Purpose. The pharmacology, pharmacokinetics, clinical efficacy, adverse effects and toxicities, drug interactions, dosage and administration, and safety issues related to the use of prasterone are discussed.

Summary. Prasterone is a proprietary synthetic dehydroepiandrosterone product under investigation for use in women with systemic lupus erythematosus (SLE) who are taking glucocorticoids. Initial trials investigated prasterone as a treatment to improve disease activity and symptoms in women with mild to moderate SLE. The Food and Drug Administration (FDA) did not approve prasterone’s labeling for these indications. Subsequent trials have focused on prasterone as a treatment to limit bone loss in women who have SLE. A study was conducted to assess bone mineral density in patients who had been taking glucocorticoids for six months or longer. The patients in the prasterone group showed an increase in bone mineral density, while the placebo group demonstrated a loss.

The most common adverse effects of prasterone therapy were acne and hirsutism. Hematuria, hypertension, and serum creatinine concentration increases have also occurred. Interactions of prasterone potentially exist with 5-alpha reductase inhibitors and additive or antagonistic effects could possibly occur with androgens, estrogens, oral contraceptives, and progestins. In clinical trials, oral prasterone dosages of 100-200 mg/day were administered. These dosages have resulted in supraphysiologic hormone levels.

Conclusion. FDA has granted orphan drug status for the prevention of loss of bone mineral density in SLE patients taking glucocorticoids. FDA is requesting additional Phase III trial data for the treatment of SLE and the prevention of loss of bone mineral density.

Index terms: Androgens; Bone density; Contraceptives, oral; Dosage; Drug interactions; Drugs; Estrogens; 5-Alpha reductase inhibitors; Lupus erythematosus; Mechanism of action; Pharmacokinetics; Prasterone; Progestins; Steroids, cortico-; Toxicity

Prasterone (Prestara, formerly known as Aslera or GL701) is a proprietary synthetic DHEA product manufactured by Genelabs Technologies, Inc., and Watson Pharmaceuticals. In 1994, the Food and Drug Administration (FDA) classified DHEA as a nutritional supplement under the Dietary Supplement Health and Education Act of 1994.

Systemic lupus erythematosus (SLE) is a relapsing and remitting autoimmune disease with widely varying clinical manifestations that can affect various parts of the body such as the skin, joints, heart, lungs, brain, blood, and kidneys. The disease occurs 5 to 10 times more frequently in women than in men and is 2 to 3 times more prevalent among African-Americans, Hispanics, Asians, and American Indians. Glucocorticoids are the mainstay of treatment for SLE flares. At the onset of the disease, before corticosteroid treatment is initiated, patients with SLE often have abnormalities of androgen and estrogen metabolism, as well as low serum levels of dehydroepiandrosterone (DHEA), a weak adrenal steroid, and its sulfate ester DHEA-S. These endocrine abnormalities can be summarized as a high-estrogen, low-androgen state. It is hypothesized that exogenous administration of androgens may have a beneficial effect. DHEA is believed to have androgenic and immunologic effects that may be beneficial in the treatment of SLE and the adverse effects associated with chronic glucocorticoid administration.
The Formulary Review section contains monographs provided to AJHP by the Clinical Knowledge Service, Drug Monograph Group, of the University Health System Consortium (UHC), Oak Brook, IL. The monographs are written by drug information specialists and pharmacotherapists from UHC member institutions and VHA institutions, undergo peer review by UHC and VHA pharmacists and physicians, and appear here some months after initial distribution. They have been edited by AJHP and contain new abstracts. For more information, see the initial installment in the December 1, 1997, issue or call Karl A. Matuszewski, M.S., Pharm.D., or Mary Ellen Bonk, Pharm.D., at UHC (630-954-1700).

Prasterone

Prasterone (DHEA, GL701, Prepharma; Genelabs Technologies, Inc., Redwood City, CA, and Watson Pharmaceuticals, Corona, CA) is a synthetic oral formulation of DHEA.

