SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

CETURA 0.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION Each

tablet contains 0.5 mg oestradiol as oestradiol hemihydrate.

Excipient(s) with known effect: lactose, sodium

Contains 159 mg lactose as lactose monohydrate per tablet.
Contains less than 1 mmol sodium (23 mg) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

CETURA is a white, round tablet with a score line on one side. The score line can be used to divide the tablet into two equal parts.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CETURA is used for:

- Pubertal induction in girls (with Turner syndrome for example)

4.2 Posology and method of administration

Oral administration Pubertal

induction in girls

Girls: starting dose 5 µg (0.005 mg)/kg BW/day in one single dose.

Increase the dose every 6-9 months until breakthrough bleeding occurs. Titration schedule: 0.25 mg (½ tablet), 0.5 mg (1 tablet), 1 mg (2 tablets), 1.5 mg (3 tablets), 2 mg (4 tablets).
In children with a body weight of less than 50 kg, the starting dose is higher than 5 µg (0.005 mg)/kg BW/day if half a tablet is prescribed. The treating physician must determine the appropriate starting dose for children weighing less than 50 kg.

The maximum dose is 2 mg/day.

After 2 years or if spotting or breakthrough bleeding occurs, a cyclical progestogen must be added. The progestogen must be given during the first 12-14 days of the month (e.g. 5-10 mg dydrogesterone or 5-10 mg medroxyprogesterone/day).

Once the dosage of 2 mg oestradiol is reached, the treatment should switch to a combination pill or a contraceptive pill.

4.3 Contraindications

Do not use CETURA in cases of:
- Known hypersensitivity to oestradiol or to one of the excipients of CETURA.
- Porphyria
- A history of venous thromboembolism or active venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic condition (angina pectoris, myocardial infarction)
- Acute liver disease as long as the liver function values have not normalised.
- Oestrogen-dependent tumours
- A history of breast cancer
- Endometrial hyperplasia
- Unexplained vaginal bleeding

4.4 Special warnings and precautions for use

Medical examination/follow-up

The FSH concentration in the blood (elevated FSH) must be determined before the start of the treatment to confirm gonadal dysfunction. If the FSH is normal, consider performing a lower abdominal ultrasound to look for follicles (predictor of gonadal status).

Also perform a lower abdominal ultrasound before the start of the therapy to determine the size of the uterus.

Addition of progestogen after 2 years or after spotting/breakthrough bleeding

A progestogen must be added to the treatment to prevent endometrial hyperplasia. In case of pubertal induction, this should be done after 2 years of oestrogen therapy or sooner if spotting or breakthrough bleeding occurs. Cyclical progestogen is not started immediately, to allow for normal breast and uterus development at this age.

Cases requiring extra caution

Extra caution with the use of CETURA is advised in patients:

- with diabetes mellitus

Oestrogens can affect peripheral insulin resistance and glucose tolerance. Patients with diabetes mellitus must be carefully monitored during treatment with oestrogens, in particular at the start of the treatment.

- with lactose intolerance

CETURA contains 159 mg Lactose. Patients with rare hereditary conditions such as lactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Long-term risks

There are insufficient data on long-term effects. Long-term data are obtained from the use of oestrogens for contraception. The use of oestrogens for contraception is associated with long-term risks. It is not known whether these increased risks also apply to girls and women who are treated for hypoestrogenism in Turner Syndrome. The treating physician must always be alert for potential cardiovascular conditions and/or malignancies.

Cardiovascular conditions

The use of hormone preparations in postmenopausal women and in premenopausal women for contraception is associated with an increased incidence of venous thromboembolism. In particular if there is a positive family history, severe obesity, and a history of systemic lupus erythematosus and other cardiovascular disorders. Furthermore, patients with a history of cardiovascular disorders (such as atrial fibrillation, hypertension, valvular heart disease) have a higher incidence of arterial thromboembolic complications. The risk of venous and arterial thromboembolism is greatest during the first year of treatment. Studies with postmenopausal women found an increased risk of coronary heart disease and cerebrovascular accidents.

Malignancies

A slightly elevated incidence of breast cancer was observed with the use of oestrogens for contraception.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on oestradiol

The metabolism of oestrogens may increase with the concomitant use of substances that are known to induce metabolising enzymes, in particular cytochrome P450 enzymes (CYP3A4) and glucuronidation enzymes (UGT). Substances that are known for their ability to induce (CYP3A4) metabolism are anticonvulsants (such as phenobarbital, phenytoin, carbamazepine), antibacterial agents (such as rifampicin, rifabutin), antiviral agents (nevirapine, efavirenz, ritonavir, nelfinavir), antimycotics (such as ketoconazole, griseofulvin) and phytotherapeutic preparations that contain St. John's wort (Hypericum perforatum). In clinical terms, increased oestrogen metabolism may lead to lower oestradiol plasma levels and changes in menstrual cycle.

