Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Oestradiol/Norethisterone acetate

Proprietary Product Name: Kliovance Low

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

January 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Strength
Decision:	Rejected
Date of Decision:	12 August 2011
Active ingredient(s):	Oestradiol Norethisterone acetate
Product Name(s):	Kliovance Low
Sponsor's Name and Address:	Novo Nordisk Pharmaceuticals Pty Ltd Level 3, 21 Solent Circuit Baulkham Hills NSW 2153
Dose form(s):	Film coated tablet
Strength(s):	Oestradiol: 0.5 mg Norethisterone acetate: 0.1 mg
Container(s):	Dial dispenser pack
Pack size(s):	28 tablets
Route(s) of administration:	Oral
Dosage:	One tablet daily

Product Background

Kliovance, containing 1 mg oestradiol (E2) as hemihydrate and 0.5 mg norethisterone acetate (NETA) is a continuous hormone replacement therapy that is currently registered for the treatment of menopausal symptoms related to oestrogen deficiency. It is also registered for the prevention of postmenopausal bone mineral density loss. The following text is included in the indication: "When prescribed solely for the prevention of postmenopausal bone mineral density loss, therapy should only be prescribed for women who are at high risk of osteoporosis and future fracture and who are intolerant of, or contraindicated for, non-oestrogen products approved for prevention of osteoporosis. Life style modifications and the risk benefit profiles of Kliovance should be taken into careful consideration and discussed with the patient, to allow the patient to make an informed decision prior to prescribing. See Precautions and Dosage and Administration".

This AusPAR describes the evaluation of an application to register a new strength of Kliovance, Kliovance Low, which contains 0.5 mg oestradiol and 0.1 mg norethisterone acetate. In continuous combined hormone preparations of this type the oestradiol component provides pharmacological treatment of menopausal symptoms, that is, hot flushes, while norethisterone acetate is added to reduce the risk of oestrogen induced endometrial hyperplasia. The 'new strength' contains half of the oestradiol and one fifth of the norethisterone acetate contained in the registered product Kliovance. Extrapolation of efficacy and safety cannot be made from Kliovance data.

The proposed indication is for:

Short term treatment of menopausal symptoms related to oestrogen deficiency in women more than one year after menopause.

The proposed dosage is that one tablet should be taken orally once a day without interruption, preferably at the same time each day. Kliovance Low should be used primarily in women after one year of amenorrhoea.

Regulatory Status

Kliovance tablets were registered in Australia in 1999 as a combination of 17β-oestradiol hemihydrate 1 mg and norethisterone acetate 0.5 mg.

The Kliovance Low formulation, named *Activelle Low* or *Activella* has been approved in the USA on 28 December 2006, Canada on 18 April 2008, the European Union (EU) on 11 September 2008 and Switzerland on 25 March 2010.

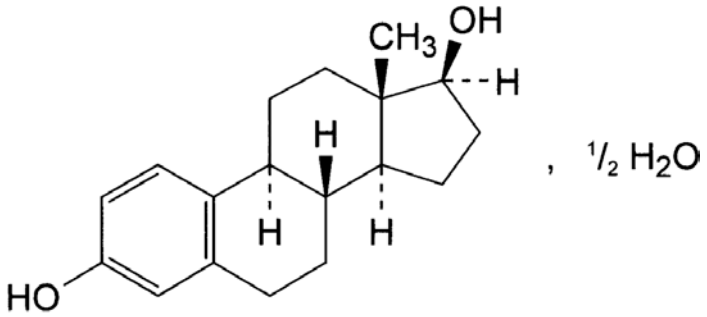
The indication in all of these countries is for:

Menopausal symptoms

II. Quality Findings

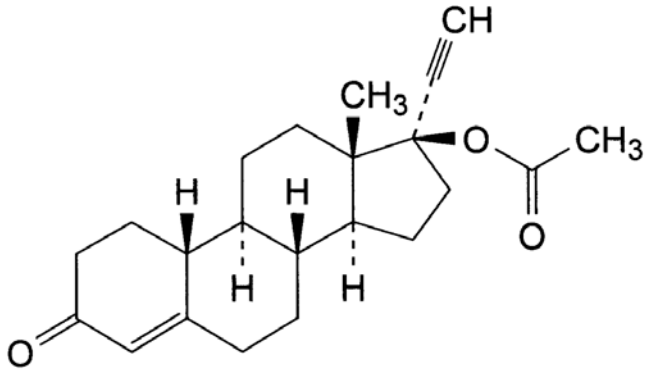
Drug Substance (active ingredient)

Oestradiol and norethisterone acetate are synthetic steroids.[1] Both have multiple chiral centres but the drugs used are single enantiomers. Norethisterone acetate is an ester, not a salt. Tablets are formulated with the hemihydrate (that is,½H_2O) of oestradiol:



oestradiol hemihydrate

(or estradiol hemihydrate)



norethisterone acetate

(norethindrone acetate in USA)

Both drugs are practically insoluble in water, so they are micronised before tablet manufacture. Both are the subject of British Pharmacopoeia (BP) and United States

[1] The international non-proprietary name (INN) of oestradiol is oestradiol. It is planned to move to the INN in Australia in the next few years.

Pharmacopeia (USP) monographs. Control of the drug substances was considered acceptable.

Drug Product

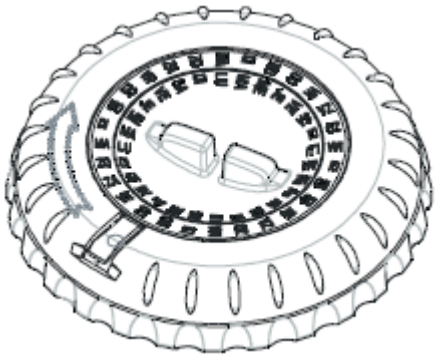
There are many oestradiol products registered in Australia. There are various registered norethisterone as well as norethisterone acetate products.

Kliogest containing oestradiol 2 mg and norethisterone acetate 1 mg tablets are currently registered by Novo Nordisk, and are also used as a component in Trisequens. Kliovance containing oestradiol 1 mg and norethisterone acetate 0.5 mg tablets are currently registered by Novo Nordisk. The proposed product is thus a new, lower strength tablet with a different ratio of the steroids:

	oestradiol	norethisterone acetate	ratio
Kliogest	2 mg	1 mg	2
Kliovance	1 mg	0.5 mg	2
Kliovance Low	*0.5 mg*	*0.1 mg*	*5*

The proposed Kliovance Low tablets are 6 mm in diameter, white, film coated and engraved with 'NOVO 291' and the sponsor's logo. The formulation is conventional. Clinical trials used the proposed commercial formulation (as well as a related 0.5 mg oestradiol/0.25 mg norethisterone acetate tablets).

Kliovance Low tablets are presented in a dial dispenser pack (like Kliogest and Trisequens). This holds 28 tablets. The centre dial is turned either by the fingers or by use of a coin to set the day of the week. After a tear-off tab is removed, a tablet can be tipped through a slot in the lid. The lid can only be turned after the tablet has been removed. The centre dial is printed with 28 consecutive weekdays.



The tablets are the subject of both a BP monograph (*Estradiol and Norethisterone Acetate Tablets*) and a USP monograph (*Estradiol and Norethindrone Acetate Tablets).*

The sponsor did not provide sufficient stability data to support the proposed shelf life. A shorter shelf life has thus been set in keeping with adopted guidelines.

The chemistry and quality control aspects of the finished product were otherwise acceptable.

Biopharmaceutics

The bioavailability study ALD-1640 compared the bioavailability of:

- the proposed 0.5 mg oestradiol + 0.1 mg norethisterone acetate tablets (dose: 2 tablets);
- the registered Kliovance (1 mg oestradiol + 0.5 mg norethisterone acetate tablets) (dose: 1 tablet);
- and an intermediate 0.5 mg oestradiol + 0.25 mg norethisterone acetate formulation (dose: 2 tablets).

Thus there were different norethisterone doses: 0.2 or 0.5 mg/day). The study was an open, three way crossover trial in 24 healthy, postmenopausal women. Doses were separated by 3 week wash out periods.

Blood samples were collected pre-dose for 1.5 hours and then over 72 hours after dosing and analysed for oestradiol, oestrone, oestrone sulfate and norethisterone. The acetate ester is rapidly cleaved *in vivo*, so that only norethisterone can usefully be measured. Baseline correction was made for the endogenous species.

Bioequivalence is most directly assessed with oestradiol and norethisterone. Both the proposed 0.5 + 0.1 mg tablet and the 0.5 + 0.25 mg tablet were bioequivalent to the registered Kliovance 1 + 0.5 mg tablet (with dose correction for norethisterone) as shown in Table 1:

Table 1: Bioequivalence data

oestradiol (baseline corrected)		**[0.5+0.1] vs *Kliovance***	[0.5+0.25] vs *Kliovance*
90% confidence intervals (CI)	C_{max}	**90.1 - 113.6%**	85.1 - 107.3%
	$AUC_{0-\infty}$	**90.3 - 104.8%**	94.3 - 108.8%
norethisterone		**[0.5+0.1] vs *Kliovance***	[0.5+0.25] vs *Kliovance*
90% confidence intervals (CI)	C_{max}	**106.2 - 120.5%**	92.3 - 104.7%
	$AUC_{0-\infty}$	**94.7 - 111.2%**	89.4 - 104.6%

C_{max}: maximum plasma concentration
$AUC_{0-\infty}$: area under the plasma concentration time curve from time zero to infinity

Advisory Committee Considerations

This application is to register a new strength. Such applications are not normally considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality Summary and Conclusions

There were no outstanding chemistry and quality control issues. Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The submission consisted of the studies shown in Table 2:

Table 2: Bioavailability, efficacy and safety studies for Kliovance Low

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design and Type of Control	Test Product, Dosage Regimen, Route of Administration	Number of Subject	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy Safety	KLIM/PD/7/USA	Vol. 21, Sec 5.2 p. 15	Dose finding, efficacy and safety Oestrogen Deficiency Symptoms	Randomised, double blind, parallel-group active controlled	E2 1 mg E2 1 mg + NETA 0.1 mg E2 1 mg + NETA 0.25 mg E2 1 mg + NETA 0.5 mg Tablet, once daily, oral	1176	Healthy, postmenopausal women	12 months
Efficacy	EST/PD/4/N+S	Vol. 25, Sec. 5.1 p. 15	Efficacy and Safety Prevention of Osteoporosis	Randomised, double blind, parallel Placebo	E2 0.5 mg E2 1 mg E2 2 mg Placebo Tablet, once daily, oral	171	Hysterectomised, perimenopausal and postmenopausal women	24 months
Efficacy	KLIM/PD/11/USA	Vol. 27, Sec 5.1 p. 15	Efficacy and Safety Prevention of Osteoporosis	Randomised, double blind, parallel Placebo	E2 0.25 mg, E2 0.5 mg E2 1 mg E2 1 mg + NETA 0.25 mg E2 1 mg + NETA 0.5 mg, E2 2 mg + NETA 1 mg, Placebo Tablet, once daily, oral	527	Healthy, postmenopausal women	26 months

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design and Type of Control	Test Product, Dosage Regimen, Route of Administration	Number of Subject	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	ALD-1640	Vol. 1, Sec 1.2 p. 18	Comparative BA study between new formulation and marketed formulation	Three-way cross-over	E2 0.5 mg + NETA 0.1 mg x 2 E2 0.5 mg + NETA 0.25 mg x 2 E2 1 mg + NETA 0.5 mg x 1 Tablet, single dose, oral	24	Healthy, postmenopausal women	Single dose
Efficacy	ALD-1537	Vol. 5, Sec 5.1 p. 15	Efficacy and Safety Oestrogen Deficiency Symptoms	Randomised, double blind, parallel Placebo	E2 0.5 mg + NETA 0.1 mg, E2 0.5 mg + NETA 0.25 mg, Placebo, Tablet, once daily, oral	577	Healthy, postmenopausal women	24 weeks
Efficacy	KLIM/PD/8/USA	Vol. 18, Sec 5.1 p. 15	Efficacy and Safety Oestrogen Deficiency Symptoms	Randomised, double blind, parallel-group, placebo-controlled	E2 0.25 mg E2 0.5 mg E2 1 mg E2 2 mg Placebo Tablet, once daily, oral	333	Healthy, postmenopausal women	12 weeks
Efficacy	KLIM/PD/9/USA	Vol. 20, Sec 5.1 p. 15	Efficacy and Safety Oestrogen Deficiency Symptoms	Randomised, double blind, parallel-group, placebo-controlled	E2 1 mg E2 1 mg + NETA 0.5 mg Placebo Tablet, once daily, oral	92	Healthy, postmenopausal women	12 weeks

ALD 1640 and ALD 1537 studied the formulation proposed for registration and have been evaluated in this report. The other studies were previously evaluated by the TGA for Kliovance in previous submissions.

Pharmacokinetics

Study ALD 1640

Introduction

The primary objective of this study was to determine the extent of bioavailability of oestradiol 0.5 mg + NETA 0.1 mg and oestradiol 0.5 mg + NETA 0.25 mg, compared to oestradiol 1 mg + NETA 0.5 mg, (*Activelle*, an already registered overseas combination) by calculating the rate (C_{max}) and extent ($AUC_{0-\infty}$) of absorption (Table 3). The formulation of the registered reference product (*Activelle*) appears to be identical to that of the Australian registered product Kliovance, as per the Australian Register of Therapeutic Goods (ARTG). This study is also described in *Section II.*

Table 3: Details of ALD 1640

Study identification	Design, Subjects, duration	Products, Dose	Pharmacokinetic variables and parameters	Safety
ALD 1640 Phase 1 March-June 2005 Sponsor: Novo Nordisk Denmark	Single dose open label 3 way crossover relative bioavailability study, 3 formulations of E2+NETA, 3 periods randomised sequence; single dose after overnight fast, 72 hours (h), 3 week (wk) washout. Healthy post-menopausal women, n = 24, age 50-70 years, total duration 13 weeks including screening/follow-up. Bioequivalence criteria (confidence interval [CI]) ratios AUC(0-t), C max, (0.80-1.25).	**Test products** **A:** 2 tablets of "Activelle Low Dose" oestradiol 0.5 mg + NETA 0.1 mg **B:** 2 tablets of "Activelle Low Dose" oestradiol 0.5 mg + NETA 0.25 mg Batch No. **Reference Product** **C:** 1 tablet of "Activelle" oestradiol 1.0 mg + NETA 0.5 mg	E2, E1, E1S (72 hrs sampling) NET (36 hrs) plasma concentrations C max and AUC for E2, E1 and E1S (calculated with and without baseline correction) and NET. Comparisons between treatments used ANOVA based on log transformed values. Bioequivalence criteria fulfilled for oestradiol, oestrone, NET.	No serious adverse events (SAEs) reported. No withdrawals due to adverse events (AEs). Total treatment emergent AEs (TEAEs) n=69 A: n = 22 B: n = 30 C: n = 17. 14 moderate, 8 severe; 22 possibly causal drug event relationship included dysgeusia, buttock pain, diarrhoea, abdominal pain, back pain, extremity pain, sensation of heaviness, arthralgia, rosacea, rash.