Pharmacology

Endogenous DHEA is a carbon 19 steroid with the chemical name 5-androstene-3β-ol-17-one. It is formed predominantly in the adrenal cortex, although it can also be synthesized in the gonads, gastrointestinal tract, and brain. DHEA is reversibly converted to the sulfate ester DHEA-S and DHEA-S are the most abundant endogenous adrenal steroids in the body and have mild androgenic properties. The serum level of DHEA-S tends to be two to three times greater than the corresponding level of DHEA. DHEA-S is inactive and converted peripherally to biologically active DHEA. Concentrations of endogenous DHEA and DHEA-S peak in early adulthood and decline steadily throughout adult life (approximately 2% per year); the DHEA-S concentration in a 70–80-year-old is approximately 10% to 20% that of a young adult.

Endogenous DHEA and prasterone are known to have direct and indirect effects, although their mechanisms of action are not fully understood. Endogenous DHEA exerts its action primarily by indirect mechanisms in peripheral target tissues following its bioconversion to androgens and estrogens. DHEA and DHEA-S are the precursors to approximately 50% of androgens in adult men, 75% of estrogens in premenopausal women, and nearly 100% of active estrogens in postmenopausal women. Concentrations of both DHEA and DHEA-S are higher in the brain than in other organs and appear to act directly as neurosteroids via interaction with neurotransmitter receptors (γ-aminobutyric acid–benzodiazepine receptor complex and N-methyl-D-aspartate) in the brain.

DHEA may also have immunomodulatory effects. Decreased interleukin (IL)-2 secretion has been described as a common feature in both murine models and humans with SLE. Studies with DHEA in murine SLE models have shown that T lymphocytes produced increased quantities of interferon-gamma and IL-2 and decreased amounts of other interleukins, such as IL-4, IL-5, and IL-6. Only in vitro data are available demonstrating increased IL-2 production by peripheral blood T lymphocytes with administration of exogenous DHEA in humans.

Bioavailability and pharmacokinetics

DHEA has a low oral bioavailability—approximately 3% of that achieved by a subcutaneously administered dose. Peak plasma levels of prasterone and DHEA-S are reached within 1.5 to 3 hours after administration. When prasterone was administered to healthy subjects at 200 mg/day, serum DHEA concentrations of approximately 1 μg/dL and concentrations of DHEA-S of >400 μg/dL were achieved by one week. These serum levels were maintained for up to one month with concomitant glucocorticoid administration.

Most of an orally administered dose of DHEA undergoes sulfonation to DHEA-S in the intestine where it is absorbed, thereby avoiding hepatic clearance. The rapid and continuous interconversion of DHEA and DHEA-S means that DHEA-S can serve as a stable reservoir for DHEA. A total of 19 different DHEA metabolites have been confirmed, with an additional 12 me-
DHEA and DHEA-S are substrates for the cytochrome P450-3A4 enzyme (CYP3A4). \(^{24}\)

Approximately 90% of DHEA is bound to albumin, with lesser amounts bound to cortisol-binding globulin and to the sex hormone-binding globulin. \(^{25}\) DHEA-S is strongly bound to albumin and undergoes renal tubular reabsorption. \(^{3}\) The elimination half-lives of prasterone and its sulfated metabolite range from 5 to 12 hours and from 11 to 25 hours, respectively, and vary with age and sex. \(^{21-23}\)

Table 1 contains serum half-life data on DHEA and DHEA-S in healthy women receiving a single dose of oral prednisone 20 mg followed by prasterone 200 mg daily for 29 days. \(^{22}\)

Table 2 contains the half-life data (calculated after baseline correction) on DHEA and DHEA-S after oral administration of 50 and 100 mg of DHEA to healthy women and elderly men for three days. \(^{23-26}\)

**Indications**

Initial trials investigated prasterone as a treatment to improve disease activity and symptoms in women with mild to moderate SLE. In June 2001, Genelabs received a “not approvable” letter from FDA for these indications. \(^{27}\) Subsequently, trials have focused on prasterone as a treatment to limit bone loss in women who have SLE and are taking glucocorticoids. \(^{13}\)

