

Executive Summary

NDA:	21-239	Submission Dates:	
Brand Name:	Aslera™	Original NDA:	09/26/00
Generic Name:	Prasterone	Original Amendment N-BB:	02/09/01
Dosage Form:	Capsules		
Strength:	50 mg		
Applicant:	Genelabs Technologies Redwood City, CA		
OCPB Division:	DPEIII		
Reviewer:	Abimbola Adebawale Ph.D.		
Team Leader:	Dennis Bashaw Pharm.D.		

I. Introduction and Background

Genelabs Technologies, Inc. is seeking the approval of Aslera™, for the following proposed indications: 1) Improvement in disease activity and/or its symptoms in women with mild to moderate Systemic Lupus Erythematosus (SLE) and, 2) Reduction of corticosteroid requirements in steroid-dependent women with mild to moderate SLE.

Aslera™ consists of the active ingredient prasterone, a synthetic form of the 19-carbon steroid endogenous hormone Dehydroepiandrosterone, (DHEA). Most endogenous DHEA is produced by the adrenal cortex and is secreted as its inactive sulfate ester, DHEA-Sulfate (DHEA-S), which is subsequently converted by DHEA sulfatases to DHEA which in turn is metabolized to androgenic and estrogenic hormones (as shown in Figure below). DHEA-S is the most abundant circulating adrenal steroid in humans.

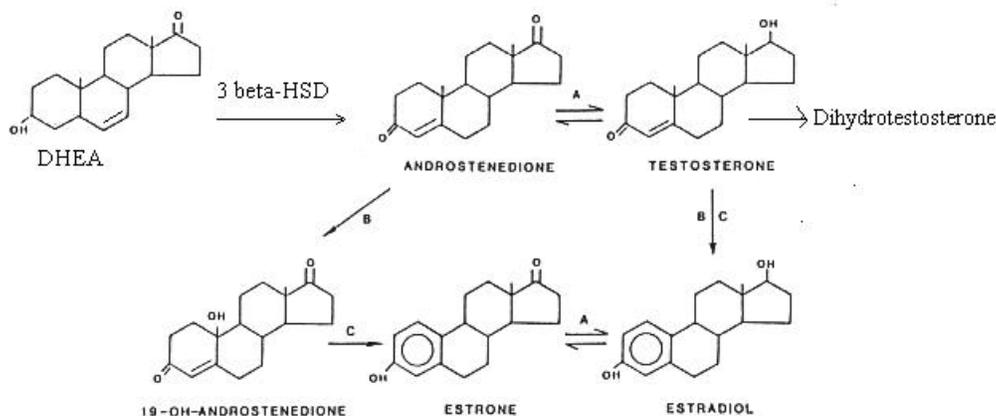


Figure: Aromatization and androgenic conversion of DHEA. Enzymes: (A) 17 beta-HSD; (B) 19-hydroxylase; (C) aromatase.

modified from Parker LN. Adrenal androgen metabolism. In Adrenal Androgens in Clinical Medicine. Academic Press, 1989, p8.

SLE is a multisystem disease commonly affecting the skin, joints, and kidney, and it is often accompanied by constitutional symptoms such as malaise and fatigue. Other internal

organs can be involved with the disease, such as the lungs, heart, and CNS, and these can often dominate the clinical picture. It is about 8 to 10 times more common in females than in males with approximately 65% of patients developing SLE between 16-55 years of age.

The epidemiology and natural history of SLE have suggested that hormonal influences may play a key role in disease development and progression. Decreased levels of androgens [androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate and testosterone] have been observed in female lupus patients especially in those with active disease, with circulating levels of DHEA and DHEA-S being approximately 50% decreased. Also studies in NZB/W murine mouse model of SLE have suggested that androgens, including DHEA, would be effective in SLE. The recommended dose is 200mg (four 50 mg capsules) of Aslera™ to be taken in the morning as a single dose once a day prior to any food intake.

II. Overview of the Clinical Studies Included in the NDA

Section 6 of NDA 21-239 included 3 studies and 80 literature references. The 3 studies conducted were 2 bioequivalence studies in post-menopausal healthy women (GL97-02 and GL99-01) and one drug interaction study (GL-96-02) in pre-menopausal healthy women. The 3 studies were reviewed. The applicant only provided a review of the literature on the distribution, metabolism and excretion of DHEA and DHEA-S. The Literature references as they related to distribution and metabolism and excretion of DHEA were reviewed. The drug product was referred to as GL-701 in all the clinical trials and the drug substance as DHEA. In support of this NDA the applicant also conducted two adequately controlled clinical trials; a corticosteroid reduction study in SLE patients assessing two different doses of GL701 (GL 94-01) and a disease improvement study in SLE patients with mild to moderate active disease (GL 95-02).