Secondary objectives were to evaluate the area under the plasma concentration time curve from time zero to time t (AUC_{0-t}), half-life ($t_{½}$), and safety and tolerability.

Subjects were healthy post-menopausal women (n = 24). This included smoking (up to 5 cigarettes/day) and non-smoking subjects, as well as subjects with borderline high blood pressure, screened in the 28 days prior to dosing, including for gynaecological history. Exclusion criteria included hormone therapy; oral oestrogen and/or progestin replacement therapy within 8 weeks, transdermal within 4 weeks, injections within 6 months, implants removed within 4 weeks; history of breast or oestrogen dependent cancer, for example, endometrial; abnormal genital bleeding; diabetes mellitus; thromboembolic disease; blood pressure (BP) > 150/90; endometrial hyperplasia; body mass index (BMI) > 35.0 kg/m^2; and drugs known to influence oestrogen metabolism.

Methods

Pharmacokinetic data analysis

Analysis included all subjects with at least one intake of the study drug and at least one post-dose measurement. Pharmacokinetic variables C_{max} and AUC for oestradiol (E2), the metabolites oestrone (E1) and oestrone sulphate (E1S), and norethindrone (NET) as the measurable form of norethisterone acetate were calculated for untransformed and log transformed data. Comparisons between treatments for AUC and C_{max} were performed using mixed effects analysis of variance (ANOVA) based on log transformed values. AUC and C_{max} were calculated for primary endpoints for E2 and E1 after baseline corrections for endogenous pre-dose levels. There were no subjects or observations excluded due to non-fulfilment of inclusion/exclusion criteria at entry or protocol violations interfering with pharmacokinetics of substances.

Statistical analysis

Primary endpoints were $AUC_{0-\infty}$ and C_{max} for E2, E1 and NET. Although designed as a trial to investigate relative bioavailability only, the sample size was calculated as for a bioequivalence trial, assuming an intra-individual variability of 21.9% for the most highly variable parameter, lnC_{max} for E2 after baseline correction and a true ratio between treatments between 0.95 and 1.053. A sample size n = 21 completers was expected to provide 80% power for proof of bioequivalence. There was a problem with reliable $t_{1/2}$ assessment for several analytes that prevented the use of extrapolated $AUC_{0-\infty}$ as the primary variable in many subjects, causing the secondary endpoint AUC_{0-t} to be substituted for assessment of bioavailability of E1 and E2, in a formal revision of the statistical plan. The observation of unreliability of the terminal rate constant is described in the report as "not uncommon in pharmacokinetic analyses of endogenous substances". Bioequivalence could be declared if the 90% confidence intervals (CI) for the ratios of AUC and C_{max} were fully contained within the limits (0.80, 1.25).

Absorption

Bioavailability

Pharmacokinetic results for E2 are shown in Table 4.

Table 4: Oestradiol (E2), baseline corrected: Pharmacokinetic Results (geometric means and %CV)

Treatment A: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.1 mg norethisterone acetate (NETA)]
Treatment B: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.25 mg norethisterone acetate (NETA)]
Treatment C: 1 tablet of 'Activelle®' [1.0 mg estradiol + 0.5 mg norethisterone acetate (NETA)]

Parameter	A (n=24)	B (n=24)	C (n=24)
AUC(0-∞) [h*pg/mL]	704.1 (42%)[a]	725.4 (41%)[a]	695.4 (41%)[c]
AUC(0-t) [h*pg/mL]	529.7 (56%)	542.1 (54%)	553.2 (55%)
C_{max} [pg/mL]	24 (38%)	22.7 (38%)	23.7 (37%)
t_{max} [h]: median and range	6.5 (0.5-16.0)	7.0 (0.5-16.0)	6.0 (0.5-16.0)
$t_{½}$ [h]	14.5 (27%)[a]	15.5 (38%)[b]	14.0 (29%)[c]

[a] n=16; [b] n=17;, [c] n=18
AUC(0-∞) : AUC by trapezoidal rule, extrapolated to infinity
AUC(0-t) : AUC by trapezoidal rule, 0 - last quantifiable sample
C_{max} : observed maximal concentration
t_{max} : time of maximal concentration
$t_{1/2}$: terminal half-life, from k

Pharmacokinetic results for NET are shown in Table 5.

Table 5: Norethisterone (NET): Pharmacokinetic Results (geometric means and %CV)

Treatment A: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.1 mg norethisterone acetate (NETA)]
Treatment B: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.25 mg norethisterone acetate (NETA)]
Treatment C: 1 tablet of 'Activelle®' [1.0 mg estradiol + 0.5 mg norethisterone acetate (NETA)]

Parameter	A (n=24)	B (n=24)	C (n=24)
AUC(0-∞) [h*pg/mL]	9710.6 (41%)[a]	22956 (44%)[a]	22481 (41%)[c]
AUC(0-t) [h*pg/mL]	8407.2 (43%)	19834 (51%)	21043 (41%)
C_{max} [pg/mL]	2375.4 (41%)	5160.4 (43%)	5249.5 (47%)
t_{max} [h]: median and range	0.8350 (0.67-1.25)	1.0 (0.67-1.5)	0.7033 (0.67-1.250)
$t_{½}$ [h]	11.44 (36%)[b]	9.51 (24%)[a]	9.78 (32%)[c]

[a] n=20, [b] n=21, [c] n=22

Bioequivalence

Parameters of primary analysis AUC $_{0-\infty}$, AUC_{0-t} and C_{max} of E2, E1 and NET were compared statistically. The primary analysis was restricted to AUC_{0-t} and C_{max} with baseline correction. The results for E2 and NET are shown in Tables 6 and 7 respectively.

Table 6: Statistical results for oestradiol (E2), baseline corrected

Parameter - Method	Ratio A / C with 90% Confidence Interval	Ratio B / C with 90% Confidence Interval
AUC(0-t) - Mixed (ln)	95.75% (89.39%, 102.56%)	98.01% (91.49%, 104.97%)
AUC(0-∞) - Mixed (ln)	97.26% (90.28%, 104.77%)	101.28% (94.31%, 108.75%)
C_{max} - Mixed (ln)	101.18% (90.12%, 113.59%)	95.59% (85.14%, 107.31%)

Table 7: Dose adjusted statistical results for NET

Parameter - Method	Ratio A / C with 90% Confidence Interval	Ratio B / C with 90% Confidence Interval
AUC(0-∞) - Mixed (ln)	102.60% (94.68%, 111.17%)	96.70% (89.39%, 104.59%)
C_{max} - Mixed (ln)	113.12% (106.23%, 120.45%)	98.30% (92.31%, 104.67%)
	Difference A - C with 90% Confidence Interval	Difference B - C with 90% Confidence Interval
t_{max} [h] - difference, nonparametric	0h (0h, +0.125h)	0h (0h, +0.165h)

Summary

This study was designed to examine relative oral bioavailability of the components of two tablets of treatment A (same formulation of Kliovance Low proposed for registration) with one tablet of standard treatment C (same formulation as registered Kliovance).

The baseline corrected AUC $_{0-t}$ and C_{max} of oestradiol (E2) and oestrone (E1) comparisons fulfilled criteria for bioequivalence. Dose adjusted AUC $_{0-\infty}$ and C $_{max}$ of NET for the two doses fulfilled criteria for bioequivalence. The minimal lower and maximal upper bounds of the 90% confidence intervals were 89.39% and 120.45%, respectively.

Evaluator comment

The data provide no information on the absolute bioavailability of the constituent components at the dose proposed or whether the proposed combination product formulation has optimal bioavailability compared to an oral solution or micronised preparations of the same strengths of components.

Elimination

Metabolism and Pharmacokinetics of metabolites

Oestrone (E1) and oestrone sulphate (E1S), metabolites of oestradiol, were measured as specified in the protocol. Oestrone parameters were analysed as pre-specified in the protocol as part of the comparison of bioavailability (Tables 8 and 9). E1S results are shown in Table 10.

Table 8: Oestrone (E1), baseline corrected: Pharmacokinetic Results (geometric means and geometric % CV)

Treatment A: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.1 mg norethisterone acetate (NETA)]
Treatment B: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.25 mg norethisterone acetate (NETA)]
Treatment C: 1 tablet of 'Activelle®' [1.0 mg estradiol + 0.5 mg norethisterone acetate (NETA)]

Parameter	A (n=24)	B (n=24)	C (n=24)
AUC(0-∞) [h*pg/mL]	4369.4 (37%)[a]	3954.2 (31%)[b]	4320.8 (30%)[c]
AUC(0-t) [h*pg/mL]	2910.4 (70%)	2980.7 (58%)	2979.0 (67%)
C_{max} [pg/mL]	172.5 (43%)	174.6 (38%)	178.40 (33%)[o]
t_{max} [h]: median and range	6.0 (1.0-9.0)	7.0 (3.5-9.0)	6.0 (2.0-9.0)[o]
$t_{½}$ [h]	10.7 (44%)[a]	9.58 (41%)[b]	11.77 (25%)[c]

[a] n=13, [b] n=14, [c] n=13, [o] n=23

Table 9: Statistical results of E1, baseline corrected

Parameter - Method	Ratio A / C with 90% Confidence Interval	Ratio B / C with 90% Confidence Interval
AUC(0-t) - Mixed (ln)	97.70% (90.14%, 105.87%)	100.06% (92.32%, 108.43%)
AUC(0-∞) - Mixed (ln)	103.93% (95.75%, 112.81%)	96.52% (88.94%, 104.75%)
C_{max} - Mixed (ln)	98.34% (90.80%, 106.49%)	99.50% (91.88%, 107.75%)

Table 10: Oestrone sulphate (E1S), baseline corrected

Treatment A: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.1 mg norethisterone acetate (NETA)]
Treatment B: 2 tablets of 'Activelle Low Dose' [0.5 mg estradiol + 0.25 mg norethisterone acetate (NETA)]
Treatment C: 1 tablet of 'Activelle®' [1.0 mg estradiol + 0.5 mg norethisterone acetate (NETA)]

Parameter	A (n=24)	B (n=24)	C (n=24)
AUC(0-∞) [h*pg/mL]	125060 (41%)[a]	117218 (40%)[b]	120673 (45%)[b]
AUC(0-t) [h*pg/mL]	95902 (62%)	97338 (53%)	101333 (54%)
C_{max} [pg/mL]	10789 (44%)	8246 (39%)	9097 (38%)
t_{max} [h]: median and range	1.0 (0.5-3.5)	1.25 (0.5-7.0)	1.5 (0.5-3.5)
$t_{½}$ [h]	11.2 (22%)[a]	11.4 (26%)[b]	11.4 (20%)[b]

[a] n=17; [b] n=18

Pharmacokinetics in the target population

The population studied was healthy post-menopausal women.

Evaluator comment

The target population is post-menopausal women with moderate to severe menopausal symptoms requiring treatment. This is acceptable for a bioequivalence study.

Pharmacokinetics in special populations

Elderly

Women aged 50 to 70 years were eligible to be included. Of 24 treated subjects, the age range was 51 to 69 years, the median 59 years, mean 58.7(SD 4.4).

Evaluator comment

This is not considered an elderly population.

Weight

Mean weight was 67.88 kg (standard deviation [SD] 10.48), range 51-84 kg. Mean BMI was 25.79 (SD 3.34), range 20-32 kg/m ^{2}.

Evaluator comment

The study included overweight and obese subjects.

Race

All women in this study were Caucasian.

Impaired renal function

This study provided no information on pharmacokinetics in subjects with renal impairment; known or suspected renal impairment was an exclusion criterion. Serum creatinine was measured at screening, and urine dipstick analysis performed at screening and follow up.

Impaired hepatic function

This study provided no information on pharmacokinetics in subjects with hepatic impairment; known or suspected hepatic impairment was an exclusion criterion. Liver function tests (LFTs) were measured at screening.

Evaluator's comments on pharmacokinetics in special populations

The bioequivalence study included healthy post menopausal women of high body weight.

Exposure relevant for safety evaluation

All subjects (n = 24) received the dosages as specified in the trial protocol, that is, a total dose of (1 mg + 2 x 0.5 mg + 2 x 0.5 mg) = 3 mg oestradiol and (0.5 mg + 2 x 0.25 mg + 2 x 0.1 mg) = 1.2 mg NETA.

Other PK information

A published PK study on the bioavailability of a different strength of NETA, 0.5 mg, alone or in combination with E2 1 mg, was summarised in the submission but data were not provided.

Evaluator's overall conclusions on pharmacokinetics

The test preparation A, in Study 1640, has the same formulation as the Kliovance Low combination proposed for registration but the proposed daily dose was not used. The

reference product C (*Activelle*) has the same formulation as that currently on the ARTG for Kliovance.

Bioequivalence for dose adjusted rate and extent of absorption was shown with regard to oestradiol (E2) and norethisterone (NET) between 2 tablets of the test preparations (A or B) and a single tablet of the reference preparation (C, *Activelle*) because all confidence intervals in the pre-specified concentration dependent endpoints of the PK analysis were within the acceptance range 0.8 to 1.25. There was evidence for dose proportional pharmacokinetics of NET for the range 0.2 mg to 0.5 mg as administered in this study but this does not include the 0.1 mg daily dose proposed for registration.

Pharmacodynamics

In Study ALD 1537 vaginal Maturation Index and pH were measured. Maturation value increased in the active treatment arms but showed slight decrease for placebo. Vaginal pH decreased in those receiving ALD 0.1 (the product proposed for registration), and ALD 0.25, but remained the same for placebo.

Efficacy

Introduction

The pivotal study is ALD 1537, a randomised double blind trial of two strengths of oestradiol/NETA compared with placebo in treating oestrogen deficiency symptoms in 577 healthy menopausal women over 24 weeks. The study was consistent with recommendations for hormone replacement therapy (HRT) treatments for the 'lowest dose for the shortest possible time'.[2] The trial did not include previously registered higher strength products.

Other studies tabulated above (Table 2) do not provide data relating directly to the safety and efficacy of the combination, strength and the indication proposed for registration but have been previously evaluated. KLIM/PD/8/USA included oestradiol 0.5 mg, the oestradiol strength now proposed for registration but without concomitant NETA administration, for the indication "relief of menopausal symptoms". This study was evaluated in the original clinical evaluation for the registration of Kliovance, as were KLIM/PD/7/USA and KLIM/PD/9/USA.

KLIM /PD/11/USA and EST /PD/4/N+S were evaluated for the osteoporosis extension of indications for Kliovance.

