PRASTOVA SR Tablets (Dehydroepiandrosterone)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Qualitative and Quantitative Composition

Each film-coated sustained release tablet contains:

Dehydroepiandrosterone.....75 mg

(Micronized)

Dosage Form and Strength

Film-coated tablets of Dehydroepiandrosterone 75 mg for oral use.

Clinical Particulars

Therapeutic Indications

As a supplement in:

- Women with diminished ovarian reserve; and
- Poor responders undergoing *in vitro* fertilization (IVF).

Posology and Method of Administration

One tablet of **PRASTOVA SR** daily.

Contraindications

- Hypersensitivity to DHEA, DHEA-S or any of the excipients in the formulation
- Patients with any form of cancer or at risk of cancer; DHEA has promoted growth of some tumour types (e.g. breast cancer, prostate cancer)
- Pregnancy
- Lactation

Special Warnings and Precautions for Use

General

- Patients at risk of breast cancer (in women, including postmenopausal women) and prostate cancer; risk may be higher during DHEA long-term supplementation.
- Patients with hypercholesterolaemia or ischaemic heart disease (lowering of HDL has occurred during DHEA therapy).
- Patients with or a history of psychiatric disorders (risk of exacerbation).

- Risk of mania may be increased during concomitant use with anti-depressants (tricyclic or SSRIs) and/or alcohol, or with high doses, or in patients with a history of mood disorders.
- Liver disease or renal impairment (pharmacokinetic data lacking).

Monitoring Laboratory Parameters

For therapeutic use, there are no adequate data to support monitoring of DHEA-S levels during DHEA therapy.

Drug Interactions

- Reduces the effectiveness of phenothiazines (acetophenazine, carbamazepine, chlorpromazine, chlorprothixene, clozapine, ethopropazine, fluphenazine, mesoridazine, methdilazine, perazine, perphenazine, pipotiazine, prochlorperazine, promazine, promethazine, propiomazin, thioridazine, trifluoperazine, triflupromazine), haloperidol, lithium, loxapine, molindone, olanzapine, quetiapine, risperidone and valproic acid.
- Development of manic symptoms reported with co-administration of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.
- Increased risk of oestrogenic adverse effects reported with co-administration of conjugated oestrogens, esterified oestrogens, oestradiol, oestradiol cypionate, estropipate and ethinyl estradiol.
- Increased risk of adverse androgenic and hepatic effects reported when co-administered with testosterone.
- Increased central nervous system depression when co-administered with triazolam.

Potential interactions between DHEA and pharmaceuticals include enhanced sedation seen in patients on benzodiazepines and related CNS-active drugs, as well as possible thyrotoxicosis in patients taking thyroid hormones.

Use in Special Population

Patients with Renal Impairment

No data available, not known.

Patients with Hepatic Impairment

No data available, not known.

Pregnant Women

DHEA is contraindicated to be used in pregnancy.

Lactating Women

DHEA is contraindicated to be used in lactation.

Undesirable Effects

Cardiovascular Effects

Benign premature atrial contractions and occasional premature ventricular contractions occurred in a 55-year-old man after administration of DHEA 50 mg daily for 2 weeks.

Dermatologic Effects

Endocrinologic-related cutaneous manifestations in women have included oily skin, acneiform dermatitis, facial hirsutism, and enhanced perspiration odour; these have occurred with variable frequency.

Endocrine Effects

Significant increases in oestrogens and, particularly, androgens, with attendant adverse effects, can occur during DHEA therapy/supplementation. Acne, oily skin, facial hirsutism, hair loss, mood changes, voice deepening, enhanced perspiration odour, and other signs of masculinization have been reported with variable frequency in women. None of these effects have been clearly dose-related.

Metabolic Effects

Although beneficial reductions in total and LDL cholesterol have been observed during DHEA supplementation in some clinical studies, this has not been confirmed in others. Potentially deleterious reductions in HDL cholesterol, at times significant, have also been reported in various patient groups (men and women). The HDL-lowering effect is likely due to increased androgenicity, and is probably dose-related. With use of low doses in postmenopausal women, one study reported increases in HDL cholesterol, as well as beneficial changes in other lipid parameters.