**Clinical efficacy**

Three Phase III clinical trials evaluating prasterone as a treatment to minimize SLE symptoms and decrease steroid requirements have been published. This section includes a review of these early clinical trials to provide an overview of the efficacy and safety profile of prasterone. The primary endpoints used in these trials were not consistent because of interpatient variability of the disease processes and the lack of a validated model for evaluating changes in SLE disease activity in a clinical trial. \(^{19}\)

### Table 1.
**Dehydroepiandrosterone (DHEA) and Sulfate Ester of Dehydroepiandrosterone (DHEA-S) Half-lives at Treatment Day 29 with Prasterone 200 mg/day plus Prednisone Therapy**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>DHEA Mean ± S.D. Half-life (hr)</th>
<th>DHEA-S Mean ± S.D. Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected for endogenous DHEA and DHEA-S</td>
<td>Not calculated</td>
<td>15.9 ± 3.6</td>
</tr>
<tr>
<td>Corrected for endogenous DHEA and DHEA-S</td>
<td>10.8 ± 6.2</td>
<td>12.3 ± 3.4</td>
</tr>
</tbody>
</table>

*Adapted from reference 22.

Nonetheless, subanalyses of these trials found positive effects on bone mineral density in women who had SLE and were also taking corticosteroids. As a result, the drug is being evaluated for its effects on bone mineral density in patients who have SLE and are taking corticosteroids on a long-term basis.

**Treatment of SLE symptoms or reduction in corticosteroid use.** Efficacy indexes used in clinical trials to evaluate disease activity are listed in Table 3. \(^{28,29}\)

Trial GL94-01 was a randomized, double-blind, placebo-controlled, multicenter study that evaluated 100- and 200-mg daily doses of oral prasterone in women with SLE who had been treated with moderate doses of prednisone (10–30 mg/day) or an equivalent corticosteroid for at least 12 months. \(^{30}\) The primary efficacy variable was a reduction in corticosteroid usage to ≤7.5 mg/day of prednisone for a minimum of 2 consecutive months, without worsening disease activity. Patients were treated for 7 to 9 months. A significant difference in the primary endpoint was not seen in the total study population, but a statistically significant difference \((p = 0.031)\) was reported in the 200-mg prasterone group versus the placebo group in patients with active disease (defined as Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score of ≥2 at study entry \([n = 137])\). \(^{30}\) See Table 4 for details of the published prasterone Phase III trials.

### Table 2.
**Dehydroepiandrosterone (DHEA) and Sulfate Ester of Dehydroepiandrosterone (DHEA-S) Half-lives Following 50 or 100 mg/day of DHEA for Three Days**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>DHEA Mean ± S.D. Serum Half-life (hr)</th>
<th>DHEA-S Mean ± S.D. Serum Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg/day</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Women (mean ± S.D. age, 23.3 ± 4.1 yr)</td>
<td>8.9 ± 3.6</td>
<td>7.6 ± 2.7</td>
</tr>
<tr>
<td>Elderly men (mean ± S.D. age, 58.8 ± 5.1 yr)</td>
<td>5.35 ± 2.16</td>
<td>4.04 ± 1.02</td>
</tr>
<tr>
<td></td>
<td>50 mg/day</td>
<td>100 mg/day</td>
</tr>
<tr>
<td></td>
<td>13.2 ± 2.7</td>
<td>12.1 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>12.66 ± 5.02</td>
<td>10.63 ± 4.30</td>
</tr>
</tbody>
</table>

*Adapted from references 23 and 26.
Trial GL95-02 was a randomized, parallel-group, double-blind, placebo-controlled, multicenter study comparing 200 mg/day of prasterone with placebo in 381 patients with mild to moderate active SLE (Systemic Lupus Activity Measure [SLAM] scores of ≥7; SLEDAI scores of >2). Patients enrolled in the study continued on standard SLE medications, including prednisone ≤10 mg, antimalarials, and immunosuppressive agents, provided that the medication regimen had been stable for more than six weeks. The primary efficacy variable was improvement or stabilization of disease activity without clinical deterioration over the 12-month study period. In patients with active disease at baseline (SLEDAI score of >2), statistically significant improvements and disease stabilization were seen in the prasterone group compared with the placebo group (p = 0.017). This study was the first to integrate three SLE domains (disease activity, organ damage, and health-related quality of life) into an overall responder endpoint.

