioequivalence study was carried out under fasted conditions in 60 healthy post-menopausal female subjects, aged 42-61 years. Each subject received a single dose (10 mg) of one of the two dydrogesterone formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 8, 12, 24, 36, 48 and 72 hours hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
60 Subjects enrolled in the study. One subject withdrew consent for Period 2 due to personal reasons, but was included in the list of completed subjects as she completed three periods of the study. Four subjects were discontinued from the study for not reporting to the facility for subsequent periods of the study. In total 56 subjects were eligible for pharmacokinetic analysis. The intra-subject variability on C_{max} for the reference product was 51.98%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dydrogesterone, 10 mg under fasted conditions.

Treatment N=56	**AUC_{0-t} (pg.h/ml)**	**$AUC_{0-\infty}$ (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**
Test	14831 ± 4622	16807 ± 5128	4149 ± 2122	1.00 (0.50 - 5.02
Reference	16807 ± 5128	16674 ± 5408	3798 ± 2266	1.00 (0.50 - 5.00)
***Ratio (90% CI)**	1.02 (0.99 – 1.04)	--	1.12 (1.02 – 1.23)	N.A.

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: (C1B00662), pivotal, n=60

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, balanced, crossover bioequivalence study was carried out under fasted conditions in 60 healthy post-menopausal female subjects, aged 40-63 years. Each subject received a single dose (10 mg) of one of the two dydrogesterone formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

60 Subjects enrolled in the study. All 60 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dydrogesterone, 10 mg under fasted conditions.

Treatment N=60	**AUC_{0-t} (pg.h/ml)**	**$AUC_{0-\infty}$ (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**
Test	13568 ± 4085	15374 ± 4344	2673 ± 1017	1.0 (0.5 - 5.0)
Reference	14037 ± 4044	15796 ± 4154	3328 ± 1854	1.0 (0.5 - 5.0)
***Ratio (90% CI)**	0.96 (0.93 – 0.99)	--	0.84 (0.75 - 0.95)	N.A.

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3: (C1B00805), pilot, n=16

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, balanced, crossover bioequivalence study was carried out under fasted conditions in 16 healthy post-menopausal female subjects, aged 40-58 years. Each subject received a single dose (10 mg) of one of the two dydrogesterone formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

16 Subjects enrolled in the study. All 16 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dydrogesterone, 10 mg under fasted conditions.

Treatment N=16	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	10500 ± 3765	1200 7± 4220	2110 ± 940	1.0 (0.5 - 4.02)
Reference	10559 ± 3544	2082 ± 4055	2361 ± 998	1.38 (0.50 - 3.50)
***Ratio (90% CI)**	0.99 (0.92 – 1.07)		0.88 0.71 - 1.09	

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
Results of the pivotal study C1B00662 and the pilot study (C1B00805) both demonstrated that 90% confidence intervals calculated for C_{max} are **not** within the bioequivalence acceptance range of 0.80 – 1.25.
Results of the first pivotal study C1B02339 demonstrated that 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25.
Upon request, the MAH provided pooling of studies as a supportive additional sensitivity analysis, which is in line with ICH M13A (and associated Q&A 4.1). For parameter C_{max} a significant study-by-treatment effect is observed between both pivotal studies. This is also apparent from the C_{max} ratios (90% CI) of the individual studies reported.

Eventually, the design study (C1B02339) is considered the leading study, as this study was specifically designed to overcome the issue of high variability, which was observed in the first two-way crossover study (C1B00662). The leading study confirmed the acceptability of the overall evidence provided. In addition, the widened acceptance range for C_{max}, based on 51.98% intra-subject variability on C_{max} for the reference product (study C1B02339), covered the observed 90% CI of the T/R C_{max} ratio in both individual studies C1B0062 and C1B02339. It is therefore accepted that also the totality of evidence supports bioequivalence between the test and reference product.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to

Dydrogesteron Adalvo. At the time of approval, the most recent version of the RMP was version 0.1 with final sign off 6 March 2024.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Duphaston 10. The MAH demonstrated with three (two pivotal, one pilot) bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management was adequately addressed. This generic medicinal product can be used instead of the reference product. For further discussion on the demonstration of bioequivalence, see section VI.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dydrogesteron Adalvo 10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Duphaston 10, film-coated tablets 10 mg. Duphaston 10 is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

This procedure was discussed in a Break-Out Session (BOS) and in the CMDh. The following concerns were discussed:

On 8 November 2024, a Break-Out Session (BOS) with the RMS NL, two CMSs and the MAH was organised as there was disagreement between the RMS and one CMS regarding the demonstration of bioequivalence by the submitted BE-studies. The objecting CMS argued that the large differences between the BE studies indicate that at least one of the studies was either conducted improperly or compromised by other factors, and it remains unclear which of the studies should be valid. Therefore bioequivalence cannot be concluded.
The RMS agreed with the CMS that the difference in C_{max} between both pivotal studies is atypical from a statistic perspective. However, the RMS considered the data provided still acceptable due to the following reasons: there were no triggers for inspection during the assessment of both pivotal studies, the batches used were representative from a quality perspective, more weight was assigned to study C1B02339 due to more observations compared to study C1B00662, and the intra-subject variability on the C_{max} for the reference product of 52% as calculated in the replicate study is considered reliable. According to the RMS, the high variability in C_{max} indicated that acceptance range widening for the 90% CI of T/R C_{max} ratio is justified. The CMS did not agree with this conclusion.

The procedure was referred to the CMDh for further discussion on the issue of bioequivalence. The discussion in the CMDh took place in the meeting of January 2025. There was an oral explanation with the MAH. The MAH explained their development program and confirmed that the bio batches of both pivotal studies are representative, acceptable batches produced by the same manufacturing process in advance of the first pivotal study. No evidence was found which suggests that the second study has low credibility. Also, there was no signal detected which could account for the different outcome.
The CMDh took a trend vote with a majority in agreement with the position of the RMS.

After the discussion at the CMDh, the positive position of the RMS NL was supported by all CMSs, especially by the argument of potential widening of the reference range.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dydrogesteron Adalvo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 February 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-