III. Pharmacokinetics

Absorption: Baseline concentrations of endogenous DHEA exhibited diurnal variations in endogenous production, while DHEA-S levels showed little variation during the day in premenopausal women in Study GL-96-02. Exogenous administration of GL701 produced levels of DHEA and DHEA-S that were up to 400 and 1400 fold greater than endogenous serum concentration. Following single and multiple dose (7 and 28 days) oral administration of GL701 200 mg/day to pre- and post- menopausal women, the adjusted serum concentration versus time profile for DHEA and DHEA-S demonstrated a parallel increase in serum concentrations of DHEA and DHEA-S between 2-3 hours after oral administration of exogenous DHEA. The T_{max} of adjusted serum concentrations for DHEA (2.09 ± 1.34 - 2.9 ± 1.0) and DHEA-S (2.32 ± 0.7 - 2.4 ± 0.9) after oral administration of DHEA were similar to one another (yet C_{max} and the AUC_(0-inf) for DHEA-S were approximately 500 – 1600 fold greater than DHEA. The absorption profiles suggested that conversion of orally administered DHEA to DHEA-S was rapid in the intestinal cells. There was a wide variability of ~ 30 – 70% associated with the pharmacokinetic parameters. The observed mean $t_{1/2}$ for disappearance of orally administered DHEA [22.5 (10.8) hours] and DHEA-S [18.97 (6.0) hours] following a single oral dose of GL701 200 mg/day were similar.

Distribution: Endogenous DHEA is widely distributed in the body. A literature reference reported that central and peripheral volumes of distribution (V1 and V2) for DHEA in premenopausal women (aged 18-35 years old) was 33.7 ± 2.5 and 27.5 ± 9.9 liters, respectively, and 38.5 ± 6.09 and 30.4 ± 7.3 liters, respectively for normal men (aged 23-33 yrs). Approximately

88.1% of circulating DHEA is bound to albumin, 7.88% to sex hormone binding globulin (SHBG), and <0.1% to corticosteroid binding globulin (CBG), leaving 3.93% unbound in normal women in the follicular phase of the menstrual cycle. In contrast to DHEA, DHEA-S is strongly bound to albumin in blood and undergoes renal tubular reabsorption, both of which contribute to the very slow clearance of DHEA-S from blood and a long $t_{1/2}$.

Metabolism: DHEA is metabolized in most tissues but primarily in the liver. The principal metabolite of DHEA in the liver is androstenedione, which is further metabolized into a number of androgenic (e.g. testosterone) and estrogenic (e.g. estradiol) steroids on a tissue-specific basis. Androstenedione also undergoes aromatization in peripheral tissues, primarily fat, to C-18 steroids including estrone and estradiol. The mean metabolic clearance rate (MCR) of DHEA in 34 women of reproductive age was reported to be $1,935 \pm 125$ L/day and the mean MCR for DHEA-S was reported to be 12.5 ± 1.0 L/day in women. Thus the MCR of DHEA-S is about a 150 fold less than that of DHEA probably because DHEA-S is more strongly bound to albumin and there is direct as well as indirect metabolism of DHEA-S, so that a quantitative difference in metabolites would be present. In animal studies DHEA has been reported to induce CYP4A and CYP3A23. Preliminary studies on human liver microsomes and following administration of DHEA 200mg QD for 2 weeks to 13 elderly men and women (Age >65 years old) suggested that DHEA inhibited CYP3A mediated metabolism of triazolam. These results suggest that further investigations on the effects of DHEA and DHEA-S on human cytochrome mediated metabolism would be necessary.

Excretion: After intravenous or oral administration of radiolabeled DHEA or DHEA-S, most of the excretion is reported as urinary in the form of glucuronides and sulfates of DHEA, androstenedione, as well as a number of other 17-ketosteroids. Fifty percent (50%) of a labeled dose of injected DHEA was eliminated within 8 days, 94% in the urine and 6% in the feces.

Intrinsic Factors: Although the pharmacokinetics of DHEA in patients with renal and hepatic impairment was not conducted, metabolites may accumulate in these patients and may need further investigation. Age appears to account for a wide variation in the circulating levels of DHEA and DHEA-S. In two of the clinical pharmacology multiple dose studies (GL-96-02 and GL 99-01) the mean endogenous concentrations of GL701 was approximately 50% less in post menopausal women [247 (48) ng/dL] compared to premenopausal women [500 (3000) ng/dL].

Extrinsic Factors: The effect of chronic administration of GL701 (200mg/day for 28 days) on the pharmacokinetics and pharmacodynamics of prednisolone after oral administration of prednisone (20mg/day) was examined in 14 healthy premenopausal women with normal menstrual cycles. The 90% confidence interval for systemic exposure ratios for prednisone, total prednisolone and free prednisolone were within the Agency standard equivalence range of 80-125%, demonstrating that no clinically significant drug-drug interaction was present.

III. Biopharmaceutics

Dissolution: Dissolution data of four lots of AlseraTM (treatments A, B, and C) consisting of different polymorphic ratios of prasterone (DHEA) suggested that the drug products with the mixed ratios of polymorphs had similar dissolution profiles whilst that with the single polymorph (Treatment D, the to be marketed formulation) exhibited poorer solubility characteristics. This product also had the smallest particle size that could have also influenced its solubility. The proposed dissolution method and specification of $Q \geq 60\%$ at 60 minutes was found acceptable.

