LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Audera
(estradiol valerate, dienogest)

SE/H/2500/01/DC

This module reflects the scientific discussion for the approval of Audera. The procedure was finalised on 2024-12-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Audera Film-coated tablet.

The active substances are estradiol valerate and dienogest. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Audera 3 mg estradiol valerate (2 dark yellow tablets); 2 mg estradiol valerate and 2 mg dienogest (5 pink tablets); 2 mg estradiol valerate and 3 mg dienogest (17 light yellow tablets); 1 mg estradiol valerate (2 brown tablets); placebo (no active ingredient) (2 white tablets), film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following as concerned member states (CMS):
SE/H/2500/01/DC: CMS: CZ, DE

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Qlaira, film-coated tablet authorised in Sweden since 2009, with Bayer AB as marketing authorisation holder.

The reference product used in the bioequivalence studies are Qlaira (estradiol valerate/dienogest) 2 mg/3 mg, and Qlaira (estradiol valerate), 3 mg, film coated tablets from the German market with Jenapharm GmbH & Co. KG as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life claimed in the Summary of Product Characteristics, section 6.3.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of estradiol valerate + dienogest are well known. As estradiol valerate + dienogest are widely used, well-known active substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The present procedure (which comprises several shared procedures) initiated before 1st Sept 2024 when the 2024 CHMP ERA GL became active. As such, a 2006 CHMP ERA GL based generics waiver of Phase I based on no increase in total exposure is permissible and theoretically possible. An overview of IQVIA consumption data back to 2013 showed a reduction in all concerned states except Italy and Poland which demonstrated an increase in consumption between 2013 and 2023. Italy has increased its tablet consumption from 1.217.418 packages (Q3 2013) to 2.237.959 (Q3 2023) and Poland has increased its consumption from 449.142 packages (Q3 2013) to 613.875 packages (Q3 2023). As such, a 'generics waiver' is acceptable only for procedures *without* Italy or Poland. For those including Italy and Poland, a committment has been provided to submit an ERA (based on Letter of Access documentation from e.g., the MAH for the reference product [Qlaira] or otherwise) at the lastest within 2 yeards after approval of the ongoing procedure. Presently, no final conclusion can be drawn on the environmental risk from the two active substances for those procedures.

Conclusions
While there are no objections to approval of the proposed product from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application, the applicant has conducted two bioequivalence studies; one study comparing the estradiol valerate/dienogest to the originator product Qlaira (estradiol valerate/dienogest) and one study comparing the estradiol valerate to the originator product Qlaira (estradiol valerat).

Pharmacokinetic properties of the active substance
Dienogest
Absorption: Orally administered dienogest is rapidly and almost completely absorbed. Maximal serum concentrations of 90.5 ng/ml are reached at about 1 hour after oral administration of the tablet containing 2 mg estradiol valerate + 3 mg dienogest. Bioavailability is about 91 %.

Concomitant food intake has no clinically relevant effect on the rate and extent of dienogest absorption.

Elimination: The plasma half-life of dienogest is approximately 11 hours.

Linearity: The pharmacokinetics of dienogest is linear within the dose range 1-8 mg.

Estradiol valerate

Absorption: After oral administration estradiol valerate is completely absorbed. Cleavage to estradiol and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. This gives rise to estradiol and its metabolites estrone and estriol. Maximal serum estradiol concentrations of 70.6 pg/ml are reached between 1.5 and 12 hours after single ingestion of the tablet containing 3 mg estradiol valerate on Day 1.

Biotransformation: The valeric acid undergoes very fast metabolism. After oral administration approximately 3% of the dose is directly bioavailable as estradiol. Estradiol undergoes an extensive first-pass effect and a considerable part of the dose administered is already metabolized in the gastrointestinal mucosa. Together with the presystemic metabolism in the liver, about 95 % of the orally administered dose becomes metabolized before entering the systemic circulation. The main metabolites are estrone, estrone sulfate and estrone glucuronide.