GBL96-01 was a multicenter Asian study that was conducted in Taiwan by a licensee and not under a U.S. investigational new drug application. This randomized, double-blind, placebo-controlled study involved 120 adult women with active SLE who were maintained on a constant dose of corticosteroids and other SLE medications. Patients were treated with 200 mg/day of prasterone or placebo for 24 weeks. At the conclusion of the study, no difference in SLAM scores was seen between the placebo and treatment groups. However, in the prasterone group, there was a significant reduction in the number of flares and a significant improvement in the patient’s global assessment of treatment compared with placebo (p = 0.44). Effects on bone mineral density. Nested within trial GL95-02 was a study conducted at eight sites to assess bone mineral density in patients who had been taking glucocorticoids for ≥6 months and who had no changes in immunomodulatory medications for six weeks before entering the trial. Menopausal status and t scores were not used as entry criteria. Modifications in calcium or vitamin intake were not required. Bone mineral density was assessed using dual x-ray absorptiometry at baseline and after treatment. The primary endpoint was change in bone mineral density. Statistically significant differences were reported between the prasterone and placebo groups after 12 months. At the lumbar spine, the prasterone group had increased bone mineral density (mean ± standard error of the mean) of 1.7% ± 0.8% compared with a loss of 1.1% ± 0.5% in the placebo group (p = 0.003), and prasterone showed an increase of 2% ± 0.9% at the hip compared with a decrease of 0.3% ± 0.4% (p = 0.013) in the placebo group. The increases in bone mineral density occurred regardless of whether patients were receiving calcium supplements or exogenous estrogens. A subanalysis of postmenopausal women indicated that bone mineral density at the lumbar spine increased by 3.1% ± 1.3% in patients treated with prasterone (n = 11) compared with a loss of 1.7% ± 1.2% (p = 0.012) in those receiving placebo (n = 13). In this same population, bone mineral density at the hip increased in the prasterone group by 2.3% ± 1.7% and decreased in the placebo group by 0.59% ± 0.6% (p = 0.107).

The following trial data are available only as press releases but have influenced FDA decisions on prasterone. Trial GL02-01 was a randomized, multicenter, double-blind, placebo-controlled, Phase III trial conducted to confirm prasterone’s efficacy in improving bone mineral density in patients with SLE who were taking chronic glucocorticoids (≥25 mg/day) and standard SLE medications. A total of 155 women with SLE were randomly assigned to receive prasterone 200 mg/day or placebo for six months. The primary endpoint was bone mineral density at the lumbar spine. In October 2004, it was announced that this trial failed to show a statistically significant difference in the primary endpoint. A mean increase in bone mineral density of 0.003 g/cm² occurred in the prasterone group and a decrease of 0.005 g/cm² occurred in the placebo group (p = 0.293). The failure of this trial to reach significance may have been due to a shorter treatment period than in the GL95-02 trial, higher baseline bone mineral densities, and concurrent usage of calcium and vitamin D supplements.

Patients completing study GL02-01 were eligible to enroll in study GL03-01, a one-year, open-label extension with a primary endpoint of maintenance of bone mineral density at

<table>
<thead>
<tr>
<th>Efficacy Assessment</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Lupus Erythematosus Disease Activity Index</td>
<td>A weighted cumulative index of disease activity, damage from disease, and health status that is sensitive to change over time. It consists of 24 variables divided into 9 organ systems. Scores range from 0 to 105, with higher scores representing increased disease activity. In practice, few patients have scores of &gt;45.</td>
</tr>
<tr>
<td>Systemic Lupus Activity Measure</td>
<td>A measure of disease activity and some severity for 32 items divided into 11 organ systems and graded on a severity scale of 1 to 3. The maximum score is 86.</td>
</tr>
</tbody>
</table>