KLIM/PD/7/USA is the only study providing evidence of the acceptability of endometrial protection by 0.1 mg NETA. This is discussed in detail later in this AusPAR.

Dose response studies

Study ALD 1537 compared 0.5 mg oestradiol + 0.1 mg NETA combination tablets (ALD 0.1), as proposed for registration, with 0.5 mg oestradiol + 0.25 mg NETA (ALD 0.25) and placebo. This study is evaluated below.

There are dose response studies for oestradiol alone (Studies KLIM/PD/8/USA for menopause symptom relief and KLIM/PD/11/USA for prevention of osteoporosis, both previously evaluated for Kliovance). The dose response data for NETA, in relation to mitigation of endometrial hyperplasia, was explored in KLIM/PD/7/USA. This was evaluated for the initial registration of Kliovance.

[2] EMEA, Committee for Medicinal Products for Human Use (CHMP), 13 October 2005. Guideline on Clinical Investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in post-menopausal women, EMEA/CHMP/021/97 Rev. 1.

Main study: Study ALD 1537

This double blind, randomised, multicentre, multinational, placebo controlled, parallel group trial was designed to investigate the efficacy and safety of two low dose formulations of combined oestradiol and NETA, for menopause symptoms, compared with placebo. The active treatments were a single daily tablet of 0.5 mg oestradiol + 0.1 mg NETA (ALD 0.1) or 0.5 mg oestradiol + 0.25 mg NETA (ALD 0.25). 'ALD' refers to *Activelle low dose*; *Activelle* is the tradename for oestradiol 1 mg + NETA 0.5 mg in Europe. Both 1/0.5 and 0.5/0.1 combinations are called *Activella* in the USA.

The primary efficacy variable was the number of moderate to severe hot flushes per week. The trial period of 6 months was to allow assessment of bleeding profiles.

The study rationale states that if both NETA doses resulted in similar bleeding profiles, the lower dose combination would be selected for regulatory submission.

There were no endometrial data. The justification was that daily doses of 0.1 mg and 0.25 mg NETA were shown in KLIM/PD/7/US to be sufficient to effect endometrial protection when combined with 1 mg oestradiol, and therefore 0.1 mg NETA may be expected to provide endometrial protection for 0.5 mg oestradiol.

Objectives

Primary: To assess the change in the mean number of moderate to severe hot flushes per week.

Secondary: To assess the influence of ALD 0.1 and ALD 0.25 on Hot Flush Weekly Weighted Score, percentage of responders to treatment, bleeding pattern, Greene Climacteric scale, on the occurrence and severity of urogenital symptoms, maturational value and vaginal pH.[3]

Also assessed were safety variables, including physical and gynaecological examination, cervical smears, trans-vaginal ultrasound, mammographic changes, adverse events and laboratory assessments.

Study Participants

The post-menopausal women participants were aged 45 to 65 years with a minimum of 7 moderate to severe hot flushes per day or a minimum of 50 moderate to severe hot flushes per week during the 2 week run-in period.

Treatments

ALD 0.1 tablets contained 0.5 mg oestradiol and 0.1 mg NETA.

ALD 0.25 tablets contained 0.5 mg oestradiol and 0.25 mg NETA.

Subjects were to receive one tablet per day of ALD 0.1, ALD 0.25 or placebo, with no tablet free interval during the 6 month period.

Outcomes/endpoints

The primary endpoint was hot flushes, recorded by subjects in a diary card throughout the trial. Grading by the subject was according to the scale

[3] The Greene Climacteric Scale is intended specifically to be a brief and standard measure of core climacteric symptoms or complaints to be used for comparative and replicative purposes. A 21-item questionnaire measures a variety of menopausal symptoms on a 4-point Likert scale (0 = "not at all" to 3 = "extremely). Three separate sub-scales measure vasomotor symptoms, somatic symptoms, psychological symptoms, and an additional probe related to sexual function. Psychological symptoms can be further sub-divided to measure anxiety and depression.

1 = Mild (sensation of heat without perspiration)

2 = Moderate (sensation of heat with perspiration, able to continue activity)

3 = Severe (sensation of heat with sweating, causing the subject to stop activity).

Secondary efficacy endpoints were the Hot Flush Weekly Weighted Score (HFWWS), calculated as (number of mild hot flushes x 1) + (number of moderate hot flushes x 2) + (number of severe hot flushes x 3), Greene Climacteric Scale, urogenital symptom score, maturation value and vaginal pH. A responder analysis was also conducted.

Missing values were replaced on a daily basis using the last observation carried forward (LOCF) approach, provided data from at least one follow up trial period were present.

Statistical Considerations

Sample size calculations were provided in the sponsor's *Study Report*. Using data from KLIM/PD/8/USA, the change from baseline in the number of moderate to severe hot flushes per week had a standard deviation of approximately 30. Using a 2 sided test, $\alpha = 0.05$ and a least clinically significant treatment difference of 12 moderate to severe hot flushes per week, a sample size of 133 subjects was required in each arm for a 90% probability of detecting this difference; with 20% dropout rate, the calculation was n = 166 in each group.

There were 793 women recruited and screened during a 2 to 3 week period and 577 were randomised to receive ALD 0.1 (194) and ALD 0.25 (182) or placebo (201). The trial was double blinded to minimise bias in the evaluation of efficacy and safety data. A multicentre parallel group design was chosen to obtain the required number of subjects within the scheduled recruitment period.

Two trial populations were evaluated for efficacy. The "intention to treat" (ITT) population was all randomised subjects who were exposed to the trial drug at least once and provided some follow up data. The "per protocol" (PP) population were those who met all the inclusion/exclusion criteria, with at least 5 days non-missing hot flush data present each week and missing less than 3 tablets of trial medication in successive days. No missing data were replaced for the PP population. The PP findings were regarded as a sensitivity analysis.

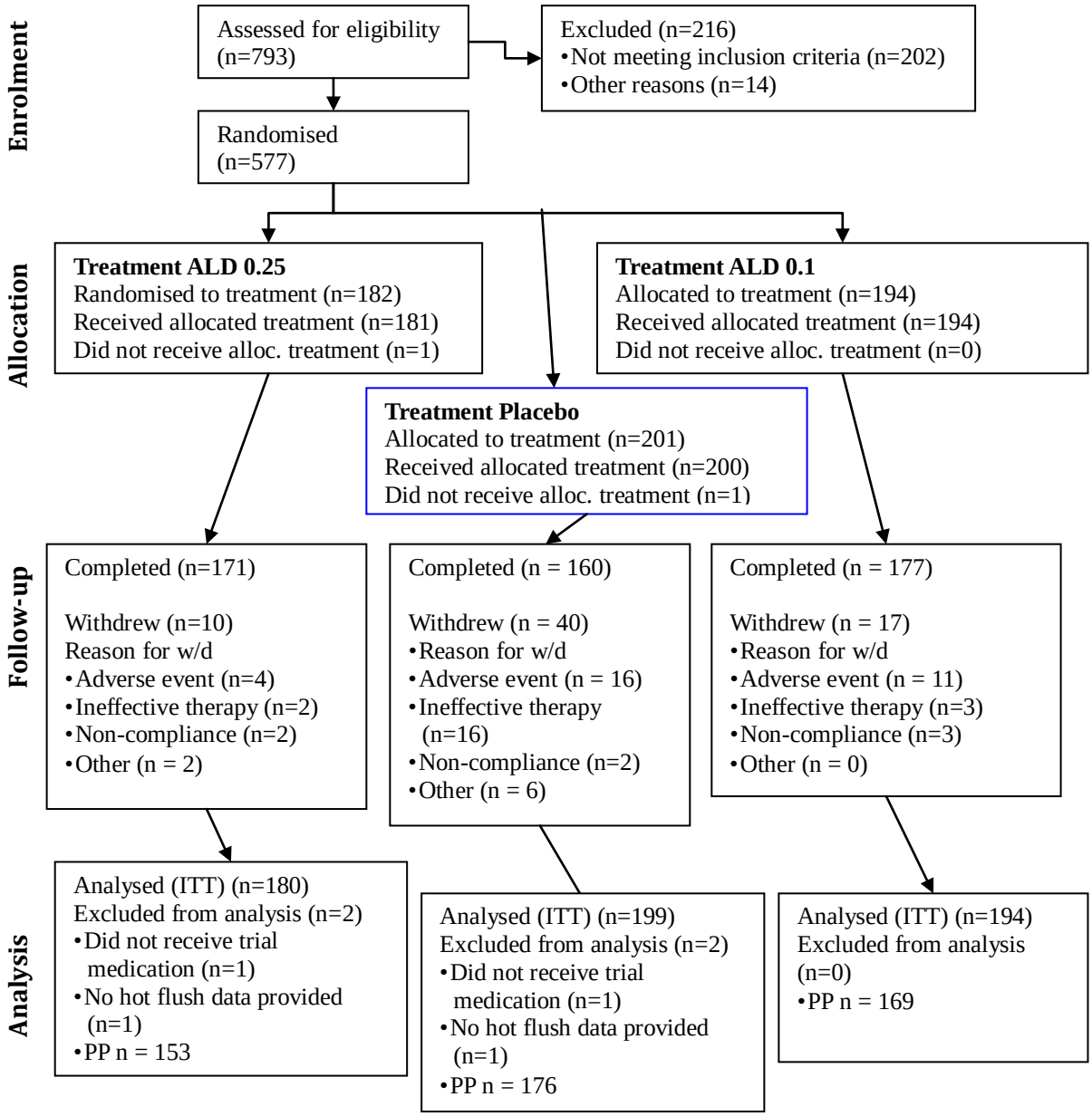
Non-parametric methodology was used due to departures from normal distribution. A test of the overall treatment effect was performed first using the Kruskal-Wallis test; that is, the null hypothesis was that the mean number of moderate to severe hot flushes for Week 8 was the same for all three treatment groups. Comparisons between the three treatment pairs were of interest. Three paired comparisons were to be performed only if overall treatment effect was statistically significant, that is, the null hypothesis was rejected. The overall treatment effect was assessed 8 weeks and at 4 and 12 weeks, with additional comparisons for Weeks 1-3, 5-11 and Week 24 separately. The stratified Wilcoxon rank sum test with country as the stratification variable was used for paired comparisons.

Results

Participant flow

The participant flow is shown in Figure 1.

Figure 1: ALD 1537, Participant flow



Recruitment

There were 77 sites in 10 countries.

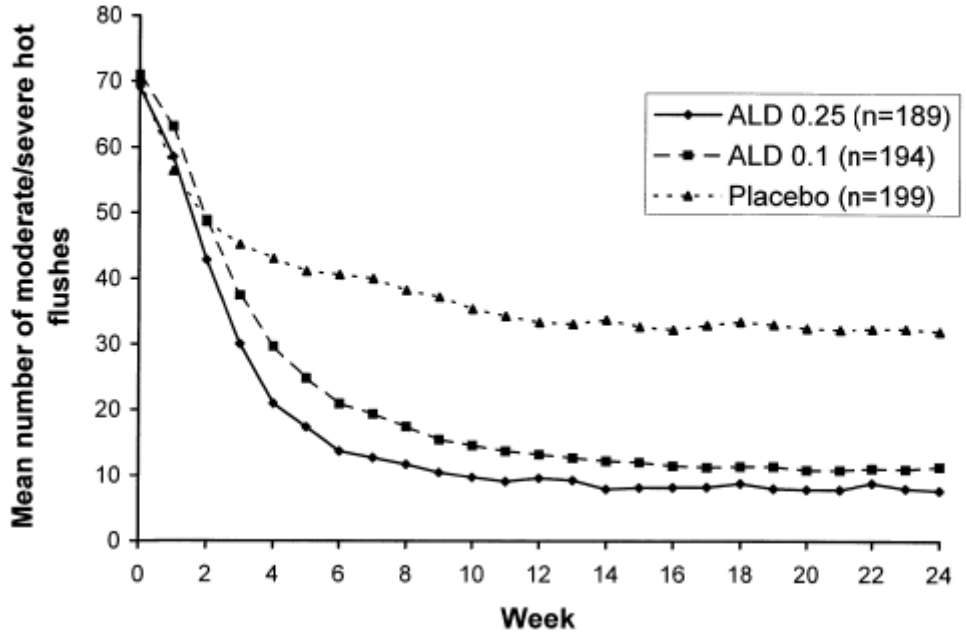
Numbers analysed

There were 573 included in the ITT analysis set; of the 577 randomised, 2 did not receive study medication and 2 did not provide hot flush data (one each in ALD 0.25 and placebo groups) (Figure 1). The PP population was ALD 0.1 n = 169 (87%); ALD 0.25 n = 153 (84%); placebo n = 176 (88%).

Outcomes and estimation

Results for the primary variable (mean number of moderate to severe hot flushes per week) by week with missing data replaced, LOCF (ITT Population) are as shown in Figure 2.

Figure 2: Mean number of moderate to severe hot flushes per week



The effect on the mean number (SD) of moderate to severe hot flushes per week at the primary time point Week 8 and at Week 24, with no data replacement, was as shown in Table 11.

Table 11: mean number (SD) of moderate to severe hot flushes per week

Week	ALD 0.1	ALD 0.25	Placebo
0	70.9 (27.4), n = 194	69.2(30.5), n = 180	70.0 (26.4), n = 199
8	16.6 (29.5), n = 187	10.1 (19.3), n = 173	35.7 (31.3), n = 181
24	9.2 (22.6), n = 169	5.6 (14.8), n = 160	26.5(28.7), n = 148

With LOCF, the summary for the same time points was as shown in Table 12.

Table 12: mean number (SD) of moderate to severe hot flushes per week with LOCF

Week	ALD 0.1	ALD 0.25	Placebo
0	70.9 (27.4), n = 194	69.2(30.5), n = 180	70.0 (26.4), n = 199
8	17.4 (29.9), n = 194	11.7 (21.4), n = 180	38.2 (33.6), n = 199
24	11.3 (25.7), n = 194	7.7 (20.2), n = 180	31.9(35.8), n = 199

The overall treatment effect, analysed using the Kruskal-Wallis test, was statistically significant at every time point from Week 4. The paired comparisons using the Wilcoxon test stratified by country showed statistically significant treatment differences for both treatments vs placebo.

In the ITT population, for ALD 0.1 minus placebo, the estimated treatment difference in reductions in hot flushes at Week 8 was -21.5 (95% CI -27.0, -16.5) and at Week 24, -19.6 (-26.0, -14.0). No significant differences were seen between ALD 0.25 and ALD 0.1 at any time points. The PP population was smaller by approximately 30 women in each active group and 20 in the placebo group and the findings were similar.

Ancillary analyses

Hot Flush Severity Score

The mean change in severity score of moderate to severe hot flushes compared with baseline was -9.1 for ALD 0.1, -10.8 for ALD 0.25, -3.4 for placebo by Week 8. This was a statistically significant treatment difference for both ALD 0.25 and ALD 0.1 compared with placebo.