Effects of oestradiol on other medicinal products

Oestradiol can affect the metabolism and the effects of other medicinal products. It may therefore be necessary to adjust the dosage of certain medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

CETURA should not be used during pregnancy. If pregnancy occurs during treatment with CETURA, the treatment must be stopped, unless it is indicated for improved uterine function.
To date, the results of most epidemiological studies that are relevant for assessing the effects of unintended foetal exposure to oestrogens have not shown any teratogenic or foetotoxic risks.

Breastfeeding

Small amounts of oestradiol are excreted in breast milk. There are no negative effects on the infant. CETURA can be safely used during breastfeeding.

Fertility
Treatment with oestradiol for hypoestrogenism has no known negative effects on fertility. There may be a positive effect on fertility in Turner syndrome patients resulting from the restoration of normal endometrial function.

4.7 Effects on ability to drive and use machines

CETURA has no effect on the ability to drive and use machines.

4.8 Undesirable effects

There are insufficient data on adverse reactions.

The following adverse reactions were reported in a controlled clinical trial in adolescents with Turner Syndrome (n=41). The frequency in the studied population is listed after each adverse reaction.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Lymphoedema (n=3, common ≥1/100, <1/10)

Blood and lymphatic system disorders
- Increased frequency and size of birthmarks (n=1, common ≥1/100, <1/10)

Nervous system disorders
- Headaches
- Exacerbation of migraines
- Mood changes

Eye disorders
- Irritation of the eyes when wearing contact lenses

Gastrointestinal disorders
- Nausea
- Vomiting

Skin and subcutaneous tissue disorders
- Erythema nodosum

Musculoskeletal and connective tissue disorders
- Muscle spasms

Reproductive system and breast disorders
- Sensitive breasts
- Painful breasts
- Enlargement of the breasts
- Discolouration of the nipples

General disorders
- Weight changes

4.9 Overdose

Symptoms of overdose are generally not severe. An overdose may manifest as nausea and vomiting. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oestrogens, ATC code: G03CA03

The active substance, synthetic oestradiol, is chemically and biologically identical to endogenous human oestradiol. It supplements the lack of natural oestrogen produced by the body. Oestradiol is responsible for stimulating and maintaining secondary sexual characteristics.

People with hypoestrogenism as a result of Turner Syndrome have an increased risk of comorbidity, such as osteoporosis. Oestrogens protect against osteoporosis.

Because oestrogens stimulate endometrial proliferation, there is an increased risk of endometrial hyperplasia and carcinoma. Addition of a progestogen to the oestrogen therapy prevents this increased risk.

5.2 Pharmacokinetic properties

Absorption
Oestradiol is fully absorbed after oral administration. After administration of a dose of 0.5 mg, oestradiol reaches a peak plasma concentration of approx. 25 pg/ml within 8 hours.

Metabolism
After oral administration, about 5-10% of the dose is immediately biologically available as oestradiol. Oestradiol is subject to a high first-pass effect, and a considerable part of the administered dose is metabolised in the gastrointestinal mucosa. Together with the presystemic metabolism in the liver, about 95% of the orally administered dose is metabolised before entering the systemic circulation. The main metabolites are oestrone, oestrone sulfate and oestradiol glucuronide.

Distribution
During circulation, oestradiol and its metabolites are bound to SHBG (37%) and albumin (61%), while about 2% circulates unbound.
Oestradiol may cause a slight, dosage-dependent increase in the serum concentrations of SHBG.

Elimination
Due to the large amount of circulating oestrogen sulfates and oestrogen glucuronides and due to the enterohepatic recirculation, the terminal half-life of oestradiol after oral administration represents a composite parameter which depends on all these processes and ranges from 13-20 hours.
Oestradiol and its metabolites are excreted primarily via the urine. About 10% is excreted via the faeces.

Steady-state conditions
The pharmacokinetics of oestradiol are affected by SHBG levels. In young women, the measured plasma oestradiol levels are a composite of the endogenous oestradiol, if present, and the administered oestradiol.

5.3 Preclinical safety data

Preclinical safety data show that oestradiol is carcinogenic. Animal studies found reproductive toxicity at higher than clinically relevant doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose Lactose monohydrate Sodium starch glycolate (type A) Magnesium stearate

6.2 Incompatibilities

None.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

CETURA 0.5 mg tablets are available in folding cartons containing 3 PVC/Alu blister strips with 10 tablets each.

6.6 Special precautions for use and other handling

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

7. MARKETING AUTHORISATION HOLDER

ACE Pharmaceuticals BV
Schepenveld 41
3891 ZK Zeewolde
ace@ace-pharm.nl

8. MARKETING AUTHORISATION NUMBER

RVG 110115

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 March 2012 Date of last renewal: 27 March 2017

10. DATE OF REVISION OF THE TEXT

Latest partial change concerns section 2: 01 October 2018