Adapted from references 28 and 29.
Table 4. Published Clinical Efficacy Trials with Prasterone for the Treatment of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design/ Patient Population/ Duration</th>
<th>Treatment Regimen</th>
<th>Outcome Measures</th>
<th>Results/Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>R, DB, PC, MC; n = 191 Phase II/III</td>
<td>Prasterone 100 mg/day (n = 63)</td>
<td>The proportion of patients achieving a response defined as a reduction in corticosteroid use to ≤7.5 mg/day for ≥2 consecutive mo</td>
<td>In the intent-to-treat population, response was achieved in 55% of the 200-mg group (p = 0.110 vs. placebo), 44% of the 100-mg group, and 41% of the placebo group.</td>
<td>Corticosteroid dose was reduced at monthly intervals by an algorithm based on a stable or improved SLEDAI score. Withdrawals due to adverse effects occurred in 9% of the 200-mg group, 6% of the 100-mg group, and 5% of the placebo group. Acne was the most common adverse effect reported; it was seen in 41% of each of the prasterone groups and 19% of the placebo group (p &lt; 0.05).</td>
</tr>
<tr>
<td></td>
<td>Women with SLE receiving prednisone 10 to 30 mg/day; 7 to 9 mo</td>
<td>Placebo (n = 64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19, 31</td>
<td>R, DB, PC, PG, MC; n = 381 Phase III</td>
<td>Prasterone 200 mg/day plus standard SLE medications (n = 189)</td>
<td>Primary: The proportion of patients achieving a response defined as improvement or stabilization over the duration of the study in 2 disease activity measures (SLEDAI, SLAM) and 2 QOL measures (patient’s global assessment, KFSS) Secondary: Time to SLE flare Change in individual scores on SLEDAI and SLAM, patient’s global assessment, and KFSS</td>
<td>In the intent-to-treat population, a total of 51.3% (97/189) of the prasterone group and 42.2% (81/192) of the placebo group were responders (p = 0.074). In patients with SLEDAI &gt;2, a total of 58.5% (86/147) of the prasterone group and 44.5% (65/146) of the placebo group were responders (p = 0.017). In patients with SLEDAI &gt;2, patients reporting a first flare were 24.5% of the prasterone group and 34.2% of the placebo group (p = 0.066). A trend toward prolongation of time to flare was seen in the prasterone group (p = 0.097).</td>
<td>Standard medications included prednisone ≤10 mg/day, antimalarials, and immunosuppressive agents. Acne was reported in 33% and 14% of the prasterone and placebo groups, respectively (p &lt; 0.05). Hirsutism was reported in 16% and 2% of the prasterone and placebo groups, respectively (p &lt; 0.05). Serious adverse events were reported in 14% (27/189) of the prasterone group and 17% (33/192) of the placebo group. Fourteen patients in the prasterone group and 16 in the placebo group withdrew from the study because of serious adverse events.</td>
</tr>
<tr>
<td></td>
<td>Women with active SLE; 12 mo</td>
<td>Placebo plus standard SLE medications (n = 192)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page
the lumbar spine. All 115 patients in this trial received prasterone 100 or 200 mg/day and were taking glucocorticoids. A preliminary analysis of the results was released in August 2005. Bone mineral density increased in patients receiving prasterone 200 mg/day, while those receiving 100 mg/day experienced a decrease in bone mineral density.

DHEA has been evaluated in other patient populations and for other indications, including its effect on lipid profiles, despite the fact that its net androgenic effects would be expected to produce the opposite effect. DHEA also improved insulin resistance, certain malignancies, osteoporosis, and certain immune responses. In postmenopausal women, DHEA has been shown to improve depression in a small, double-blind, six-week study of 22 patients using DHEA alone or in combination with antidepressive medications. In a parallel group study with prasterone 200 mg/day plus standard SLE medications and glucocorticoids, the primary outcome measure was bone mineral density at the lumbar spine. All 115 patients in this trial received prasterone 100 or 200 mg/day and were taking glucocorticoids. A preliminary analysis of the results was released in August 2005. Bone mineral density increased in patients receiving prasterone 200 mg/day, while those receiving 100 mg/day experienced a decrease in bone mineral density.