HFWWS

This score decreased from 185.8 to 48.2 for ALD 0.1, 180.5 to 32.4 for ALD 0.25, and 183.5 to 101.1 for placebo at Week 8. A statistically significant treatment difference was seen at all time points when comparing ALD 0.1 with placebo.

Percentage Responders who reported ≥ 90% improvement from baseline for HFWWS (90% CI) were as shown in Table 13.

Table 13: percentage responders

ITT	**ALD 0.1**	**ALD 0.25**	**placebo**
Week 8	44% (37-51%);	59% (52-67%)	13 % (8-17%)
Week 24	66% (59-73%)	75% (69-81%)	23% (17-28%)

Corresponding PP results at 8 weeks were 45% (37-53%) vs 62% (54-70%) vs 15% (10-21%).

Greene Climacteric Score (GCS)

The treatment difference for ALD 0.1 vs placebo total score at Week 8 was -4.0 (-5.0, -3.0). There were statistically significant reductions compared with placebo at all time points for both treatment groups. The vasomotor symptom score subset of the GCS showed a reduction from mean 4.9 at Week 0 to 1.8 at Week 8 for ALD 0.1, compared to 4.9 and 3.2 for placebo, a statistically significant treatment difference. Significant treatment differences were also seen at Week 8 for the individual psychological, difficulty sleeping and somatic scores of the GCS parameters. Urogenital symptom parameters did not show any notable differences between treatment groups, although a higher proportion of subjects in the ALD 0.25 and ALD 0.1 groups (70% and 64% respectively) reported no vaginal dryness at Week 24, compared to 54% in the placebo group.

Bleeding Profile

The bleeding profile was described under *Safety Evaluation* in the *Study Report* and further details are described the *Safety* section of this AusPAR. A summary tabulation shows the comparison of the incidence of bleeding/spotting and amenorrhoea (consecutive cycles of no bleeding or spotting) across cycles (Table 14).

Table 14: Number of days per cycle with spotting/bleeding

Treatment	Cycle 1 n (%)	Cycle 2 n (%)	Cycle 3 n (%)	Cycle 4 n (%)	Cycle 5 n (%)	Cycle 6 n (%)
ALD 0.25						
N	178	175	171	169	168	167
0 days	161 (90)	152 (87)	155 (91)	153 (91)	149 (89)	149 (89)
1 day	2 (1)	1 (1)	1 (1)	2 (1)	1 (1)	1 (1)
2 - 3 days	2 (1)	3 (2)	2 (1)	3 (2)	5 (3)	6 (4)
4 – 5 days	1 (1)	3 (2)	4 (2)	2 (1)	4 (2)	2 (1)
6 – 10 days	9 (5)	12 (7)	2 (1)	5 (3)	5 (3)	4 (2)
> 10 days	3 (2)	4 (2)	7 (4)	4 (2)	4 (2)	5 (3)
ALD 0.1						
N	189	186	182	181	177	176
0 days	168 (89)	166 (89)	156 (86)	153 (85)	157 (89)	156 (89)
1 day	5 (3)	4 (2)	4 (2)	4 (2)	1 (1)	2 (1)
2 - 3 days	5 (3)	5 (3)	5 (3)	6 (3)	4 (2)	7 (4)
4 – 5 days	5 (3)	1 (1)	1 (1)	3 (2)	3 (2)	2 (1)
6 – 10 days	4 (2)	6 (3)	11 (6)	10 (6)	8 (5)	9 (5)
> 10 days	2 (1)	4 (2)	5 (3)	5 (3)	4 (2)	0 (0)
Placebo						
N	194	183	171	166	160	157
0 days	186 (96)	172 (94)	159 (93)	160 (96)	156 (98)	153 (97)
1 day	1 (1)	3 (2)	2 (1)	0 (0)	0 (0)	1 (1)
2 - 3 days	1 (1)	1 (1)	1 (1)	2 (1)	1 (1)	0 (0)
4 – 5 days	0 (0)	3 (2)	2 (1)	2 (1)	1 (1)	1 (1)
6 – 10 days	6 (3)	3 (2)	7 (4)	0 (0)	1 (1)	2 (1)
> 10 days	0 (0)	1 (1)	0 (0)	2 (1)	1 (1)	0 (0)

Cross-reference EOT Table 101

Evaluator Comment

Study ALD 1537 compared ALD 0.1 (Kliovance Low), ALD 0.25 and placebo in women having 7 or more moderate to severe hot flushes per day, or > 50 per week. Overall there was statistically significant treatment effect for the primary endpoint, number of moderate to severe hot flushes. There was a clinically significant reduction from a mean of about 70 per week to less than 20 per week in both the active treatment arms at 8 weeks treatment duration; means were less than 10 per week at 24 weeks. For placebo the means at corresponding durations were 35 and 26 moderate to severe hot flushes per week, that is, there was 50% decrease in the mean number of moderate to severe hot flushes per week after 2 months without any active treatment.

At 8 weeks, the primary time point, 44% of subjects receiving Kliovance Low had ≥ 90% improvement in HFWWS from baseline compared to 13% receiving placebo, suggesting the number needed to treat (NNT) for benefit for relief of moderate to severe hot flushes was 3 to 4.

There was no statistical difference between the two active treatment arms ALD 0.1 and ALD 0.25. The study does not appear to have been designed as a non-inferiority study. The trial rationale states that if both NETA doses resulted in similar bleeding profiles, the lower dose combination would be selected for regulatory submission, in line with regulatory recommendations for using the lowest dose.[2] Spotting/bleeding occurred in about 10%-15% of women over 6 cycles for subjects receiving ALD 0.1 (Kliovance Low) or ALD 0.25, compared to 2%-7% for those receiving placebo.

The indication proposed is for:

Short term treatment of menopausal symptoms related to oestrogen deficiency in women more than one year after menopause.

According to the summary of baseline characteristics, >80% of women in the study were > 1 year since last menses.

Supportive studies

KLIM PD/8/USA was evaluated for the original registration of Kliovance. The primary efficacy variables were hot flushes (HFWWS and vasomotor symptoms of GCS score). In this 12 week dose finding study 0.25 mg (n = 68), 0.5 mg (n = 64), 1.0 mg (n = 67) or 2.0 mg (n = 68) oestradiol were compared to placebo (n = 66) in 333 post-menopausal women. A decrease in symptoms over time in all treatment groups was reported. A dose response was demonstrated, with significant decreases in the Greene Climacteric Scale vasomotor subscale compared to placebo for doses 0.5 mg and above, resulting in designation of 0.5 mg oestradiol daily as the lowest effective dose in this population. The time course of HFWWS for each treatment, and % responders with 90% reduction, are shown in Figures 3 and 4, respectively.

Figure 3: Mean weighted hot flush score

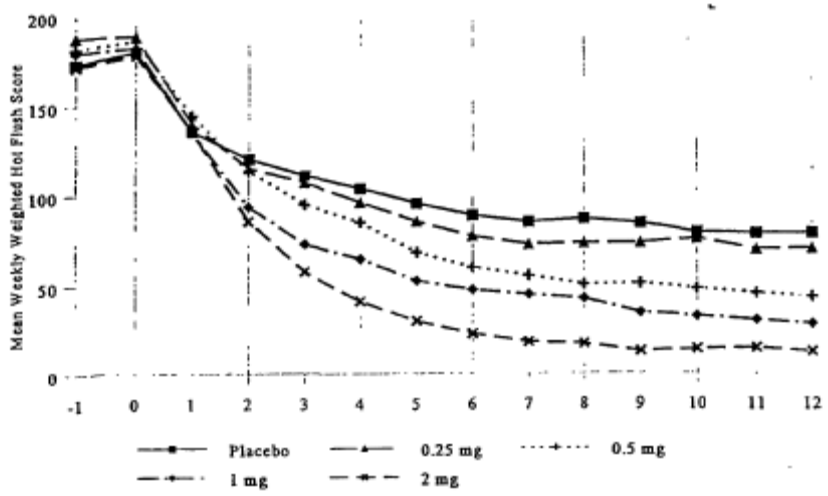
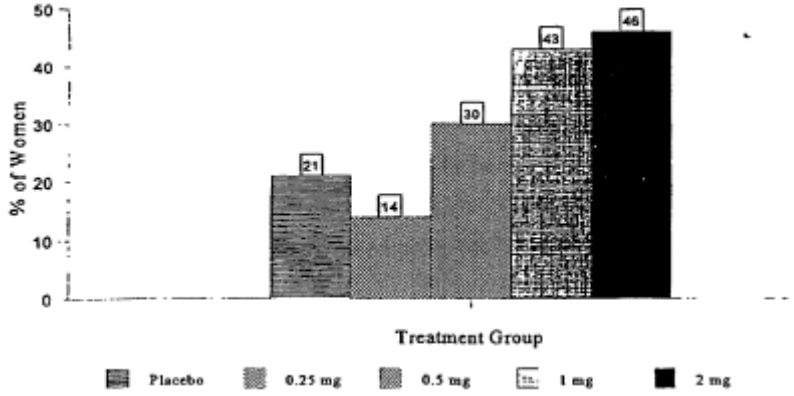


Figure 4: Women with 90% reduction in WWHS score at week 4:



The 2 mg group showed the greatest decrease, followed sequentially by the 1 mg and 0.5 mg groups at Weeks 4, 8 and 12. At Week 4, the highest proportion of women with 90% reduction in weekly weighted hot flush score was observed in the 1 mg and 2 mg groups.

Evaluator comment

The clinical evaluation report for Kliovance states that in this study a significant reduction in vasomotor symptoms (HFWWS) occurred at Week 4 with doses of 1 mg and 2 mg of oestradiol (43% and 46%), (primary efficacy analysis) and for the GCS score vasomotor symptoms from Week 4, 8 and 12 for the oestradiol 1 mg and 2 mg doses.

The 0.5 mg oestradiol dose had a greater effect after 8 weeks, as seen above. ALD 1537 had a primary time point at 8 weeks.

KLIM/PD/7/USA examined the efficacy of NETA using the endpoint of incidence of endometrial hyperplasia, and was evaluated for the original registration of Kliovance. This is discussed under *Safety*.

Evaluator's overall conclusions on clinical efficacy

ALD 1537:

- The overall treatment effect was statistically significant at every time point from Week 4.
- For ALD 0.1 vs placebo, the estimated treatment difference in moderate to severe hot flushes at Week 8 was statistically and clinically significant, -21.5 (95% CI -27.0, -16.5).
- The effect persisted at Week 24; the estimated treatment difference in moderate to severe hot flushes ALD 0.1 vs placebo was -19.6 (-26.0, -14.0).

Safety

Introduction

Safety data for the product proposed for registration derives from the PK trial 1640 and the main trial ALD 1537.

Evaluator Comment

Adequate data for post-menopausal vaginal bleeding and endometrial biopsy results are required. Other adverse events requiring scrutiny include those associated with thromboembolism, neoplasms, depressed mood, and breast symptoms.

Patient exposure

A summary of patient exposure is provided as Table 15.

Table 15: Summary of patient exposure.

Study type	Number of patients					
	Exposed to at least one dose	Exposed to the proposed dose range	With long term safety data			
			For proposed dose range		For proposed max. dose	
			≥6 months	≥12 months	≥6 months	≥12 months
Placebo and active controlled ALD-1537 PK study ALD 1640, single dose 2 tablets Postmarketing	194 24	194 24 n/a	176 n/a	0	n/a*	n/a

*The ALD 0.1 combination (E2 0.5mg+ NETA 0.1 mg) is the only dose proposed for registration in this submission.

In total there were safety data available for 218 patients exposed to the product proposed for registration. The majority of these (194) were exposed for 24 weeks.

Adverse events

ALD 1640

There were 20 subjects who experienced 69 reported adverse events (AEs). There were no serious adverse events (SAEs) and no withdrawals due to adverse events. Following administration of Treatment A (2 tablets of E2 0.5 mg + NETA 0.1 mg) 11 subjects experienced 22 AEs, compared to 14 subjects with 30 AEs following Treatment B (2 tablets of E2 0.5 mg + NETA 0.25 mg), and 11 subjects with 17 AEs following Treatment C, Activelle (E2 1 mg + NETA 0.5 mg).

For treatment A, events considered to be possibly drug related were abdominal pain and diarrhoea (n =1), back pain (n = 1), dysgeusia (n = 1) and buttock pain (n = 2). Other events were considered unrelated, although it is noted that nausea and headache, both often associated with oestrogen/progestogen preparations, were among these events.

Evaluator comment

There were no observable adverse event reporting differences between the three products in this single dose PK study.

ALD 1537

Bleeding profile

The incidence of bleeding/spotting, bleeding (moderate or heavy) and heavy bleeding was lower in the placebo group compared to the active preparations (Table 16). However there was a low incidence of withdrawal due to bleeding in all three treatment groups, with one subject in each treatment group not completing the study for this reason.

Table 16: Incidence of bleeding

	ALD 0.25 (N = 181)		ALD 0.1 (N = 194)		Placebo (N = 200)	
	N	n (%)	N	n (%)	N	n (%)
Bleeding/Spotting						
Cycle 1	178	17 (10)	189	21 (11)	194	8 (4)
Cycle 2	175	23 (13)	186	20 (11)	183	11 (6)
Cycle 3	171	16 (9)	182	26 (14)	171	12 (7)
Cycle 4	169	16 (9)	181	28 (15)	165	6 (4)
Cycle 5	168	19 (11)	177	20 (11)	160	4 (3)
Cycle 6	167	18 (11)	176	20 (11)	157	4 (3)
Bleeding (Moderate or Heavy)						
Cycle 1	178	10 (6)	189	10 (5)	194	2 (1)
Cycle 2	175	16 (9)	186	11 (6)	183	5 (3)
Cycle 3	171	11 (6)	182	13 (7)	171	7 (4)
Cycle 4	169	12 (7)	181	18 (10)	166	4 (2)
Cycle 5	168	10 (6)	177	9 (5)	160	1 (1)
Cycle 6	167	8 (5)	176	9 (5)	157	1 (1)
Heavy Bleeding						
Cycle 1	178	5 (3)	189	3 (2)	194	0 (0)
Cycle 2	175	7 (4)	186	4 (2)	183	1 (1)
Cycle 3	171	6 (4)	182	5 (3)	171	1 (1)
Cycle 4	169	5 (3)	181	2 (1)	166	0 (0)
Cycle 5	168	4 (2)	177	4 (2)	160	0 (0)
Cycle 6	167	3 (2)	176	2 (1)	157	0 (0)

Cross-reference EOT Tables 94, 95 and 97

By Cycle 6, 89% of subjects completing in both ALD 0.25 and ALD 0.1 groups had no bleeding or spotting compared to 97% in the placebo group. Conversely, 5% of subjects receiving ALD 0.1 or ALD 0.25 reported moderate or heavy bleeding compared to 1% of the placebo group.