Elimination: The plasma half-life of circulating estradiol is about 90 min. After oral administration, however, the situation differs. Because of the large circulating pool of estrogen sulfates and glucuronides, as well as enterohepatic recirculation, the terminal half-life of estradiol after oral administration represents a composite parameter which is dependent on all of these processes and is in the range of about 13-20 h.

Study C22123 (estradiol valerate/dienogest)

Methods

This was a single-dose, two-way crossover study conducted in 56 healthy volunteers, comparing estradiol valerate/dienogest 2 mg/3 mg, tablet with Qlaira (estradiol valerate/dienogest), 2 mg/3 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of dienogest and total estrone were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 7th November 2022 and 25th January 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 and Table 2 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dienogest, n=54

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1490 ± 296**	**88.48 ± 17.13**	**1.258 (0.50 - 7.0)**
Reference	**1472 ± 316**	**91.42 ± 16.40**	**1.00 (0.50 - 4.00)**
***Ratio (90% CI)**	**101.78 (99.58 - 104.01)**	**96.25 (92.55-100.11)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for total estrone, n=54, corrected baseline.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**12.582 ± 6.107**	**1.629 ± 0.611**	**1.50 (0.50 - 6.00)**
Reference	**12.363 ± 6.152**	**1.608 ± 0.658**	**1.000 (0.50 - 7.00)**
***Ratio (90% CI)**	**102.80 (98.59 - 107.19)**	**102.99 (94.27 - 112.52)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study C22124 (estradiol valerate)

Methods

This was a single-dose, two-way crossover study conducted in 56 healthy volunteers, comparing estradiol valerate 3 mg, tablet with Qlaira (estradiol valerate), 3 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of total estrone were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 11th May 2023 and 30th July 2023.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for total estrone, n=55, corrected baseline.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**19.638 ± 7.625**	**2.638 ± 1.153**	**1.50 (0.50 - 5.00)**
Reference	**18.808 ± 7.343**	**2.493 ± 1.321**	**1.50 (0.50 - 6.00)**
***Ratio (90% CI)**	**103.53 (98.59 - 108.71)**	**107.94 (99.41 - 117.20)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of estradiol valerate 1 mg and estradiol valerate/dienogest 2 mg/2 mg.

Discussion and overall conclusion

The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

In accordance with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) the general recommendation evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The main reason to ask for evaluation of bioequivalence based upon measured concentrations of the parent compound is that C_{max} of the parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite. However C_{max} of the parent compound may in this case not be the most sensitive parameter to detect formulation differences. After oral administration of therapeutic doses, estradiol plasma concentrations are very low and it is not possible to distinguish between endogenous estradiol, synthetic estradiol directly absorbed from the tablet and back converted estradiol that originated from the synthetic estradiol. Given the fast and almost complete metabolism, it is not possible to distinguish a first absorption peak for estradiol. The C_{max} peak is probably influenced by other factors like e.g. estradiol back-converted from estrone. The plasma profile of baseline-corrected estrone is characterized by an earlier, higher and more distinct peak and probably reflects the performance of the formulation better than estradiol C_{max}. Hence, the assessment of bioequivalence has been based on the total estrone.

Based on the submitted bioequivalence studies, estradiol valerate/dienogest 2 mg/3 mg and estradiol valerate, 3 mg, tablets are considered bioequivalent with Qlaira (estradiol valerate/dienogest), 2 mg/3 mg, tablet and Qlaira (Estradiol Valerate), 3 mg, tablet.

In response to questions raised, the applicant submitted data for estradiol and estrone showing that there is not less than proportional increase in AUC with increasing dose in the range of 1-3 mg. The pharmacokinetics of dienogest is linear within the dose range 1-8 mg. Thus, from a pharmacokinetic perspective it is sufficient to study the highest strength.