Table 4 (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design/ Patient Population/ Duration</th>
<th>Treatment Regimen</th>
<th>Outcome Measures</th>
<th>Results/Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 R, DB, PC, MC n = 120 Women with active SLE 24 wk</td>
<td>Prasterone 200 mg/day plus standard SLE medications and glucocorticoids (n = 61)</td>
<td>Primary: Mean change from baseline in SLAM scores Secondary: Occurrence of an SLE flare Change in SLEDAI Physician’s and patient’s global assessment (VAS)</td>
<td>Mean reductions in SLAM scores were not significantly different between the treatment and placebo groups (–2.6 ± 3.4 vs. –2.0 ± 3.8, respectively; p = 0.355). The incidence of SLE flares was significantly less in the prasterone group compared with the placebo group (18% vs. 33.9%, respectively; p = 0.44). Changes in SLEDAI scores were not significantly different between groups (p = 0.742). The mean change in the patients’ VAS scores was –5.5 ± 20 in the prasterone group and 5.4 ± 26.6 in the placebo group (p = 0.005). Mean change in physician’s VAS between groups was not significant (p = 0.104). Conclusion: Prasterone 200 mg/day reduced the number of SLE flares and improved the patients’ VAS scores of disease activity.</td>
<td>Standard medications included prednisone ≤10 mg/day, azathioprine, hydroxychloroquine, methotrexate, or cyclophosphamide. A total of 95.1% of the prasterone group and 93.2% of the placebo group completed the study. Reported adverse effects were primarily expected androgenic effects, with acne being the most common. Serious adverse events were reported in 11.5% of the prasterone group and 30.5% of the placebo group (p = 0.01) and were consistent with SLE flares or manifestations.</td>
<td></td>
</tr>
</tbody>
</table>

*DB = double-blind, KFSS = Krupp Fatigue Severity Scale, MC = multicenter, PC = placebo-controlled, PG = parallel group, QOL = quality of life, R = randomized, SLAM = Systemic Lupus Activity Measure, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, VAS = visual analog scale (100 mm).
sensitivity without affecting glucose tolerance.\(^{38}\)

In addition, there has been a correlation between bone mineral density and DHEA-S in postmenopausal women, and it has been speculated that osteoblast aromatases might have an important role in maintaining bone mineral density in the elderly by converting DHEA to estrone.\(^{39}\) However, oral DHEA was not found to affect bone turnover in middle-aged to elderly men,\(^{40}\) nor does there appear to be direct evidence of an anabolic effect of DHEA on bone metabolism, although a recent study did find markers for bone build-up.\(^{41}\)

**Adverse effects and toxicities**

The most common adverse effects reported with prasterone therapy were acne and hirsutism. In clinical trials, acne was reported in approximately 25% more patients in the prasterone group than in the placebo group \((p < 0.05)\).\(^{2,19,30-32}\) The incidence of hematuria, hypertension, and serum creatinine concentration increases was also statistically significant in the prasterone group compared with the placebo group; however, because of the relatively small number of patients reporting these increases, the clinical significance is not clear.\(^{19}\) Patients treated with prasterone reported significantly lower incidences of myalgia, joint disorder, anorexia, nasal ulcers, and skin rash than patients receiving placebo. These differences may be the result of decreases in SLE manifestations reported as adverse events in the trials.\(^{19}\) Serious adverse events were consistent with SLE flares and occurred more frequently in the placebo group than in the prasterone groups but in general did not require that the drug be discontinued.\(^{19,30-32}\)

Different adverse-effect profiles for prasterone have been reported in premenopausal and postmenopausal women.\(^{42,43}\) Among premenopausal women in one trial, acne (62%) and mild hirsutism (22%) were common; among postmenopausal women, acne occurred less frequently (31%), but greasy and oily skin, alopecia, breast tenderness, and vertigo were more frequent (15–23%). Acne was generally mild, nonpustular, and nonscarring; it increased during the first four months of therapy and subsequently improved. There were no differences in adverse effects between postmenopausal women who were concurrently taking estrogen replacement therapy and those who were not.\(^{42}\)