Bioequivalence: The serum concentration versus time profile of the three lots (treatments A, B, and C) with the different polymorphic ratios were not similar. Treatments A and C were bioequivalent but not A and B. Treatment B was bioequivalent with regards to extent but not rate of absorption when compared to Treatment A. These data demonstrated that the use of a single polymorph as the active ingredient in the to be marketed formulation as proposed is critical to ensuring product quality and performance in vivo.

Treatment A used in the well controlled clinical trial (GL-95-02) and Treatment D capsules (the to be marketed formulation) were found to be bioequivalent based on the 90% confidence intervals of AUC_(0-∞): 82.8 – 103.2 % and Cmax: 81.0 – 95.3 % being within the Agency criteria of 80-125%. The two treatments were also not found to be significantly different (p=0.12) with respect to the pharmacodynamic endpoint of changes in testosterone.

The bioequivalence of the to be marketed formulation to the clinical formulation used in the Clinical trial GL 94-01 (CTM 391) was not evaluated. The GL701 product used in study GL-94-01, was also designated as Treatment A but it had a different polymorphic ratio F1:FII:FVI (25:68:5) to the clinical trial lot (18:43:39) and the TBMF (100:0:0), and so the bioavailability might not be the same.

Food Effect: The effect of food on the drug product was not evaluated in this submission however, the drug product was administered in the morning prior to food intake in the bioequivalence studies which is consistent with the proposed label.

Analytical Methods: The assay methods used for the determination of DHEA DHEA-S, testosterone, total prednisolone, prednisone and cortisol in all the clinical pharmacology and biopharmaceutics studies demonstrated adequate sensitivity, precision (CV <20%) and accuracy.

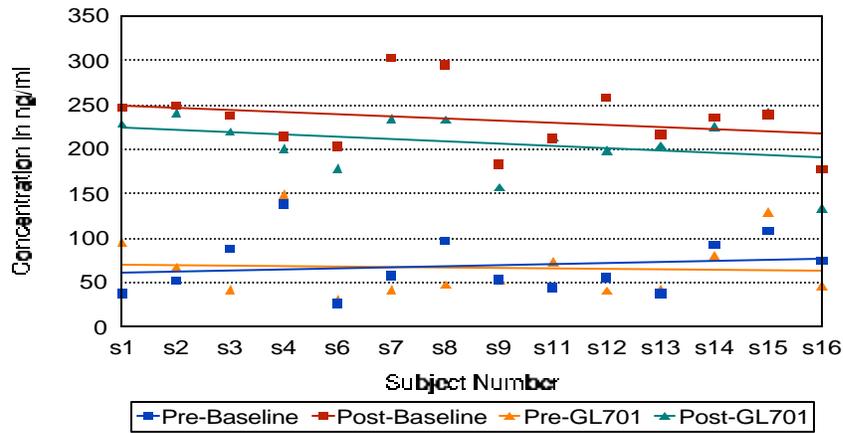
IV. Exposure -Response

Dose-Response for Efficacy and Safety: The data from the clinical trial (GL 94-01) in which two different doses of GL701 was administered to the patients 100 mg and 200 mg was suggestive of a dose response relationship. An evaluation of the relationship between the serum concentrations of androgen hormones and exposure in clinical pharmacology and biopharmaceutics studies suggested that GL701 increases the production of androgen hormones (testosterone and androstenedione) and decreases the levels of SHBG in pre and post menopausal women. Total estradiol, progesterone and estrone levels were not affected by chronic dosing with GL701 for 28 days in pre-menopausal women. The data from the clinical trial (GL 94-01) suggested a dose- serum testosterone concentration relationship in mean change from baseline for the patients who were administered 100 mg and 200 mg dose of GL701/day (Study GL 94-01). However, a preliminary review of the frequency of most occurring adverse events of (acne and hirsutism) in both groups suggested that the adverse events related to the increase in serum testosterone concentration did not show a suggestive dose response relationship.

ACTH Stimulation Test: The effects of multiple dosing with GL701 200 mg/day for 28 days on the responsiveness of the adrenal gland evaluated by the ACTH stimulation test in pre-menopausal women resulted in a decrease in the cortisol levels 1 hour after ACTH stimulation that was found to be statistically significant (p = 0.001) as shown in the graph below:

DHEA/Cortisol Response

Pre- and Post-



The mean change in ACTH stimulated cortisol before and after GL701 administration was also found to be statistically significant ($p = 0.002$). Clinically these ACTH stimulation results could represent a suppression of the adrenal glands due to chronic dosing with GL701 that may indicate some glucocorticoid activity of DHEA. The medical reviewer is currently evaluating the clinical relevance of these findings. Prednisone (20mg/day) oral administration inhibited endogenous cortisol, DHEA and DHEA-S secretion with mean baseline endogenous serum concentrations of DHEA and DHEA-S decreasing by $\sim 30\%$ and 25% respectively. This was probably due to the negative feedback of prednisone on ACTH release.