SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diethylstilbestrol 1mg film-coated tablets

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 D1on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diethylstilbestrol tablets are indicated for the treatment of castration-resistant carcinoma of the prostate in patients for whom alternative forms of therapy are not suitable (see Section 5.1).

4.2 Posology and method of administration

Posology
Adults:
Management of prostatic carcinoma: 1 - 3 mg daily.

Paediatric population
Children:

Diethylstilbestrol should not be used in children.

Special populations
Elderly: The recommended adult dose is appropriate.

Thromboembolic complications are frequent and patients treated with diethylstilbestrol should be considered for treatment with aspirin See 4.4 below.
Diethylstilbestrol stimulates breast tissue in males, breast bud irradiation may be offered before treatment. See 4.4 below

Method of administration
For oral administration.

4.3 Contraindications

Diethylstilbestrol is a synthetic non-steroidal oestrogen hormone which due to its carcinogenic potential is only justified in the management of malignant disease.

Diethylstilbestrol should not be used in children or young adults because of its carcinogenic potential.

Diethylstilbestrol is strongly contra-indicated in those who are pregnant (it is not suitable for pre-menopausal women). 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

Thromboembolic complications are frequent and patients treated with diethylstilbestrol should be given prophylaxis with aspirin (75 mg daily).

The use of diethylstilbestrol may cause tenderness, pain, enlargement and secretion of milk-like fluid from the breast. Breast bud irradiation should be considered before treatment with diethylstilbestrol.

Care should be taken when administering diethylstilbestrol preparations to patients with cardiac failure; hypertension; diabetes; epilepsy; migraine; depression; contact lenses; cholelithiasis; or if there are any evidence of renal impairment, hepatic impairment; a history of, or with cholestatic jaundice from any cause.

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.

Patient with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, Pregnancy and lactation

Diethylstilbestrol is contra-indicated in pre-menopausal women.

Diethylstilbestrol is a known human teratogen. Diethylstilbestrol is thus contra-indicated in pregnancy. In the first trimester, high doses are associated with vaginal carcinoma, urogenital abnormalities, and reduced fertility in female offspring. Increased risk of hypospadias in male offspring.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Diethylstilbestrol has been used for many years and has been found to cause serious adverse effects which have greatly limited its use. There is limited clinical trial data on adverse reactions relating to the use of diethylstilbestrol in men with carcinoma of the prostate.

The following adverse reactions have been reported from post-marketing experience over many years. Many of the reactions are dose related and, from the data available, it is not possible to indicate their frequency (see table below).

System Organ Class	Adverse reactions (frequency unknown)
Metabolism and nutrition disorders	sodium retention, fluid retention
Eye disorders	corneal irritation in patients wearing contact lenses
Psychiatric disorders	mood altered
Nervous system disorders	headache, migraine
Vascular disorders	thrombosis, cerebral thrombosis, coronary artery thrombosis, embolism, hypertension
Gastrointestinal disorders	nausea, vomiting
Hepatobiliary disorders	cholelithiasis, jaundice cholestatic
Skin and subcutaneous tissue disorders	rash, erythema nodosum, chloasma
Reproductive system and breast disorders	in both sexes, breast discomfort, breast tenderness, breast pain, breast enlargement, breast discharge. In men, gynaecomastia, testicular atrophy, impotence
Investigations	glucose tolerance decreased, weight increased

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 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.

Other effects may be withdrawal bleeding in women. 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.

In a clinical study of 231 patients with advanced prostatic cancer the following adverse effects requiring cessation of treatment were noted, where the patients either stopped or had the dose of DES reduced:

System Organ Class	Adverse reactions	Incidence
Nervous system disorders	lethargy	0.9 %
	transient ischaemic attack	0.4 %
Vascular disorders	embolism	4.8 %
Cardiac disorders	cardiac failure congestive	0.4 %
Respiratory, thoracic and mediastinal disorders	pulmonary oedema	0.4 %

Gastrointestinal disorders	nausea	4.8 %
	gastrooesophageal reflux disease	0.4 %
General disorders and administration site conditions	oedema peripheral	0.9 %
	Chest pain	0.4 %
Investigations	liver function test abnormal	0.9 %

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.

4.9 Overdose

There is no specific antidote to Diethylstilbestrol. The commonest symptoms of over dosage 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.
In a study of 231 elderly men with castration-resistant prostate cancer treated with
1–3 mg of DES, given with 75 mg aspirin and breast bud irradiation, almost 30% showed a significant prostate specific antigen (PSA) response and the median time to PSA progression was 4.6 months. Almost 20% of these patients with pain had a significant analgesic benefit. The most important toxicity was thromboembolism in 10% of men. Overall the drug has an acceptable toxicity profile and offers a palliative benefit in frail elderly men who may not be suitable for chemotherapy.

(Reference Wilkins A, Shahidi M, Parker C, Gunapala R, Thomas K, Huddart R, Horwich A, Dearnaley D. Diethylstilbestrol in castration-resistant prostate cancer. BJU Int. 2012 Dec;110(11 Pt B):E727-35)

5.2 Pharmacokinetic properties

Following oral administration, Diethylstilbestrol is readily absorbed through the gastro intestinal tract.

It is metabolised slowly in the liver and enterohepatic recycling has been reported.

5.3 Preclinical safety data

Acute and repeat dose toxicology reflect the expected hormonal effects of exposure to diethylstilbestrol. Data from mouse studies have confirmed poor reproductive outcomes and reduced fertility following in utero/neonatal diethylstilbestrol exposures in humans.

Diethylstilbestrol is classified as a carcinogen by the World Health Organization, U.S. Environmental Protection Agency, National Toxicology Program, and the International Agency for Cancer Research. Rodent models have found increases in the incidence of malignant reproductive tract tumours including uterine adenocarcinoma, cervical cancer, vaginal cancer, and mammary tumours in addition to many other types of abnormalities. Third generation effects have been studied in rodents and have shown an increased susceptibility to tumour formation in the third generation.

Many potential different genetic and epigenetic pathways have been implicated in the diethylstilbestrol-induced carcinogenesis and reproductive developmental abnormalities. Oestrogen imprinting is an important epigenetic mechanism where early-life exposure to permanently alters DNA methylation and gene expression of oestrogen-responsive genes. Once changed, the altered gene profiles can continue to be expressed without further hormonal stimulation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Magnesium stearate (E572),

Maize starch,
Ethanol,
Opadry II pink 85F24252 which consists of:
Polyvinyl alcohol,
Titanium dioxide (E171),
Polyethylene glycol/ macrogol,
Talc,
Erythrosine aluminium lake (E127),
Sunset yellow FCF aluminium lake (E110),
Indigo carmine aluminium lake (E132).

6.2 Incompatibilities

None known

6.3 Shelf life

5 years

6.4 Special precautions for storage

No special storage conditions are required for this product.

6.5 Nature and contents of container

PVC/PVdC or Alu/Alu 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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Brown & Burk UK Ltd

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Hounslow West
Middlesex
TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0153

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/01/2025

10 DATE OF REVISION OF THE TEXT

31/01/2025