Physical signs

There were no notable changes or differences between treatment groups.

Pap smears

One subject in the ALD 0.1 and one in the placebo group had abnormal smear test findings at Week 24.

Trans-vaginal ultrasound

Trans-vaginal ultrasound (TVUS) was performed at Visits 1 and 6 or at the time of withdrawal from study, with findings shown in Table 17.

Table 17: Summary of endometrial thickness

Treatment		Week 0	Week 24
ALD 0.25	Number	181	173
	Mean ± SD	2.23 ± 1.07	2.65 ± 1.64
	Median	2.00	2.40
	Range	0.00 – 4.90	0.00 – 13.00
ALD 0.1	Number	194	185
	Mean ± SD	2.29 ± 1.00	2.87 ± 1.82
	Median	2.10	2.50
	Range	0.00 – 4.80	0.00 – 12.00
Placebo	Number	200	177
	Mean ± SD	2.30 ± 1.06	2.56 ± 1.64
	Median	2.00	2.20
	Range	0.00 – 7.30	0.00 – 11.00

Cross-reference EOT Table 107

Summary of Interpretation of Transvaginal Ultrasound

		Screening		Week 24	
ALD 0.25	Total subjects	181		181	
	Normal	167	(92%)	154	(89%)
	Abnormal	14	(8%)	20	(11%)
	Not recorded	0		7	
ALD 0.1	Total subjects	194		194	
	Normal	166	(86%)	151	(82%)
	Abnormal	28	(14%)	34	(18%)
	Not recorded	0		9	
Placebo	Total subjects	200		200	
	Normal	179	(90%)	159	(89%)
	Abnormal	21	(11%)	19	(11%)
	Not recorded	0		22	

Summary of Changes in Endometrial Thickness (mm)

ALD 0.25	N	173
	Mean	0.41
	Median	0.10
	sd	1.64
	Minimum	-3.30
	Maximum	13.00
	Not recorded	8
ALD 0.1	N	185
	Mean	0.60
	Median	0.30
	sd	1.77
	Minimum	-3.00
	Maximum	8.70
	Not recorded	9
Placebo	N	177
	Mean	0.32
	Median	0.00
	sd	1.71
	Minimum	-3.00
	Maximum	10.00
	Not recorded	23

The distribution of endometrial thickness changes between the treatment groups was very similar; no differences in endometrial thickness changes were observed among treatment groups during the study.

'Endometrial thickening' was reported at the end of study if endometrial thickness estimated by TVUS was ≥ 5 mm. Endometrial thickening reported from the line listings for AEs was as shown in Table 18.

Table 18: Endometrial thickening reported as an AE

	ALD 0.25 n = 181	ALD 0.1 n = 194	Placebo n = 200
Endometrial thickening ≥ 5 mm	11 subjects, 6%	19 subjects, 10%	8 subjects, 4%

Endometrial biopsy was not a protocol planned procedure. There were 5 endometrial biopsies and 4 hysteroscopies were conducted during the trial and all results were reportedly negative with regard to endometrial abnormalities. One woman in the ALD 0.1 group with an end study TVUS endometrial thickness of 12 mm had insufficient tissue on the first biopsy and possible simple hyperplasia at follow up biopsy one month later, by which time she had been taking another HRT for 6 weeks. This case was confirmed as endometrial thickening.

Evaluator comments

Endometrial biopsy was not undertaken either at screening or end of study in ALD-1537.

TVUS was conducted for all subjects. Endometrial thickness of 5 mm is the upper limit of normal for a post-menopausal individual; persistent bleeding should lead to endometrial sampling regardless of ultrasound findings.[4] At the end of the study:

For ALD 0.1 subjects

- 10 % had endometrial thickness ≥ 5mm on TVUS vs 6% receiving ALD 0.25
- 18% were reported as having TVUS interpretation 'abnormal'
- For placebo
- 4% had endometrial thickness ≥ 5mm on TVUS
- 11 % were reported as having TVUS interpretation 'abnormal'.

Mammography

Mammograms were carried out on a subpopulation of 255 women from Nordic countries, up to 6 months prior to treatment and after 6 months. After excluding women who used HRT up to 2 months prior to the screening mammogram, 154 women were included in the assessment. Visual classification was made according the Wolfe classification for percentage breast density. In the ALD 0.1 treatment group all subjects maintained the same visual classification status for the duration of the trial, compared to one subject increased and two subjects decreased in the placebo group.

Adverse Events

In all trial groups at least 70% of subjects reported AEs but only 1% of all events were serious. The trial dropout rate was low; 94% of the ALD 0.25 group and 90% of the ALD 0.1 group completed, compared to 80% in the placebo group. AEs were recorded as a reason for withdrawal in 2% of the ALD 0.25 group but for a higher proportion (6%) of the ALD 0.1 group and for 8% of the placebo group.

[4] Stenchever et al. Comprehensive Gynaecology 4th edition 2001 Chapter 30 Neoplastic Diseases of the Uterus, pages 924-925.

Treatment emergent AEs (TEAEs) by system organ class (SOC) are shown in Table 19. *Cardiac Disorders* were reported in 2% of ALD 0.25 and 4% of the ALD 0.1, compared to 6% of the placebo group. One subject in the placebo group died of a myocardial infarction. *Vascular Disorders* were reported very commonly and most frequently in the ALD 0.1 group (30%). More common AEs which were considered related are shown in Table 20. This includes large numbers of reports of 'vaginal haemorrhage', the preferred term for vaginal bleeding, reported in 51 (26%) of subjects receiving ALD 0.1, compared to 39 (22%) for ALD 0.25 and 24 (12%) for placebo.

There were no reports of thromboembolic events in any of the treatment groups.

Clinically important breast symptoms (discomfort, pain, tenderness) were reported by < 2% of subjects treated with ALD 0.1, comparable to the placebo group. Neoplasms occurred in 7% of ALD 0.1 compared to 5% of placebo subjects; the line listings showed these to be mainly uterine leiomyomas (n = 5 and 6 respectively) but it was noted there were three ovarian cysts reported in the ALD 0.1 group and two uterine polyps, all considered possibly or probably related. For ALD 0.1 treatment, depression was reported in 3 subjects and anxiety in 5, compared to 3 and 1 respectively in the placebo group.

Table 19: Treatment-emergent adverse events according to SOC, safety population

	ALD 0.25 (N = 181) n (%) events	**ALD 0.1 (N = 194)** n (%) events	**Placebo (N = 200)** n (%) events
Number of subjects reporting AEs	127 (70) 571	147 (76) 673	139 (70) 520
Respiratory, Thoracic and Mediastinal Disorders	50 (28) 79	60 (31) 101	54 (27) 81
Nervous System Disorders	54 (30) 162	58 (30) 153	50 (25) 132
Vascular Disorders	43 (24) 109	59 (30) 108	36 (18) 64
Gastrointestinal Disorders	34 (19) 66	43 (22) 86	49 (25) 79
Musculoskeletal and Connective Tissue Disorders	34 (19) 60	48 (25) 86	31 (16) 55
Reproductive System and Breast Disorders	21 (12) 23	27 (14) 28	20 (10) 20
Skin and Subcutaneous Tissue Disorders	10 (6) 11	14 (7) 17	16 (8) 20
Neoplasms Benign, Malignant and Unspecified	7 (4) 7	14 (7) 14	10 (5) 10
General Disorders and Administration Site Conditions	6 (3) 7	14 (7) 19	6 (3) 7
Infections and Infestations	11 (6) 12	10 (5) 12	4 (2) 4
Cardiac Disorders	4 (2) 5	7 (4) 8	11 (6) 13
Psychiatric Disorders	6 (3) 10	8 (4) 10	4 (2) 4
Renal and Urinary Disorders	5 (3) 5	8 (4) 10	4 (2) 5
Injury, Poisoning and Procedural Complications	4 (2) 4	5 (3) 5	4 (2) 5
Eye Disorders	5 (3) 5	3 (2) 4	4 (2) 4
Ear and Labyrinth Disorders	2 (1) 2	4 (2) 4	3 (2) 3
Investigations	2 (1) 2	2 (1) 2	3 (2) 4
Surgical and Medical Procedures	0 (0) 0	3 (2) 3	1 (1) 1
Immune System Disorders	1 (1) 1	1 (1) 1	1 (1) 6
Metabolism and Nutritional Disorders	1 (1) 1	2 (1) 2	0 (0) 0
Endocrine Disorders	0 (0) 0	0 (0) 0	1 (1) 1
Hepatobiliary Disorders	0 (0) 0	0 (0) 0	1 (1) 1
Social Circumstances	0 (0) 0	0 (0) 0	1 (1) 1

Table 20: AEs considered related, occurring in ≥ 2%

	ALD 0.25 (N = 181) n (%) events	ALD 0.1 (N = 194) n (%) events	Placebo (N = 200) n (%) events
Number of subjects reporting AEs Considered Related to Trial Product	71 (39) 231	89 (46) 253	59 (35) 155
Vaginal Haemorrhage	39 (22) 103	49 (25) 97	23 (12) 48
Headache	22 (12) 70	21 (11) 62	16 (8) 36
Endometrial Thickening	11 (6) 11	18 (9) 18	7 (4) 7
Uterine Leiomyoma	3 (2) 3	5 (3) 5	3 (2) 3
Nausea	2 (1) 3	5 (3) 5	3 (2) 7
Hot Flush	1 (1) 1	3 (2) 3	5 (3) 5
Breast Tenderness	1 (1) 1	1 (1) 1	4 (2) 4
Ovarian Cyst	0 (0) 0	3 (2) 3	0 (0) 0
Migraine	3 (2) 13	1 (1) 1	1 (1) 1
Abdominal Pain	0 (0) 0	2 (1) 2	3 (2) 3
Upper Abdominal Pain	3 (2) 3	1 (1) 1	0 (0) 0
Dyspepsia	0 (0) 0	3 (2) 4	1 (1) 2

Cross-reference EOT Table 67

Evaluator comments

- The incidence of treatment-related vaginal haemorrhage in the ALD 0.25 and ALD 0.1 treatment groups was twice that reported for placebo over 6 months. It is noted that the TGA-adopted guidelines indicate that bleeding assessment should be done for 12 months.[2]
- The incidence of endometrial thickening shown on ultrasound in the ALD 0.1 group was more than twice that for placebo.
- There were three ovarian cysts in the ALD 0.1 group, and two uterine polyps, considered possibly or probably related. TGA-adopted guidelines state that patients with uterine polyps are recommended to be excluded from enrolment.[2]

Serious adverse events and deaths

ALD 1640

There were no SAEs or deaths.

ALD 1537

There were 14 subjects with SAEs, 3% of the safety population and distribution was similar in all treatment groups. There was one death, a subject in the placebo group who suffered a myocardial infarction.

A subject with breast cancer had received treatment with ALD 0.25 for 173 days in the trial but had been on HRT for 10 years prior to entering the trial and causality could not be assessed.

None of the 5 reports with SAEs occurring in the ALD 0.1 treatment group were considered related to the trial medication. According to the event narrative for the benign breast neoplasm, the subject, aged 47, did not have the screening mammogram until 11 days *after* the first study drug dose. The mammogram showed a 'benign breast lump' and a subsequent biopsy 'revealed florid epithelial cells and hyperplasia'. The study drug was discontinued and the patient withdrawn from the trial on the same day. She was treated with lumpectomy. Causality was considered unlikely.

Laboratory findings

Many subjects had markedly elevated oestradiol levels, commonly 100-200 pg/mL and ranging up to 500 pg/mL. In answer to a request for clarification, the sponsor provided amended listings specifying that elevated oestradiol results were at 12 and 24 weeks, consistent with the other data provided.

Haematology

The only difference noted in abnormal laboratory values was in the ALD 0.1 group in which three subjects had reduced platelet counts at Weeks 12 and 24, and one and two subjects had elevated platelet counts at Week 12 and 24 respectively.

Biochemistry

In the active treatment groups the most frequent changes from normal to abnormal values was for the creatinine level, which at Weeks 12 and 24 was elevated above the normal range in 10 and 7 subjects in the ALD 0.25 group, 12 and 10 subjects in the ALD 0.1 group, and 5 and 6 subjects in the placebo group.

Other variables

There were no adverse changes or treatment differences between active treatments and placebo in lipids, glucose and haemostatic parameters including fibrinogen and factor VII levels.

Discontinuation due to adverse events

ALD 1537

The incidence of withdrawal was higher in the placebo group (20%) than both the ALD 0.25 (6%) and the ALD 0.1 (9%) treatment groups. Ineffective therapy as a reason was highest in the placebo group (8%) compared to ALD 0.25 (1%) and ALD 0.1 (2%). Withdrawals due to AEs were highest in placebo (n = 16, 8%), vs ALD 0.1 (n = 11, 6%) and ALD 0.25 (n = 4, 2%).

It was noted that in 8 of the 11 ALD 0.1 subjects withdrawn due to AEs, the events were considered possibly or probably related. These included hypertension, fluid retention, musculoskeletal pain, depression, vaginal bleeding and endometrial thickening, headache, benign breast neoplasm, and abdominal pain, nausea and increased LFTs.

Endometrial hyperplasia

Information from previously evaluated study KLIM/PD/7/USA

This was a double blind, randomised, parallel group, multicentre, dose finding efficacy and safety study in postmenopausal women, comparing 1 mg oestradiol in combination with low doses of NETA with 1 mg oestradiol alone. It was evaluated in the clinical evaluation for Kliovance registration. The primary objective was to determine the lowest effective dose of NETA in combination with 1 mg oestradiol that substantially reduced the incidence of endometrial hyperplasia after 12 months, compared to 1 mg oestradiol treatment alone.

Treatments were 1 mg E2 alone (n=296), 1 mg E2 + 0.1 mg NETA (n = 294) (the combination currently proposed for registration), 1 mg E2 + 0.25 mg NETA (n = 291), and 1 mg E2 + 0.5 mg NETA (n = 295). The primary efficacy variable was incidence of endometrial hyperplasia; secondary variables included endometrial histology, endometrial thickness, and bleeding.

