SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diethylstilbestrol 1 mg Tablets
Apstil

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of diethylstilbestrol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Pink, biconvex, film-coated tablets, plain on one side and inscribed APS over 1313 on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Diethylstilbestrol tablets are indicated for the treatment of carcinoma of the prostate and metastatic post-menopausal carcinoma of the breast.

Diethylstilbestrol is a synthetic non-steroidal oestrogen hormone. It has been in use for many years. However, due to its carcinogenic potential, the use of diethylstilbestrol is now only justified in the management of malignant disease.

It may be used to suppress androgenic hormonal activity in the management of androgen-dependent carcinomas such as carcinoma of the prostate in males and some post-menopausal carcinomas such as breast cancer in females.

4.2. Posology and method of administration

Posology

Adults: Management of prostatic carcinoma: 1 - 3 mg daily.
Management of post-menopausal breast carcinoma: 10 - 20 mg daily.

Children: Diethylstilbestrol should not be used in children.

Elderly: The recommended adult dose is appropriate.

Method of administration

For oral administration

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Diethylstilbestrol is contra-indicated in those who are pregnant (it is not suitable for pre-menopausal women); and children. It is also contra-indicated in the following conditions; oestrogen-dependent neoplasms especially of the genital tract; pre-menopausal carcinoma of the breast; endometrial hyperplasia or uterine fibromyomata (fibroids). Diethylstilbestrol should not be given where there is undiagnosed vaginal bleeding; a history of herpes gestationis; porphyria; moderate to severe hypertension; severe or active liver disease; hyperlipoproteinaemia; any cardiovascular or cerebrovascular disorder or a history of thrombo-embolism or conditions predisposing to it such as sickle cell anaemia, untreated polycythaemia and pulmonary hypertension.

4.4. Special warnings and precautions for use

Diethylstilbestrol should not be used in children or young adults because it has carcinogenic potential.

Care should be taken when administering diethylstilbestrol preparations to patients with cardiac failure; hypertension; diabetes; epilepsy; migraine; depression; contact lenses; cholelithiasis; any evidence of renal dysfunction; hepatic impairment; a history of, or with cholestatic jaundice from any cause e.g. jaundice of pregnancy or following the use of oral contraceptives.

During treatment with diethylstilbestrol, blood pressure should be monitored at regular intervals and if hypertension develops treatment should be stopped. In addition, if surgery is contemplated or signs or symptoms of thrombosis develop treatment should be discontinued. This is because of the significant increase in risk of deep vein thrombosis in the presence of high oestrogen activity.

In patients who suffer from diabetes, glucose tolerance may be lowered, and the need for insulin or other anti-diabetic drugs may be increased.

In thyroid disease or investigations of thyroid function, thyroid hormone binding globulin may be increased leading to increased circulating total thyroid hormone, which may lead to difficulty in interpreting thyroid function tests.

<u>Excipients</u>
Patient with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Oestrogens may antagonise diuretics and reduce the effect of anti-hypertensives.

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

4.6. Fertility, pregnancy and lactation

Diethylstilbestrol is contra-indicated in pre-menopausal women.

4.7. Effects on Ability to Drive and Use Machines

None known.

4.8. Undesirable effects

As high doses of diethylstilbestrol in early pregnancy have caused vaginal carcinoma in female offspring 16-20 years later, it should not be used in pre-menopausal women.

As with other oestrogens the following hormonal disturbances may occur, fluid retention, headache, nausea and vomiting, weight gain, hypertension, breast discomfort, chloasma, skin rashes, erythema nodosum, cholelithiasis and cholestatic jaundice. Venous and arterial thrombosis, thromboembolism and possibly cerebral and coronary thrombosis are also risks.

In women, diethylstilbestrol may cause an increase in the size of uterine fibromyomata, endometrial proliferation and/or an aggravation or recurrence of endometriosis and an excessive production of cervical mucous. The risk of endometrial neoplasia is increased significantly.

In both sexes the use of diethylstilbestrol may cause tenderness, pain, enlargement and secretion of milk-like fluid from the breast. It also may aggravate corneal discomfort in patients with contact lenses and be associated with fluctuating moods (both elation and depression) and headaches including an increase in incidence of migraine.

The general metabolic effects of diethylstilbestrol include sodium and water retention, reduced glucose tolerance and changes in body weight (usually increases).

In men there will be some feminisation, e.g. gynaecomastia and testicular atrophy, and impotence.

Other effects may be withdrawal bleeding in women and an increased incidence of cholelithiasis. In the event of prolonged usage there is an increased risk of endometrial carcinoma. Hypercalcaemia and bone pain may occur in women treated for breast cancer.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the

Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

There is no specific antidote to diethylstilbestrol. The commonest symptoms of overdosage are nausea and vomiting. Management may include gastric lavage associated with special care of plasma electrolytes and any other appropriate symptomatic relief. Should the overdose (abuse) be in female children, an oestrogen-withdrawal bleed may be induced.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: L02A A01 (endocrine therapy, oestrogens)

Like other oestrogens action of diethylstilbestrol is intracellular. It is bound to a receptor protein in the cytoplasm and translocated to the nucleus where binding to chromatin occurs. Specific mRNA and specific proteins are then synthesised.

The pharmacological action of oestrogens is complex and not fully understood, but it is believed that oestrogen receptors contained in tumour cells account for the palliative action of diethylstilbestrol.

5.2. Pharmacokinetic properties

Following oral administration, diethylstilbestrol is readily absorbed through the gastrointestinal tract. It is metabolised slowly in the liver and enterohepatic recycling has been reported.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets contain:
Magnesium stearate (E572)
Maize starch
Anhydrous Lactose

The coating contains:
Opadry II Pink 85F24252: Titanium dioxide (E171)
Erythrosine Aluminium Lake (E127)
Sunset Yellow (E110)
Indigo Carmine (E132)
Talc
Polyvinyl alcohol
Macrogol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years

6.4. Special precautions for storage

Store in a dry place below 25˚C, protect from light.

6.5. Nature and contents of container

Blister strips in packs of 10, 28, 30, 56, 60 and 100 tablets.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 0289/5188R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 25/07/1990
Date of latest renewal: 06/04/2001

10. DATE OF REVISION OF THE TEXT

07/03/2024