This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in January 2018

Summary of Product Characteristics

1. Name of the medicinal product

Agnucaston®
Film-coated tablets

2. Qualitative and quantitative composition

1 film-coated tablet contains:
AgnI casti fructus dry extract (7-11:1) 4.0 mg
Extraction solvent: ethanol 70 % (v/v)

Excipients:
Lactose monohydrate 25.0 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

The film-coated tablets are green-blue, round, biconvex with a dull surface.

4. Clinical particulars

4.1 Therapeutic indications

Premenstrual syndrome, mastodynia.

4.2 Posology and method of administration

1 film-coated tablet once daily.

Agnucaston should be taken over a period of several months (3 months) without interruption even during mensturation.

A doctor has to be consulted if Agnucaston is taken for more than 3 months.

Renal impairment: no data is available

Hepatic impairment: no data is available

Agnucaston should not be used in children and adolescents under 18 years of age.

Oral administration. The film-coated tablets should be swallowed unchewed with sufficient liquid (e.g. a glass of water). There is no information available regarding the crushing/splitting of the product. It is recommended that the film coated tablet is not chewed, split or crushed.

4.3 Contraindications

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

Pregnancy.

4.4 Special warnings and precautions for use

Use with caution in
- Patients who suffer or suffered from an oestrogen-sensitive malignant tumour.
- Patients using dopamine agonists, dopamine antagonists, oestrogens and anti-oestrogens (see section 4.5 Interaction with other medicinal products and other forms of interaction).
- patients with a history of a pituitary disorder. Agnucaston is thought to act on the pituitary-hypothalamic axis.
- patients with prolactin secreting tumours of the pituitary gland. Agni casti fructus may mask symptoms of the tumour.

Product specific special warnings:

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Children and Adolescents
There is insufficient data on the use of this medicinal product in children. It should not therefore be used in children and adolescents under 18 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

Because of the possible dopaminergic and oestrogenic effects of *Agnus castus*, interactions with dopamine agonists, dopamine antagonists, oestrogens and anti-oestrogens cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Agnucaston in pregnant women. There are not sufficient animal studies available with respect to reproductive toxicity. Agnucaston must not be taken during pregnancy.

Lactation
It is unknown whether the active substance or metabolites are excreted in human milk. A risk to the newborns cannot be excluded. There are not sufficient data available regarding safety during lactaction. Data from reproductive toxicity studies suggest that Vitex agnus-castus may affect lactation. Agnucaston should not be used during lactation.

Fertility
There are no specific studies on the influence on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Severe allergic reactions with face swelling, dyspnoea and swallowing difficulties have been reported. (Allergic) skin reactions (including rash, urticaria), headache, dizziness, gastrointestinal complaints (including nausea, abdominal pain), acne, as well as menstrual irregularities may occur.
There is no data on the frequency of these potential undesirable effects.

At the first signs of a hypersensitivity reaction, Agnucaston should not be administered again.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

No case of overdose has been reported.
Treatment of overdose: In case of overdose, symptomatic treatment should be initiated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: herbal medicine for the treatment of menstrual disorders

ATC-Code: G02CX03

There is evidence that aqueous-alcoholic Agni casti fructus extracts inhibit prolactin release *in vitro*. The inhibitory effect on prolactin release was also confirmed in animal experiments. In human pharmacology there is yet no data to support a lowering of elevated prolactin levels. However, several clinical studies showed evidence that slightly elevated prolactin levels in women and increased prolactin release due to stress (so-called "latent hyperprolactinaemia") are reduced through administration of *Agnus castus* extract.

In vitro studies showed that the lactotrophic pituitary cells are the site of action and the mechanism of action is dopaminergic.

Bicyclic diterpenes have been identified as a substance group that contributes to the prolactin reducing effects of Agni casti fructus extract BNO 1095. These substances bind to the human dopamine receptor subtype 2 and lower in a concentration-dependent manner the prolactin release in cultured rat pituitary cells.

5.2 Pharmacokinetic properties

There are no studies on pharmacokinetics and bioavailability because not all active substances are known in detail.

5.3 Preclinical safety data

Acute toxicity
The Agni casti fructus extract BNO 1095 has a low toxicity. One-time administration resulted in no fatalities in rats and mice. The LD_{50} values exceed the highest dose of 1684 mg/kg.

Subacute toxicity
The toxicity of BNO 1095 applied in repeated doses to rats was examined up to a dose of 842 mg/kg. Oral administration over four weeks resulted in a no-observed-effect-level („NOEL“) of 42 mg extract/kg body weight which is a multiple above the recommended human dose of 4 mg/patient and day.

Chronic toxicity
Oral administration to rats over 26 weeks with doses up to 84 mg/kg resulted in no substance-related changes for the therapeutic dose range. The no-observed-adverse-effect-level („NOAEL“) in this study amounted to 3 mg extract/kg body weight.

Mutagenicity
Four different test approaches proposed for evaluating the genotoxic potential produced no evidence for any genotypic or chromosome-damaging effects of the Agni casti fructus extract, neither in isolated mammal cells nor in whole animals. In the Ames test and in cultured mammal cells (mouse lymphoma cells), the extract caused no mutations either with or without metabolic activation. Oral administration to rats also caused no increased DNA synthesis in liver cells, a fact that would be evidence for a repair of possible damage. The micro nucleus test on the mouse that evaluates the damage of chromosomes after *in vivo* application was also negative.

Reproductive toxicity
There are no studies available on the toxicity to reproduction of the Agni casti fructus extract.

Carcinogenicity
There are no studies available on the tumorigenic potential of Agni casti fructus extracts after long-term administration.

6. Pharmaceutical particulars

6.1 List of excipients

Ammonio methacrylate copolymer (type A), ferric oxide yellow (E172), indigo carmine laquer (E132), potato starch, lactose monohydrate, magnesium stearate, macrogol 6000, microcrystalline cellulose, povidone 30, colloidal anhydrous silica, talc, titanium dioxide (E171), sorbic acid, sodium hydroxide.

Note for diabetics:
Agnucaston contains per single dose 0.1g carbohydrates on average.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Pack of 30 film-coated tablets

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

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Israel
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8. Manufacturer

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92318 Neumarkt

8. Marketing authorisation number

159-79-34979-00

9. Date of first authorisation

January 2018

10. Date of revision of the text

April 2020

11. General classification for supply

Over the counter (OTC), For sale in pharmacies only.