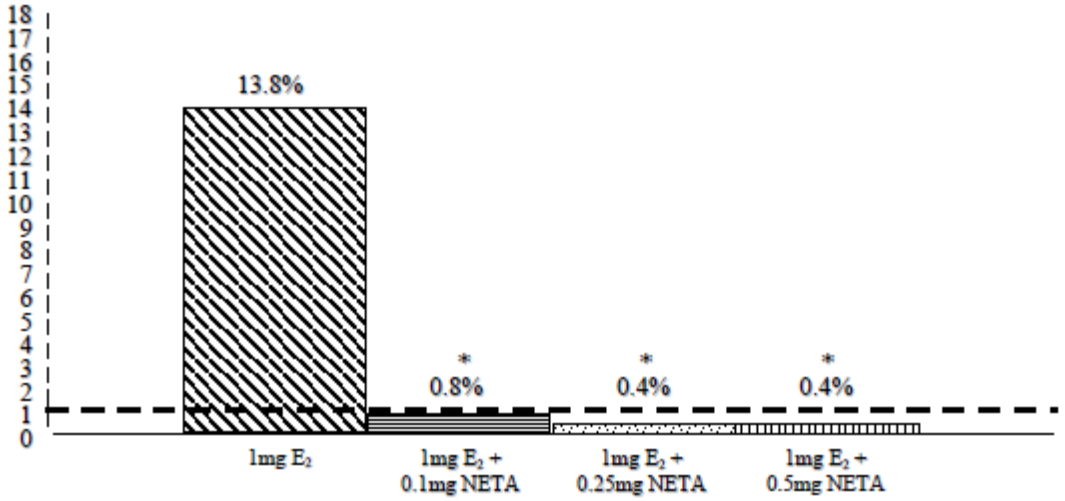
Endometrial hyperplasia rates were < 1% with all E2 + NETA combinations, compared to 13.8% in the unopposed E2 1 mg group. The 0.1 mg dose was considered sub-therapeutic

when selected for a treatment arm in KLIM/PD/7/USA but the overall result was considered by the sponsor to indicate that NETA was a potent progestogen in preventing the endometrial hyperplasia that is associated with unopposed 1 mg oestradiol treatment. The incidence of endometrial hyperplasia is shown at Figure 5.

Breakthrough bleeding rates at 12 months were 42 % for the NETA 0.1 mg, 27 % for NETA 0.25 mg, and 23% for NETA 0.5 mg combinations with E2 1 mg.

Figure 5: Number of Endometrial Hyperplasias at the end of Study KLIM/PD/7/USA

Study duration: 12 months	E_2 (mg)	E_2 (mg) + NETA (mg)		
Composition	1	1+0.1	1+0.25	1+0.5
Number of Hyperplasias/Number of biopsies [%]	34/247 [13.8%]	2/249 [0.8%]	1/251 [0.4%]	1/241 [0.4%]



* Significantly different ($p < 0.001$) vs. 1mg E_2

For 1 mg E2 + 0.1 mg NETA hyperplasia biopsy results were one simple hyperplasia without atypia and one complex hyperplasia with atypia. In comparison, for 1 mg E2 + 0.25 mg NETA there was one complex hyperplasia with atypia, and for 1 mg E2 + 0.5mg NETA there was one simple hyperplasia without atypia.

From individual pathologist readings, the combination of 1 mg E2 + 0.5 mg NETA was found to provide the best protection against hyperplasias. This was based on a quantitative evaluation of the number of hyperplasias as well as a qualitative assessment of cytological atypia, which was incorporated because of the high risk of progression from complex hyperplasia with atypia to endometrial carcinoma.

There was an expected inverse relationship between NETA dose and reported endometrial proliferation. The proportion of women with bleeding remained constant over time in the E2 1 mg + NETA 0.1 mg group, but decreased in the E2 1 mg + NETA 0.5 mg (Kliovance) group.

The sponsor's *Clinical Summary* for this submission states the reason for concluding endometrial safety for Kliovance Low without specific data for the product:

"The incidence of endometrial hyperplasia for each of the E2 + NETA combination groups was less than 1%, comparable to the rate observed in postmenopausal women not receiving HRT or receiving currently marketed oestrogen/progestogen combinations and in accordance with the recommendations of EMEA and FDA. The results from the study KLIM/PD/7/USA clearly demonstrate that doses of NETA of 0.25 and 0.1 mg were sufficient for endometrial protection during treatment with E2 1 mg per day. By halving the dose of E2 from 1 mg to 0.5 mg (and thus reducing the endometrial proliferative effect) and maintaining the NETA dose at 0.1 mg as in ALD 0.1, the same or an improved effect on endometrial protection is expected."

From the minutes of the 202nd meeting of the Australian Drug Evaluation Committee (ADEC, which preceded the ACPM), when Kliovance was considered, the following was noted:

"Study PD/7/USA (Table 11) assessed the lowest effective dose of NETA for endometrial protection and bleeding control. This randomised double blind 12 month study compared E2 1 mg alone, versus E2 1 mg/NETA 0.1 mg, versus E2 1 mg/NETA 0.25 mg, versus E2 1 mg/NETA 0.5 mg in 1176 women. The incidence of endometrial hyperplasia was 13.8 % in the unopposed E2 group compared to < 1 % in the combined E2/NETA groups. This degree of endometrial protection is of the order previously accepted by ADEC for combination HRT products. Bleeding control was most satisfactory in the E2 1 mg/NETA 0.5 mg (Kliovance) group, with breakthrough bleeding rates at 12 months of 42 % for the NETA 0.1 mg, 27 % for NETA 0.25 mg, and 23% for NETA 0.5 mg."

Evaluator comment

In KLIM/PD/7/USA NETA 0.1 mg combined with 1 mg oestradiol resulted in one simple hyperplasia and one complex hyperplasia with atypia from 249 biopsies. The sponsor extrapolated that NETA 0.1 mg would be sufficient for endometrial protection when combined with the lower strength of 0.5 mg oestradiol in Kliovance Low, as in ALD 1537.

Endometrial sampling was not undertaken in ALD 1537 to confirm this expectation.

EU Guidelines adopted by the TGA state that endometrial biopsy is the gold standard for safety in evaluation of a new strength of combination HRT. "For a new combination of oestrogen/progestogen (e.g. new administration scheme or new strength) or a new progestogen in a fixed combination, endometrial data are required".[2]

However an exception is "for a known progestogen, with the same administration route and the same progestogen dose as in known fixed combination with oestrogen, where data on endometrial safety can be extrapolated from the fixed combination if exposure to the oestrogen is similar or lower."

Endometrial safety for this product therefore rests on the acceptability of the extrapolation from data for the 1 mg E2 + 0.1 mg NETA combination studied in KLIM/PD/7/USA.

Recommendations in current guidelines for endometrial safety indicate that a new product should be comparable to or better than currently marketed products, have data including bleeding profiles from 300 subjects for 12 months and the upper limit of a two sided 95% confidence interval of the observed frequency of endometrial events should not exceed 2%. In KLIM/PD/7/USA 294 subjects were in the 1 mg oestradiol + 0.1 mg NETA combination arm and the incidence of hyperplasia was 2/249 (0.8%) vs one case each (0.4%) for the other two strengths investigated. This was greater than the 0.26% incidence of hyperplasia mentioned in the current HRT guidelines for recently registered combinations in Europe; confidence intervals were not provided.

Overall the outcome of KLIM/PD/7/USA was that the lowest NETA dose, 1 mg E2 + 0.1 mg NETA was *not* chosen for further development, not only because of the biopsy findings of one case of complex hyperplasia with atypia as well as a case of simple hyperplasia but also a higher incidence of bleeding, compared to the optimal combination 1 mg E2 + 0.5 mg NETA which was registered as Kliovance. As the 1 mg E2 + 0.1 mg NETA combination is not registered, additional clinical data are unavailable to support and confirm endometrial protection with this combination, yet this is relied upon to justify lack of endometrial biopsy data for the product proposed for registration.

The clinical evaluation for Kliovance noted that in KLIM/PD/7/USA a cut off at 4 mm did not clearly differentiate normal from abnormal endometrium on ultrasound. This is consistent with the guidance advice that ultrasound cannot replace biopsy.[2]

Summary of Safety Information for Kliovance Low from submitted data.

ALD-1537

No endometrial biopsy data were systematically collected in this trial.

Bleeding profiles were available for 6 months only.

Adverse event reports showed

- the incidence of treatment related vaginal haemorrhage was 25% with Kliovance Low compared to 12% with placebo
- the incidence of moderate to severe bleeding with ALD 0.1 was 10% after cycle 4 and 5 % after cycle 6, compared to 2% and 1% respectively for placebo
- the incidence of endometrial thickening was double that compared to placebo
- three ovarian cysts were reported, with follow up not recorded
- two uterine polyps were reported, with follow up not recorded; these subjects would have been excluded under current guidelines.

KLIM/PD/7/USA

Statistical incidence of endometrial hyperplasia from endometrial biopsy data for 1 mg E2 + 0.1 mg NETA was 2/249 biopsies (0.8%), significantly less than for 1 mg unopposed oestradiol and clinically acceptable, that is, < 1%. This product was not further investigated but the data are relied upon as for a "known combination" from which to extrapolate endometrial safety for Kliovance Low.

Postmarketing experience

No postmarketing data were provided but the evaluator noted that the product appears to be marketed in the USA. The sponsor should provide relevant postmarketing reports, including any analysis of the incidence of bleeding, endometrial hyperplasia, endometrial thickening and other events related to the lower dose of progestogen and oestrogen. It appears this would be the only means of confirming the sponsor's expectations of adequate endometrial protection.

Evaluator's overall conclusions on clinical safety

- Safety data for Kliovance Low are limited to the 6 month trial data from ALD 1537 and do not include endometrial biopsy data specific to the product proposed for registration.
- Clear information from the specific trial data available for this formulation (ALD 1537) must be provided in the PI. This includes incidence of bleeding and endometrial

thickening. It is suggested that tabulation of events considered related occurring in > 2% for both ALD 0.1 and placebo may be appropriate.

- Postmarketing data are not available.
- PI warnings and precautions should be at the same level as for Kliovance.
- There are no safety data from direct comparison with Kliovance.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

A number of questions were asked and answered during the evaluation process.

It was clarified that concomitant medications referred to the 6 months before screening.

The laboratory data were clarified to show that elevated oestradiol levels were obtained at visits 12 and 24 weeks, not at screening. Follow up for adverse events was intended to be until recovered or all queries resolved for serious/severe/possibly/probably related events, except for 'chronic conditions' which could be closed with an outcome of 'recovering' or 'not recovered'.

No new or additional data were provided.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

Study 1640

Test preparation A was the same formulation as the Kliovance Low combination proposed for registration. The reference product C, *Activelle*, had the same formulation as that currently on the ARTG for Kliovance.

Criteria for bioequivalence were fulfilled for the dose adjusted rate and extent of absorption was shown with regard to oestradiol (E2) and norethisterone (NET) between 2 tablets of the test preparations (A or B) and a single tablet of the reference preparation (C, Activelle); confidence intervals in the pre-specified concentration dependent endpoints of the PK analysis were within the acceptance range 0.8 to 1.25.

The study demonstrated dose proportional pharmacokinetic parameters for NET between 0.2 mg and 0.5 mg.

Pharmacodynamics

Vaginal Maturation Index and pH were measured. Maturation value increased in the active treatment arms but showed slight decrease for placebo and vaginal pH decreased in those receiving ALD 0.1 and ALD 0.25, but remained the same for placebo.

Clinical efficacy

There are no data comparing efficacy with the registered strength Kliovance.

ALD 1537

This 24 week study (n = 577) compared a single daily dose of combination tablets 0.5 mg oestradiol + 0.1 mg NETA (ALD 0.1, ITT n = 194) or 0.5 mg oestradiol + 0.25 mg NETA (ALD 0.25, ITT n = 180) with placebo (ITT n = 199). The primary outcome variable was the number of hot flushes per week.

- The overall treatment effect was statistically significant at every time point from Week 4.
- The paired comparisons of both treatments vs placebo showed statistically significant reductions in hot flushes.
- For ALD 0.1 compared to placebo, the estimated treatment difference in moderate to severe hot flushes at Week 8, the primary time point, was statistically and clinically significant; -21.5 (95% CI -27.0, -16.5).
- The effect persisted at Week 24, -19.6 (-26.0, -14.0).
- No significant differences were seen between ALD 0.25 and ALD 0.1 at any time points.

Clinical safety

There are no data comparing safety with the registered strength Kliovance.

There were 24 healthy subjects exposed to a single dose in PK study 1640 and 176 exposed to one tablet of the Kliovance Low formulation daily for the full 24 weeks in study ALD-1537.

Adverse events

Study 1640: In the single dose PK there were no observable adverse event reporting differences between the three products.

ALD 1537: At least 70% of subjects reported AEs but only 1% were classified as serious. Completers in each group were ALD 0.1 group 90%, ALD 0.25 group 94% and placebo group 80%.

Reports of "vaginal haemorrhage" were very common (26%, 22%, 12%).

Cardiac disorders were reported in 4% of the ALD 0.1 and 2% of ALD 0.25 groups, compared to 6% of the placebo group.. There were no reports of thromboembolic events in any of the treatment groups. Breast symptoms were reported by < 2% of subjects in ALD 0.1 and ALD 0.25 groups. This incidence was comparable to the placebo group.

In AEs occurring commonly (≥ 2%) and considered related:

- The incidence of treatment related vaginal haemorrhage in the ALD 0.25 and ALD 0.1 treatment groups was approximately 25% compared to 12% for placebo
- The incidence of "endometrial thickening" in the ALD 0.1 group was 9% compared to 6% for ALD 0.25 and 4% for placebo
- There were three ovarian cysts, reported from the ALD 0.1 group only
- There were two uterine polyps reported from the ALD 0.1 group only.

Serious adverse events and deaths

SAEs occurring in the ALD 0.1 group were intervertebral disc disorder, concussion and depression, dizziness, ankle fracture and benign breast neoplasm. One subject in the placebo group died of a myocardial infarction.

Laboratory findings

Oestradiol levels were high in many subjects after treatment. Other changes were not considered clinically significant.

Indicators Specific to HRT

Endometrial biopsy was not specified in the protocol of ALD 1537. Endometrial safety therefore depends upon extrapolation from data obtained from KLIM/PD/7/USA for the combination with double the dose of oestrogen and the same dose of progestogen, that is, 1 mg oestradiol and 0.1 mg NETA, with reported endometrial hyperplasia incidence of 2/249 (0.8%).

Bleeding profile The duration of the study was 6 months only. By Cycle 6, 89% of subjects completing in both ALD 0.1 and ALD 0.25 groups had no bleeding or spotting compared to 97% in the placebo group. Conversely, 5% of subjects receiving ALD 0.1 or ALD 0.25 reported moderate or heavy bleeding compared to 1% of the placebo group.

Endometrial thickness (TVUS) Mean endometrial thickness was within the normal range for all treatment groups. At the end of the study:

For ALD 0.1 subjects

- 10 % had endometrial thickness ≥ 5mm on TVUS
- 18% were reported as having TVUS interpretation "abnormal"

For placebo

- 4% had endometrial thickness ≥ 5mm on TVUS
- 11 % were reported as having TVUS interpretation "abnormal"

Mammography In the ALD 0.1 treatment group all subjects maintained the same visual classification status for the duration of the trial, compared to one subject increased and two subjects decreased in the placebo group.