The results of studies C22123 (estradiol valerate/dienogest) and C22124 (estradiol valerate) with 2 mg/3 mg and 3 mg formulation **can** be extrapolated to the other strengths; estradiol valerate/dienogest 2 mg/2 mg and estradiol valerate 1 mg according to conditions in the Guideline on the investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1, section 4.1.6.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The Applicants of Audera have 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 the product.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Venous thromboembolism (VTE) • Arterial thromboembolism (ATE)
Important potential risks	• None
Missing information	• None

The summary of safety concerns is based on the latest HaRP assessment report published at the CMDh website for dienogest/ethinylestradiol (which is also in compliance with the Summary of safety concerns in the latest approved RMP version of the reference product Qlaira).
The proposed summary of safety concerns is endorsed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Of note: The reference product has non-conditioned follow-up questionnaires for spontaneous case reports of VTEs and ATEs. Corresponding follow-up questionnaires are not proposed for Audera, which can be agreed for a generic application.

Part V Risk minimisation measures
Summary table of pharmacovigilance activities and risk minimisation measures per safety concern:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Venous thromboembolism	Routine risk minimisation measures: SmPC sections "4.1 Therapeutic indications", "4.4 Special warnings and precautions for use", "4.6 Fertility, pregnancy and lactation" and "4.8 Undesirable effects". *Pil sections "2 2. What you need to know before you take Estradiol valerate/dienogest" and "4 Possible side effects"* Contraindication in SmPC section "4.3 Contraindications" Warning in case of appearance of conditions or risk factors, and recommendations for the early detection of thrombboembolism is included "4.4 Special warnings and precautions for use" How to detect early signs and symptoms of thrombboembolism is included in PL, section 2. - Prescription only medicine. Additional risk minimisation measures: Checklist for prescribers Patient information card	None
Arterial thromboembolism	Routine risk minimisation measures: SmPC sections "4.4 Special warnings and precautions for use" and "4.8 Undesirable effects". PL section 4	None

	Contraindication in SmPC section "4.3 Contraindications" Warning in case of appearance of conditions or risk factors, and recommendations for the early detection of thromboembolism is included "4.4 Special warnings and precautions for use How to detect early signs and symptoms of thromboembolism is included in PL, section 2. - Prescription only medicine. <u>Additional risk minirnisation rneasures:</u> Checklist for prescribers Patient information card	

Additional Risk minimisation measures (RMMs), ie checklist for prescribers and patient information card, are proposed. Objective: To inform the professionals and women on the risks of thromboembolism associated with CHCs and to help remind them of the most important risk factors to consider when discussing the most suitable contraceptive method. Also, for women to be aware of the risks and remain vigilant for signs and symptoms thromboembolic events. This is in accordance with the latest HaRP assessment report for dienogest/ethinylestradiol and is thus endorsed.
Draft versions of the Checklist for prescribers and the Patient information card are provided in the RMP Annex 6, and these are considered adequate. However, final lay-out and wording of the Checklist for prescribers and the Patient information card will be agreed with NCAs prior to launch of the product.

<u>Part VI Summary of the RMP</u>
The Summary of the RMP is endorsed.

<u>Conclusion RMP assessment</u>
The submitted Risk Management Plan, **version 0.1**, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 results show that the package leaflet 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

The quality of Audera is found adequate. There are no objections to approval of Audera from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

See section VII.3 for conditions pursuant to Article 21a.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
To submit an ERA via variation application following the current ERA guidance or to provide a letter of access from the reference product (Qlaira) owner to share ERA data. The ERA from the reference product owner will be revised according to the current ERA guidance if applicable.	2 years after End of Procedure

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  To encourage safe prescribing of combined hormone contraceptives (CHCs), to inform about extent and characteristics of VTE and ATE risk with CHCs and to promote early diagnosis, treatment, and prevention of complications from VTE and ATE, education material to prescribers and patients should be provided.

  Draft versions of Prescriber´s checklist and Patient information card are enclosed in the RMP Annex 6. The final lay-out, wording and distribution plan shall be agreed with NCAs prior to launch of the product.

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

VII. APPROVAL

The decentralised procedure for Audera, Film-coated tablet was positively finalised on 2024-12-11.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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