Effects on lipoproteins and erythrocyte sedimentation rate have been reported, but their significance is not known. Some studies have reported small, nonsignificant decreases in low-density lipoprotein cholesterol (LDL-C)\(^{30,42}\) and high-density lipoprotein cholesterol (HDL-C).\(^{42}\) However, other studies have reported that DHEA significantly lowers HDL-C.\(^{30,31,44,45}\) Likewise, some trials found nonsignificant changes in serum LDL-C, apolipoprotein A1, and triglyceride concentrations, while others reported statistically significant decreases.\(^{30,32,45}\) Results reported on the effects of prasterone on complement levels have also varied. Significant and nonsignificant decreases in mean C3 and C4 complement levels compared with placebo have been reported.\(^{30,32,46,47}\)

During clinical trials, severe adverse events occurred at a similar rate in the prasterone and placebo groups; asthenia was the most common serious adverse event reported (8.7%, 6.3%, and 8.6% in the prasterone 200 mg, prasterone 100 mg, and placebo groups, respectively). The largest difference between the prasterone and placebo groups was in severe abdominal pain reported in 6 (2.4%) of the 253 patients receiving prasterone 200 mg, 2 (3.2%) of the 63 patients receiving prasterone 100 mg, and none of the patients receiving placebo.\(^{19}\)

**Drug interactions**

In a study evaluating the interaction between prasterone 200 mg/day and a single 20-mg dose of prednisone, prasterone did not alter the pharmacokinetics (maximum plasma concentration, half-life, area under the curve, and serum protein binding) or the effects of prednisone or prednisolone on cortisol secretion. The adrenocorticotropic hormone (ACTH)-stimulated plasma cortisol concentrations were mildly reduced during prasterone administration, but the 24-hour urinary free cortisol excretion was unchanged. The mechanism underlying the mild suppression of ACTH-induced cortisol release is not known.\(^{22}\)

Medications that induce the CYP3A4 enzyme (e.g., phenytoin, carbamazepine) may increase DHEA and DHEA-S metabolism, thereby decreasing the circulating concentrations of these hormones. The metabolism of triazolam, alprazolam, and midazolam may be inhibited by prasterone, resulting in elevated benzodiazepine levels. In a study of patients receiving a single 0.25-mg dose of triazolam and 200 mg/day of prasterone, triazolam clearance decreased by 0.6–42%\(^{7,15,48}\). DHEA sulfatase inhibitors such as danazol, used as steroid-sparing therapy for patients with SLE, may decrease the conversion of DHEA-S to DHEA.\(^{24}\)

In case reports, elevated serum DHEA levels have been observed to reduce the effectiveness of carbamazepine, clozapine, haloperidol, lithium, loxapine, molindone, olanzapine, phenothiazines, quetiapine, risperidone, and valproic acid. The proposed mechanism is that DHEA is a precursor to androgenic steroids, which may precipitate mania; therefore, caution should be exercised in patients who have bipolar or other central nervous system disorders.\(^{49}\)

Interactions based on the pharmacologic actions of prasterone potentially exist with 5-α-reductase inhibitors such as finasteride, which could be antagonized by prasterone. Either additive or antagonistic effects
could possibly occur with androgens, estrogens, oral contraceptives, and progestins. In addition, since prasterone has been shown to inhibit platelet aggregation in larger doses (e.g., 300 mg three times daily), the effects of anticoagulants and platelet inhibitors such as aspirin, clopidogrel, ticlopidine, and warfarin may be potentiated. Because DHEA levels may be regulated by insulin through an unknown mechanism, there may be additive effects with antidiabetic agents. Lastly, aromatase inhibitors such as aminoglutethimide, anastrozole, exemestane, letrozole, and testolactone could interfere with the biotransformation of DHEA, and, conversely, DHEA could interfere with the efficacy of these agents. 

Dosage and administration

In clinical trials, oral prasterone dosages of 100–200 mg/day were administered for up to 12 months in patients with SLE. These dosages have resulted in supraphysiological hormone levels. Because of the long half-life of DHEA-S and the ongoing interconversion of DHEA and DHEA-S, a single morning dose is sufficient to maintain DHEA-S concentrations throughout the day. Since oral administration of hormones can cause nausea, it is suggested that prasterone be taken with food to minimize indigestion and gastrointestinal irritation.