Discontinuation due to adverse events

Withdrawals due to AEs were ALD 0.1 n = 11 (6%), ALD 0.25 n = 4 (2%), placebo n = 16 (8%). In 8 of the 11 ALD 0.1 subjects withdrawn due to AEs, the events were considered possibly or probably related. These events included hypertension, fluid retention, musculoskeletal pain, depression, vaginal bleeding and endometrial thickening, headache, benign breast neoplasm, and abdominal pain, nausea and increased LFTs.

Benefit risk assessment

Benefits

The benefits demonstrated for Kliovance Low are in treating post-menopausal women with frequent moderate to severe hot flushes. This is based on a 24 week trial that showed clinically and statistically significant greater mean reduction in hot flushes in 194 postmenopausal women, at least 6 months post menopause and suffering at least 7 moderate to severe hot flushes per day, compared to 200 similar women assigned to placebo treatment.

Risks

From the available data, the risks of adverse events with Kliovance Low follow the expected profile for continuous HRT. In particular there is evidence for spotting/bleeding in at least 10% of subjects treated, and "endometrial thickening" on TVUS occurred in a similar proportion, that is, very commonly.

Endometrial biopsy data were not collected in this trial and therefore there has been no formal confirmation of the expectation that NETA 0.1 mg would be sufficient for endometrial protection when combined with 0.5 mg oestradiol in Kliovance Low.

Extrapolation of endometrial safety is proposed from the data obtained in KLIM/PD/7/USA for the combination 1 mg oestradiol+ 0.1 mg NETA, which may be considered consistent with TGA-adopted EU guidelines. However this has limitations, in that the incidence of endometrial hyperplasia is derived from two cases, one of which was assessed as complex hyperplasia with atypia. This would be relied upon exclusively to support endometrial safety for the product proposed for registration.

There is no direct evidence comparing Kliovance Low with the currently registered Kliovance, so that the requirement that a new product is better than a currently marketed HRT with respect to endometrial safety has not been fulfilled.

No information is available on endometrial thickening or potential for endometrial hyperplasia if treatment is continued for longer than 6 months. Bleeding profiles are not available for 12 months use, as specified for continuous combined products in the adopted guideline.

There is therefore a potential risk that because this dose will be considered "safer" than higher dose HRT products, it will be prescribed more widely and for longer durations, without comparative data to support such clinical use.

Balance

On balance, the safety data provided for evaluation were not considered adequate to support registration.

The significant deficiencies are

- Lack of endometrial biopsy data to confirm the expectation of endometrial protection.
- No comparison with the registered product Kliovance.
- No postmarketing safety data were provided although the product is marketed in the USA.

Conclusions

The evaluator concluded that registration cannot be recommended based on the available information. If the product is registered, the evaluator indicated that the PI should be revised taking into account issues raised in the evaluation, including the reinstatement of a Boxed Warning and should contain relevant findings specific to Kliovance Low, including AEs from the main trial ALD 1537.

V. Pharmacovigilance Findings

Risk Management Plan

The Office of Product Review (OPR) was of the opinion that because Kliovance Low contained a lower dose of oestradiol than Kliovance, it was less likely to pose a safety concern and a Risk Management Plan was not required.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

All outstanding chemistry and quality control aspects were addressed and the evaluator recommended approval from a chemistry and quality control point of view.

The bioavailability study ALD 1640 was discussed by the evaluator. Bioequivalence was demonstrated in relation to Kliovance regarding oestradiol and norethisterone as seen in Table 1. The submission was not considered by PSC.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The evaluator noted that several studies that have been previously submitted (and evaluated by the TGA) have been resubmitted. Two studies, ALD 1640 and ALD 1537, which used the formulation proposed for marketing, have been evaluated in this report.

Pharmacokinetics

The primary objective of Study ALD 1640 was to compare the extent of the bioavailability of oestradiol 0.5 mg + NETA 0.1 mg and oestradiol 0.5 mg + NETA 0.25 mg, to oestradiol 1 mg + NETA 0.5 mg, (*Activelle*, an already registered combination) by calculating the rate (C_{max}) and extent ($AUC_{0-\infty}$) of absorption. The evaluator noted that the formulation of *Activelle* appears to be identical to that of the Australian registered product Kliovance.

The evaluator noted that the baseline corrected AUC_{0-t} and C_{max} of oestradiol (E2) and oestrone (E1) comparisons fulfilled criteria for bioequivalence. Dose adjusted $AUC_{0-\infty}$ and C_{max} of NETA for the two doses fulfilled criteria for bioequivalence.

Efficacy

The evaluator noted that the pivotal study is ALD 1537. It was stated that the other (previously evaluated) studies did not provide data "directly relating to the safety and efficacy of the combination, strength and the indication proposed for registration". One of these studies (KLIM/PD/ 7/USA) provided evidence of the acceptability of endometrial protection by 0.1 mg NETA and was discussed by the evaluator.

ALD 1537 was a double blind, randomised, multicentre, multinational, placebo controlled, parallel group trial designed to investigate the efficacy and safety of two low dose formulations of combined oestradiol and NETA, for menopause symptoms, compared with placebo. The active treatments were a single daily tablet of 0.5 mg oestradiol + 0.1 mg NETA (ALD 0.1) or 0.5 mg oestradiol + 0.25 mg NETA (ALD 0.25).

The primary efficacy endpoint was the number of moderate to severe hot flushes per weeks at 6 months. The severity scale was also predefined and several secondary endpoints were used and discussed by the evaluator. The results are shown in Figure 2 and Tables 11 and 12.

The evaluator noted that "the overall treatment effect, analysed using the Kruskal-Wallis test, was statistically significant at every time point from Week 4. The paired comparisons using the Wilcoxon test stratified by country showed statistically significant treatment differences for both treatments vs placebo". However there was no statistically significant difference between the active treatment groups. The PP population showed a similar trend.

The secondary efficacy endpoints were also discussed. In relation to the Greene Climacteric Score (GCS), there were statistically significant reductions compared to placebo at all time points for both treatment groups. In relation to specific subsets in relation to GCS, no statistically valid comparisons can be made as these subsets have not been factored into pre-study statistical considerations.

There was no statistically significant difference between active and placebo groups in relation to bleeding patterns.

Overall, the evaluator concludes that this study "does not appear to be designed as a non inferiority study". It is also not designed to show a difference between the active groups.

Safety

The safety results of ALD 1537 were discussed in detail by the evaluator. In relation to bleeding profile, the issue of note was that moderate to severe bleeding was reported in 5% (active) and 1% in placebo.

Endometrial biopsy was not a protocol planned procedure and therefore is inadequate.

Trans-vaginal ultrasound (TVUS) was performed at baseline and at the end of treatment. No significant difference in relation to endometrial thickness between groups was seen. There were 10% (in the active groups) with endometrial thickness ≥ 5mm; 18% were reported as abnormal findings on TVUS. In relation to placebo, these figures were lower, being 4% and 11% respectively. TVUS is not recommended to replace the biopsy for evaluation of endometrial hyperplasia.

There were no trends relating to treatment related AEs, SAEs and withdrawals due to AEs.

KLIM/PD/7/USA was a double blind randomised parallel group multicentre dose finding study in postmenopausal women comparing 1 mg oestradiol in combination with low doses of NETA with 1 mg oestradiol alone. Endometrial biopsy was conducted at baseline and at the end of treatment.

The results are shown in Figure 5.

The evaluator stated that for 1 mg E2 + 0.1 mg NETA hyperplasia biopsy results were: one simple hyperplasia without atypia and one complex hyperplasia with atypia. In comparison, for 1 mg E2 + 0.25 mg NETA there was one complex hyperplasia with atypia, and for 1 mg E2 + 0.5mg NETA, there was one simple hyperplasia without atypia.

The evaluator stated that "there was an expected inverse relationship between NETA dose and reported endometrial proliferation. The proportion of women with bleeding remained constant over time in the E2 1 mg + NETA 0.1 mg group, but decreased in the E2 1 mg + NETA 0.5 mg (Kliovance) group".

The lack of endometrial biopsy data with the proposed dose strength was considered a significant deficiency.

This has been justified by the sponsor as: "the incidence of endometrial hyperplasia for each of the E2 + NETA combination groups was less than 1%, comparable to the rate observed in postmenopausal women not receiving HRT or receiving currently marketed oestrogen/progestogen combinations and in accordance with the recommendations of EMEA and FDA. The results from the study KLIM/PD/7/USA clearly demonstrate that doses of NETA of 0.25 and 0.1 mg were sufficient for endometrial protection during treatment with E2 1 mg per day. By halving the dose of E2 from 1 mg to 0.5 mg (and thus reducing the endometrial proliferative effect) and maintaining the NETA dose at 0.1 mg as in ALD 0.1, the same or an improved effect on endometrial protection is expected."

However, the evaluator expressed concerns on the lack of endometrial biopsy data. The main issues are as follows:

1. The sponsor had chosen not to develop the lowest dose combination (1 mg E2 + 0.1 mg NETA) used in KLIM/PD/7/USA because of the abnormal biopsy finding (one case of hyperplasia with atypia and one case of simple hyperplasia) and a higher incidence of bleeding compared to Kliovance (1 mg E2 +0.5 mg NETA). It is assumed that a lower

dose of oestradiol would enhance endometrial protection. Yet, no data are provided to support this assertion.

2. The current guidelines on endometrial safety state that a new product should be comparable to or better than currently marketed products. In this context the incidence of hyperplasia (0.8%) is greater than the 0.26% mentioned for recently registered products in Europe. In addition, there is no direct comparative data with Kliovance to show that this product is better than a currently registered product as recommended in the TGA-adopted EU guideline.[2]
3. No information is available on endometrial thickening or potential for endometrial hyperplasia if treatment is continued for longer than 6 months. Bleeding profiles are not available for 12 months use, as specified for continuous combined products in the TGA-adopted guideline.
4. There was no postmarketing safety data provided.

Overall conclusion of the evaluator

The evaluator concluded that on balance, safety data provided are not adequate to support registration. The reasons are discussed above.

The evaluator also recommended that should the product be recommended for registration, the boxed warning should be reinstated and all recommendations regarding the product information (not discussed in this AusPAR) be adopted.

Risk-Benefit Analysis

Delegate Considerations

The Delegate agreed with the evaluator's conclusion and recommendations.

The main reason for rejection is the lack of any direct endometrial safety data on the proposed product.

The current evidence based on Study KLIM/PD/7/USA showed that the combination of 1 mg E2 +0.1 mg NETA produced abnormal biopsy findings. No data were provided with the reduced E2 (0.5 mg) that is proposed in Kliovance Low, to show that it is the minimum effective dose.

Similarly, in order to ascertain the safety profile of Kliovance Low, no comparative endometrial safety data with Kliovance, a registered product, is submitted.

Overall, the Delegate recommended rejection, due to lack of endometrial safety submitted to support registration.

Response from Sponsor

The sponsor noted that discussion about the risk benefit profile of HRT has intensified since the publication of data from the Women's Health Initiative (WHI) and Million Women studies, resulting in a shift in clinical practice towards use of the lowest effective dose for each woman for the shortest period of time required to address symptoms. This view is supported by regulatory agencies including TGA, with current guidelines recommending "for the initiation and continuation of treatment, the minimum effective dose for the shortest duration should be used".[2] Current clinical opinion does not mandate that the lowest dose should be used for all women as each woman will clinically require a different dose to treat symptoms. It should be noted that in filing for registration of Kliovance Low, the sponsor was not looking to replace any existing therapies but was seeking to provide healthcare professionals with a lower dose option of continuous combined oestradiol (E2; 0.5 mg) and norethisterone acetate (NETA; 0.1 mg). The same

principles have been applied to the development and marketing of a large range of doses for oral contraceptives.

Like the established higher dose products, Kliovance (1 mg E2 + 0.5 mg NETA) and Kliogest (2 mg E2 + 1 mg NETA), Kliovance Low is intended for once daily administration in women with an intact uterus for the treatment of menopausal symptoms related to oestrogen deficiency more than one year after menopause. Novo Nordisk's development of Kliovance Low was undertaken in line with the regulatory positions endorsed by ADEC and the scientific evidence base underpinning the principle of lowest effective dose.

Real world clinical experience for more than 4 years supports the efficacy and safety profile of Kliovance Low. Marketing authorisation for Kliovance Low was granted in the US on 28 December 2006 and on 11 September 2008 in the EU. Kliovance Low, marketed under various names, was first launched in the US on 05 April 2007, with subsequent launches in Canada, Israel, Norway, Portugal, Spain and Sweden.

The sponsor noted that efficacy of Kliovance Low has been substantiated. Data from study ALD -1537 have demonstrated the efficacy of the combination of 0.5 mg E2 + 0.1 mg NETA (Kliovance Low) in improving vasomotor symptom relief, showing a statistically significant treatment effect for the primary endpoint, number of moderate to severe hot flushes. The TGA clinical evaluator and the Delegate do not contest the efficacy of Kliovance Low.

The Delegate's issues were addressed by the sponsor.

The sponsor had chosen not to develop the lowest dose combination...

Direct dose response relationship between unopposed oestrogen and endometrial hyperplasia

While not submitted with the current application, the sponsor indicated it wished to draw on data available in the public domain to confirm the well documented positions held with reference to treatment with unopposed oestrogens. In a systematic review of 45 trials to assess the risk of endometrial hyperplasia in hormone therapy in postmenopausal women, three main findings were established:

1. unopposed oestrogen therapy increases the risk of endometrial hyperplasia,
2. a dose response relationship and duration of treatment response relationship exists between unopposed oestrogen and risk of hyperplasia and
3. the addition of a progestogen to unopposed oestrogen in the treatment of women with intact uteri resulted in a significant reduction in the risk of endometrial hyperplasia.[5] Taking these findings into consideration, widely accepted guidance in clinical practice recommend the lowest effective dose of oestrogen with the addition of a low dose progestogen for the treatment for this patient group.[6,7]

[5] Furness S, Roberts H, Marjoribanks J, Lethaby A, Hickey M, Farquhar C. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub3.

[6] Sturdee DW, Pines A. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. Climacteric. 2011; 14: 302-320.

[7] Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society Menopause: J North American Menopause Soc 2010; 17: 242-255.

An increased rate of hyperplasia with unopposed E2 therapy compared with ccHRT was demonstrated in KLIM/PD/11/USA

The sponsor refuted the Delegate's claims that data were not provided to support the assertion that a lower dose of E2 enhances endometrial protection. The relationship between dose and duration of treatment with unopposed E2 and the exerted proliferative effect is strongly evidenced by the supportive study KLIM/PD/11/USA (KLIM/11), initially evaluated for Kliovance extension of indication (osteoporosis), which was also included for evaluation with the current application.