Hepatic Effects

No significant changes in transaminases or other hepatic function tests were seen during long-term use (e.g. 6 months) in some studies. One case of hepatitis has been reported in a patient with high pre-treatment antinuclear antibody (ANA) titres. Causality is uncertain.

Psychiatric Effects

Manic reactions during DHEA therapy (50 - 500 mg daily) have been described in at least three case reports. Symptoms began after 2 weeks to 2 months of supplementation in cases providing these data; psychotic features accompanied one case.

Renal Effects

No significant changes in renal function tests were observed during long-term use (e.g. 6 months) in some studies.

Urogenital Findings

No change in endometrial thickness was observed during 6 months of oral treatment in one study involving early and late postmenopausal women; uterine bleeding was also absent during this period. Two women undergoing IVF reported marginal lengthening of their menstrual cycles/irregular menses.

Carcinogenic Effect

DHEA is capable of enhancing tumour growth; it has been associated with promotion of the growth of breast cancer in women and prostate cancer.

Despite being a steroid hormone, DHEA appears to be relatively safe if given at normal physiological

doses.

Overdose

Doses above 1,500 mg/day have been known to result in insulin resistance in humans and pre-neoplastic pancreatic lesions in rats.

Pharmacological Properties

Pharmacodynamic Properties

Dehydroepiandrosterone (DHEA) is a steroid produced by the adrenal glands in response to adrenocorticotropin (ACTH) stimulation; production also occurs in the brain by undefined pathways. DHEA is an intermediate in the conversion of cholesterol to oestrogens and androgens. Circulating DHEA is predominantly (90%) in the form of its sulphate ester, dehydroepiandrosterone sulphate (DHEA-S). Plasma levels of DHEA and DHEA-S are substantially higher than those of any other adrenal steroid.

Other than serving as precursors to androgens (e.g. testosterone) and oestrogens (e.g. oestrone), the physiologic roles of DHEA and DHEA-S have remained unclear. There is decline in plasma levels of these steroids with age and low levels are associated with various disease states, related or unrelated to age.

No specific mechanism or binding site (receptor) for DHEA or its sulphate ester in any disease, condition or setting has been confirmed. Actions of DHEA and DHEA-S may be related to their conversion to oestrogens and androgens, or other metabolites, which exert effects in target tissues or may be due to direct actions.

Pharmacokinetic Properties

Absorption

Data regarding absolute bioavailability is lacking; however, good oral bioavailability is reported. Variation of bioavailability among nutritional supplement formulations is expected.

Distribution

Protein binding of 10 - 20% and 80 - 90% has been reported for DHEA and DHEA-S, respectively. DHEA penetrates the blood-brain barrier. Cerebrospinal fluid (CSF) levels of DHEA-S have ranged from 0.2 - 5% of corresponding plasma levels; higher concentrations of DHEA-S have been found in brain tissue compared to CSF. After intravenous administration, the distribution half-life was found to be 17 minutes. There is limited data regarding the volume of distribution and some evidence reported a volume of distribution of 17 - 38 L for DHEA and 9 L for DHEA-S.

Metabolism

DHEA is converted (sulphated) to DHEA-S ester in the intestine (oral doses), liver and other tissues (oral, transdermal or parenteral doses) by sulphotransferases. There is some interconversion of DHEA-S to DHEA, although this substantially favours formation of the sulphate ester. DHEA and DHEA-S are converted to androgens and oestrogens in peripheral tissues via several enzymes (e.g. 3-beta-hydroxysteroid dehydrogenase, 5-alpha reductase, aromatase, 17-beta-hydroxysteroid dehydrogenase). DHEA undergoes hepatic 17-alpha- and 17-beta hydroxylation; DHEA-S undergoes

16- alpha hydroxylation. Cytochrome P450 (CYP)-3A4 is involved in the hepatic metabolism of both steroids; activity of this isoform is higher in women, which may contribute to the lower DHEA-S levels observed in women. The following metabolites are reported: androstenedione (active); androsterone sulphate (active); oestradiol (active); oestriol (active); oestrone; dihydrotestosterone; 7-oxo-prasterone (active); prasterone sulphate (DHEA-S); and testosterone (active).