Safety issues

In addition to DHEA-S, DHEA gives rise to a number of poorly characterized metabolites that may have some unforeseen and largely unexplored adverse effects. Prasterone is not recommended in patients with hepatic impairment, and no dosing recommendations have been made for patients with renal impairment. Prasterone is contraindicated in children under the age of 18 years because it could interfere with the onset of puberty, natural growth, and maturation. Prasterone is classified in pregnancy category X and should not be used in women who are breastfeeding or receiving treatment for infertility.

The safety of prasterone has not been established; therefore, caution should be used in certain populations, specifically HIV-positive patients and patients with AIDS (because of DHEA's potential immunomodulating effects), bipolar disorder, mania, diabetes mellitus, endometrial hyperplasia, erectile dysfunction, G6PD deficiency (because endogenous DHEA inhibits the enzyme glucose-6-phosphate dehydrogenase), porphyria, and hormone-sensitive malignancies, and those undergoing surgery. DHEA and, presumably, prasterone are contraindicated in the following groups: patients with breast, endometrial, hepatocellular, ovarian, prostate, uterine, or vaginal cancers; prostatic hypertrophy; abnormal vaginal bleeding; and infertility.

Economic issues

Cost information is not available. Pharmacoeconomic studies evaluating the cost avoidance of the adverse effects of corticosteroids in this patient population are warranted.

Similar agents under consideration

Several other synthetic DHEA products are under investigation for indications other than SLE. Fluasterone, a synthetic DHEA analogue that is not metabolized to either testosterone or estrogens in humans, is thought to be more effective and to lack the adverse effects associated with endogenous DHEA. It is being evaluated in Phase II trials for the treatment of cardiovascular disease and actinic keratosis. Infabloc Pharmaceuticals is conducting Phase II trials with IP-1001, a synthetic oral DHEA product for the treatment of the signs and symptoms of Crohn’s disease. It is also evaluating the antiinflammatory properties of IP-1003, a combination product with DHEA as its primary active ingredient in inflammatory bowel disease. Clinical trials are planned to begin in 2006.

Recommendations and critical issues

Initially, prasterone was evaluated for the treatment of SLE on the basis of (1) lower DHEA levels among patients with SLE, (2) positive effects demonstrated in murine models of SLE, and (3) the immunomodulatory effects of DHEA, which suggest a potential benefit in SLE. Overall, trials evaluating prasterone for the treatment of SLE symptoms or for the reduction of corticosteroid dosage did not show significant efficacy, and the drug was given a not approvable recommendation by FDA in 2001. However, subanalyses of these trials detected positive effects on bone mineral density. As a result, Genelabs began developing prasterone as a treatment to limit bone loss in women with SLE who are taking glucocorticoids. In August 2002, the company received an approvable letter from FDA contingent on the successful completion of study GL02-01, a Phase III confirmatory study in women with SLE who are taking glucocorticoids, with change in bone mineral density at the lumbar spine as its primary endpoint. In October 2004, it was announced that preliminary results from this confirmatory trial had failed to meet the primary endpoint.

Prasterone’s approval status is uncertain at this time. More studies are needed to establish the precise role of this drug, to clarify its effects on lipids, insulin sensitivity, and hormone-sensitive cancers and to compare it with active therapies. FDA has confirmed to Genelabs that the indication defined as “prevention of loss of bone mineral density in SLE patients taking glucocorticoids” qualifies for
orphan drug exclusivity under the original orphan drug designation received by the company in 1994.23 Genelabs is in discussions with FDA regarding its continued development of prasterone. FDA is requesting additional Phase III trial data for either indication, the treatment of the signs and symptoms of lupus or the prevention of loss of bone mineral density. Based on a January 2006 press release, it appears that the company will assess the viability of pursuing an indication for the signs and symptoms of SLE.26 Genelabs plans to pursue an indication for treating the signs and symptoms of SLE and is designing a protocol for an additional study. However, the company does not believe that it will conduct the study on its own.27

Conclusion

FDA has granted orphan drug status for the prevention of loss of bone mineral density in SLE patients taking glucocorticoids. FDA is requesting additional Phase III trial data for the treatment of SLE and the prevention of loss of bone mineral density.

References