In KLIM/11, women with an intact uterus were given unopposed E2 (1 mg, 0.5 mg, 0.25 mg) or one of three various doses of continuous combined HRT (ccHRT) (2 mg E2 + 1 mg NETA, 1 mg E2 + 0.5 mg NETA, 1 mg E2 + 0.25 mg NETA), over 26 months. In the unopposed E2 treatment groups, after one year of treatment, three cases of hyperplasia were reported in the 1 mg E2 group and one case of hyperplasia was reported in the 0.5 mg E2 group. After two years of treatment, an additional five cases of hyperplasia were reported in the 1 mg E2 group, with no additional cases of hyperplasia occurring in the 0.5 mg E2 group. This is in contrast with the ccHRT treatment groups in which no cases of endometrial hyperplasia were reported during the study.

The addition of a low dose progestogen to oestrogen treatment reduces the risk of endometrial hyperplasia in women with an intact uterus.

KLIM/11 was also supportive of the role of progestogen in ccHRT in the protection of the endometrium from the hyperproliferative effects of oestrogens. The results show that no cases of endometrial hyperplasia were reported in the ccHRT treatment groups compared with unopposed E2 treatment groups.

0.1 mg of NETA taken continuously with 1 mg E2 provides adequate endometrial protection.

A dose of 0.1 mg of NETA taken continuously with a 1 mg dose of E2, which is twice the dose contained in Kliovance Low, provides adequate endometrial protection. The 12 month study, KLIM/PD/7/USA (KLIM/7), demonstrated a statistically significant ($p<0.001$) reduction in the incidence of endometrial hyperplasia in the ccHRT treatment group compared with the unopposed E2 treatment group. In the unopposed 1 mg E2 group the incidence of hyperplasia at the study end was 14.6%, compared with less than 1% for the ccHRT groups: 0.4% in the 1 mg E2 + 0.5 mg NETA group, 0.4% in the 1 mg E2 + 0.25 mg NETA group and 0.8% in the 1 mg E2 + 0.1 mg NETA group. The frequency of endometrial abnormalities associated with the ccHRT groups was low and within those seen in the background population (annual incidence of endometrial abnormalities in non-treated postmenopausal women of approximately 1%).[8] Moreover the 0.1 mg NETA group did not differ with respect to this safety outcome.

In terms of absolute figures, the rate of endometrial hyperplasia reported in the ccHRT groups compared with that seen in the unopposed E2 group was low. In the ccHRT groups, the number of cases of endometrial hyperplasia seen per number of available biopsies was: 1/241 in the 1 mg E2 + 0.5 mg NETA group, 1/251 in the 1 mg E2 + 0.25 mg NETA group and 2/249 in the 1 mg E2 + 0.1 mg NETA group, compared with 36/247 in the unopposed 1 mg E2 group.

Moreover, the clinical evaluator for the current application references a statement from the ADEC Minutes (where Kliovance [1 mg E2 + 0.5 mg NETA] was discussed), that "this degree of endometrial protection is in the order previously accepted by ADEC for combination HRT products". It should be emphasised that this result pertains to the

[8] Kurman RJ, Felix JC, Archer DF, Nanavanti N, Arce JC, Moyer DL. Norethinderone acetate and estradiol-induced endometrial hyperplasia. Obstet Gynecol 2000; 96: 373-379.

lowest dose ccHRT used in KLIM/7 (1 mg E2 + 0.1 mg NETA) which contains twice the dose of E2 compared with the proposed formulation, Kliovance Low. It is therefore expected that 0.1 mg NETA should be sufficient to exert a protective effect on the endometrium if opposing the lower dose of 0.5 mg E2. Supporting this, a recent meta-analysis looking at hormone therapy in postmenopausal women and the risk of endometrial hyperplasia concluded that for 1 mg E2, 0.1 mg of NETA taken continuously will give endometrial protection.[5]

The protective effect of 0.1 mg NETA was also supported by the results of transvaginal ultrasound (TVUS) performed in the 24 week study ALD 1537 to determine endometrial thickness as a measure of endometrial hyperplasia. Although endometrial assessment was not determined by endometrial biopsy as recommended in the TGA-adopted EU guideline, the results of the TVUS are valid and should be considered by ACPM. The incidence of endometrial thickening, defined as thickness > 5 mm, was 6% (11 subjects) in the 0.5 mg E2 + 0.25 mg NETA group, 10% (19 subjects) in the 0.5 mg E2 + 0.1 mg NETA group and 6% (8 subjects) in the placebo group. Mean endometrial thickness at the study end was within the normal range for all the treatment groups.

While comprehensive endometrial protection data are not available for the lower dose combination of E2 + NETA in Kliovance Low, the sponsor presented the following supportive clinical findings:

- In KLIM/11, treatment with unopposed E2 resulted in a hyperproliferative effect on the endometrium, seen as a higher incidence of hyperplasia. Moreover, no cases of endometrial hyperplasia were reported for subjects receiving any dose of ccHRT, demonstrating the protective effect of progestogen on the endometrium.
- In KLIM/7, a statistically significant reduction was seen in the incidence of hyperplasia between the unopposed 1 mg E2 group (14.6%) and the ccHRT groups (0.1%). A dose of 0.1 mg NETA combined with twice the dose of E2 (1 mg) than contained in Kliovance Low was effective in protecting the endometrium resulting in a low incidence of hyperplasia (2/249).
- In ALD 1537, at the study end (24 weeks) mean endometrial thickness was within the normal range for all treatment groups showing that 0.1 mg NETA was effective in endometrial protection.

The rate of hyperplasia seen in KLIM/7 in terms of absolute numbers and with relation to background incidence is low. Based on the current data and clinical opinion, the sponsor argued 0.1 mg NETA was effective in opposing the proliferative effect of a higher dose of E2 (1 mg) and thus providing endometrial safety, the same NETA dose would be effective in opposing the lower E2 dose contained in Kliovance Low (0.5 mg).

A new product should be comparable to or better than currently marketed products ...

Compliance with EMEA/CHMP/021/97 Rev 01

While not mandatory, the current guideline with respect to endometrial hyperplasia recommends "that incidence should be statistically less than 2% after one year of treatment, that is, the upper limit of a two sided 95% confidence interval of the observed frequency of endometrial events should not exceed 2%".[2] It should be clarified that the guideline does not require a new HRT product to show an incidence of hyperplasia below 0.26%, a figure derived from pooled data from recently authorised ccHRT products in Europe. Direct head to head trials would be required. TGA have recently approved Vagifem Low, which showed an incidence of 0.52%, which is above the 0.26% referenced and the upper limit of the two sided 95% CI was 1.86%.

The results from KLIM/7 showed that the incidence of endometrial hyperplasia in women (n=249) taking the ccHRT combination 1 mg E2 + 0.1 mg NETA, which contains twice the dose of E2 than Kliovance Low, was 0.8% (95% CI 0.097 – 2.871%) at 1 year. The sponsor accepted that the endometrial safety data presented for the 1 mg E2 + 0.1 mg NETA does not comply with the current guideline as the upper limit of the two sided 95% CI exceeds 2% but the relevance of value to Kliovance Low is not known.

On the basis of the data presented in the current application and this response, the sponsor argued that the combination of 0.5 mg E2 + 0.1 mg NETA, containing half the E2 dose of the reference product used in KLIM/7, is expected to produce a reduced proliferation stimulus. A reduction in the incidence of endometrial hyperplasia for Kliovance Low compared with the rates seen in KLIM/7 is therefore expected. It would follow that this will result in a reduction of the upper limit of the two sided 95% CI below 2%. The sponsor acknowledged that direct head to head trials would be required to satisfy this recommendation.

No information is available on endometrial thickening or potential hyperplasia if treatment is continued for longer than 6 months.

The sponsor noted that it was correct for the Delegate to state that the sponsor has not submitted data for bleeding or endometrial thickening beyond 6 months for Kliovance Low, however Novo Nordisk has committed to providing postmarketing bleeding pattern surveillance over 12 months as addressed below which should inform this discussion.

Previous data have shown that ccHRT treatment results in a continuously gradual decrease in the incidence of bleeding/spotting over time after the initial three months of therapy in a dose dependent manner.[9] Irregular bleeding in users of ccHRT is most common in the initial months of treatment with irregular bleeding gradually decreasing during continued use of ccHRT. The results from KLIM/7, conducted over 12 months, accord with these findings. The data show that addition of NETA to 1 mg E2 resulted in a continuously gradual decline in the incidence of bleeding/spotting over time after the initial three months of therapy in a dose dependent manner, while unopposed 1 mg E2 resulted in a gradual increase of bleeding days over time. Data from KLIM/7 also indicate that amenorrhoea within the initial 6-9 months of ccHRT use is a good predictor of continued amenorrhoea. Among women presenting with amenorrhoea during the initial 6-9 months, only 7.2 % reported an episode of bleeding during Months 10-12.

In ALD 1537, the bleeding trend for the Kliovance Low treatment group follows the same pattern and the sponsor provided a figure which illustrated this. It could also be seen that a lower dose of E2 produces a much lower incidence of bleeding or spotting.

Novo Nordisk's commitment to perform a Phase IV study to evaluate the bleeding pattern of Kliovance Low over 12 months

Provision of 12 months' bleeding data was also raised by the Mutual Recognition and Decentralised Procedures during the evaluation of the registration of Kliovance Low in the EU. The Reference Member State (Sweden) accepted that Kliovance Low provided an acceptable rate of bleeding during the first 6 months of use and agreed that the lack of 12 month bleeding data was not a sufficient safety concern to prevent its registration. Nonetheless the sponsor committed to completing a 12 month post-approval study to collect bleeding data. As of 16 June 2011, no SAEs have been reported during the trial period. Novo Nordisk committed to providing these data to TGA.

[9] Archer DF, Dorin MH, Heine W, Nanavati N, Arce JC. Uterine bleeding in postmenopausal women on continuous therapy with estradiol and norethindrone acetate. Endometrium Study Group. Obstet Gynecol 1999; 94: 323-329.

No trending of reports of bleeding seen during the latest PSUR (01 April 2010 to 31 March 2011)

During the reporting period of the most recent Periodic safety Update Report (PSUR), two reports of vaginal bleeding (metrorrhagia and vaginal haemorrhage) occurred in patients after initiating therapy with Kliovance Low. Both events were not serious and neither was medically confirmed. Both events had a positive dechallenge. In the cumulative data, 20 events related to vaginal haemorrhage (metrorrhagia, menstrual disorder, uterine haemorrhage, menorrhagia and polymenorrhoea) have been reported. Breakthrough bleeding and spotting may occur during the first months of treatment with Kliovance Low, consistent with higher strengths of ccHRT products. The sponsor's evaluation concluded that these events do not raise a safety concern. Furthermore, the Novo Nordisk HRT safety committee met on 31 May 2011 and reported that no safety concerns were identified during the 2011 reporting period.

Postmarketing monitoring has demonstrated a favourable risk benefit profile for patients and does not raise any additional concerns in this area. As stated previously, in filing for registration of Kliovance Low, the sponsor is not looking to replace any existing therapies but is seeking to provide healthcare professionals with a lower dose option of ccHRT. The sponsor acknowledged that there may be cases where a higher dose of ccHRT such as Kliovance or Kliogest may be required to control bleeding sufficiently. There is no reason why the prescribing physician could not make this dose adjustment if deemed necessary. All women prescribed HRT are to be closely monitored during treatment and therefore any irregularities in bleeding profiles could be addressed. Consistent with current clinical opinion, Kliovance Low provides a lower dose option for ccHRT to match individual patient's symptom and risk profiles.

There were no postmarketing safety data provided

The estimated number of patients (patient years) exposed to Kliovance Low has been calculated to be approximately 198,478 based on sales volume. A low incidence of endometrial related and vaginal bleeding events seen for Kliovance Low has been shown in postmarketing data. No safety concerns were raised during the period 1 January 2007 to 6 July 2011. Since the first US market launch of Kliovance Low in April 2007, 21 cases of endometrial related and vaginal haemorrhage adverse events have been reported in the postmarketing data, with one case of malignant neoplasm.

Overall Conclusion

Kliovance Low, developed in line with the current regulatory and clinical guidance for therapy for the treatment of menopausal symptoms related to oestrogen deficiency, is one option in a range of E2 + NETA ccHRT doses designed to treat women with varying symptom/risk profiles. Kliovance Low's combination of a lower dose E2 (0.5 mg) combined with lower dose NETA (0.1 mg) has proven efficacious in vasomotor symptom relief and no challenges to efficacy have been made by the TGA clinical evaluator or the Delegate. Moreover, clinical data submitted with this application are supportive of the safety profile of Kliovance Low. Data from trials KLIM/11 and KLIM/7 clearly demonstrate the exerted proliferative effect of E2 is associated with dose and duration of treatment, and the addition of a low dose of progestogen (0.1 mg NETA) is sufficient to reduce risk of endometrial hyperplasia.

The sponsor reiterated that it was seeking to provide an alternative lower dose ccHRT product that based on clinical use may be satisfactory for a number of women as an option to reduce their current dose of HRT. As with oral contraceptives, the dose of oestrogen and progestogen is dependent on hormone responses and endogenous levels of each woman. Upon regular medical review which should be stressed, their dose could be up-adjusted if

bleeding were observed. Novo Nordisk was committed to providing postmarketing surveillance for all of our products to ensure patient safety. Kliovance Low has been successfully on the market in the US since 2007 with no safety concerns.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the clinical evaluator and the Delegate that there was insufficient evidence of safety to support use of Kliovance Low for the proposed indication.

In expressing its view that the overall risk benefit profile for this product was negative and that the submission should be considered for rejection, the ACPM considered the following matters:

That all outstanding chemistry and quality control aspects have been addressed from a chemistry and quality control point of view.

Efficacy

The overall treatment effect, as measured by number of moderate to severe hot flushes per weeks at 6 months, was statistically significant compared with placebo at every time point from Week 4 in the pivotal efficacy study.

Safety

In general the safety profile appears to be similar to that of the registered higher combination, in the submitted data. There were no trends relating to treatment related adverse events, serious adverse events and withdrawals due to adverse events. It was noted bleeding rates were increased with the proposed product.

No data were provided to support the assertion that a lower dose of oestradiol would enhance endometrial protection. The lack of endometrial biopsy data with the proposed dose strength was considered a significant deficiency. Trans-vaginal ultrasound (TVUS) is not recommended in the relevant guidelines to replace the biopsy for evaluation of endometrial hyperplasia.

Endometrial biopsy data were inadequate. Thus there were only very limited safety data on the extent of endometrial hyperplasia from the 6 months trial data; abnormal findings on TVUS were much higher with active treatment than with placebo.

In addition, no information was available on endometrial thickening or potential for endometrial hyperplasia if treatment is continued for longer than 6 months. Bleeding profiles were not available for 12 months use, as specified for continuous combined products in the TGA-adopted EMA guideline.

The ACPM, taking into account the submitted evidence of safety and efficacy, considered this submission contained a lack of endometrial safety data with the proposed formulation leading to an unfavourable benefit risk profile for the proposed indication.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the application for a new strength of Kliovance Low.

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