Excretion

Renal elimination of 51 - 73% (intravenous DHEA-S) is reported. The elimination half-life of the parent compound in young women is 8 - 11 hours.

In young women receiving exogenous DHEA, half-life values were approximately 8 hours after 50 or 100 mg (single doses) and 11 hours after 200 mg daily (multiple doses). In elderly women receiving 200 mg doses, the elimination half-life of DHEA progressively declined, from about 12 hours after the first dose to 9 hours on day 8, and to 7 hours on day 15.

Micronization

In general, micronization of a compound enhances the dissolution rate due to the increase in surface area available to the dissolving medium. Increasing the dissolution rate usually results in more rapid and complete absorption and consequently their bioavailability and clinical efficacy. A study done in premenopausal women showed that micronization of DHEA modified absorption and biotransformation of exogenous DHEA. The area-under-the-curve ratios for DHEA-S/DHEA and DHEA-S/testosterone increased. Micronization also increased the circulating DHEA-S disproportionately to DHEA and testosterone and may therefore provide an advantage in increasing a potentially bioactive pool of circulating non-androgenic prehormone (DHEA-S) with attenuated conversion to testosterone.

Extended-Release Formulation

An extended-release formulation of DHEA would be highly desirable to maintain therapeutic concentrations in the systemic circulation over a prolonged period, according to the hormone circadian rhythm, thus improving patient compliance by a reduction of the drug administration frequency as well as the total dose of drug administered and, consequently, the incidences of possible side effects. Factors such as biochemistry, age and gender may determine that a DHEA sustained-release dosage is more effective in restoring an individual’s optimal hormone balance than a regular-release formula.

Pharmaceutical Particulars

Incompatibilities

Not Applicable

Shelf-life

Refer pack

Storage and Handling Instructions

Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from light and excess heat and moisture (not in the bathroom).

Unneeded medications should be disposed of in special ways to ensure that pets, children, and other people cannot consume them. However, you should not flush this medication down the toilet. Instead, the best way to dispose of your medication is through a medicine take-back program. Talk to your pharmacist or contact your local garbage/recycling department to learn about take-back programs in your community.

It is important to keep all medication out of sight and reach of children as many containers (such as weekly pill minders and those for eye drops, creams, patches, and inhalers) are not child-resistant and young children can open them easily. To protect young children from poisoning, always lock safety caps and immediately place the medication in a safe location – one that is up and away and out of their sight and reach.

Packaging Information

PRASTOVA SR……Blister of 7 tablets.

Patient Counselling Information

1. **What is Prastova SR is and what is it used for?**

Prastova SR contains Dehydroepiandrosterone (DHEA) 75 mg for oral use. DHEA is identical to the endogenous human DHEA, a precursor steroid which is converted into oestrogens and androgens. It is used as a supplement in women with diminished ovarian reserve and poor responders undergoing *in vitro* fertilization.

1. **Before you take Prastova SR**

Please tell you doctor if you –

- Are hypersensitive to DHEA or any of the excipients in the formulation
- Have any form of cancer or at risk of cancer
- Pregnant or breastfeeding
- Have cholesterol or heart problems
- Have history of psychiatric disorders
- Liver or kidney impairment

1. **How to take Prastova SR**

One tablet of **PRASTOVA SR** should be taken orally daily; duration as advised by your doctor.

1. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects at these dosages are small and rare, and primarily relate to androgen effects. In high doses, side effects include acne, facial hair growth, oily skin, hair loss and, occasionally, deepening of the voice.

1. **How to store Prastova SR**

Store at a temperature not exceeding 25ºC. Protect from light and moisture.

Details of Manufacturer

Synokem Pharmaceuticals Ltd., Plot No.: 56-57, Sec-6A, IIE (SIDCUL), Ranipur (BHEL)

Haridwar-249403 (Uttarakhand)

Marketed by Cipla Ltd

Registered Office: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg Lower Parel, Mumbai – 400 013, India.

Details of Permission or Licence Number with Date

27/UA/SC/P-2018

Date of Revision

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