1. NAME OF THE MEDICINAL PRODUCT

Menopret®
Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains
2.8 mg dry extract from Cimicifuga rhizoma (Black cohosh) (5-10:1)
Extraction solvent: ethanol 58 % (V/V)

Excipients with known effect:
Lactose monohydrate 17.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
The film-coated tablets are terracotta-coloured, round, biconvex with smooth surface.
The film-coated tablet has a diameter of 7.0-7.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Herbal medicinal product indicated in female adults for the relief of menopausal complaints such as hot flushes and profuse sweating.

4.2 Posology and method of administration

Posology:
Female adults in the menopause
Daily dose: 2 times daily (morning and evening) 1 film-coated tablet.

If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted.
Menopret® Film-coated tablets should not be taken for more than 6 months without medical advice.

Paediatric population
There is no relevant use of Menopret® Film-coated tablets in the paediatric population.

Special populations
No data are available for a dosing instruction in case of impaired renal function.

In the package leaflet patients with a history of liver disorder are informed not to take Menopret® Film-coated tablets without medical advice (see section 4.4 ‘Special warnings and precautions for use’ and 4.8 ‘Undesirable effects’).

Method of administration:
For oral use. Take film-coated tablets with some liquid. Do not chew or suck.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Menopret® Film-coated tablets is contraindicated for patients with a current or previous liver disorder.

4.4 Special warnings and precautions for use

In prospective clinical trials involving more than 1200 patients, black cohosh was not associated with serum enzyme elevations during treatment and no cases of clinically apparent liver injury were reported. However, products labeled as black cohosh have been linked to more than fifty instances of clinically apparent liver injury that have ranged in severity from symptomatic elevations in serum enzymes without jaundice, to acute self-limited hepatitis, prolonged hepatitis with cholestasis, autoimmune hepatitis, and acute liver failure requiring liver transplantation or with a fatal outcome. The latency to onset of liver injury ranged from 1 to 48 weeks but was usually within 2 to 12 weeks.

Patients should stop taking Menopret® Film-coated tablets and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (such as unusual tiredness, loss of appetite, weight loss, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting, diarrhoea or dark urine).

Liver function test should be performed according to clinical judgment.

If vaginal bleeding occurs or other symptoms occur, a doctor should be consulted.

Menopret® Film-coated tablets should not be used together with oestrogens unless advised by a doctor.

Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use Menopret® Film-coated tablets without medical advice. Please see section 5.3 ‘Preclinical Safety Data’.

If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Menopret® Film-coated tablets.

4.5 Interaction with other medicinal products and other forms of interaction

None reported.
No interaction studies have been performed with Menopret® Film-coated tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
There are no data from the use of ethanolic extracts from Cimicifuga racemosa in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Menopret® Film-coated tablets is not recommended during pregnancy.
Women of childbearing potential should consider using effective contraception during treatment. It is unknown whether ethanolic extracts from Cimicifuga racemosa or metabolites thereof are excreted in human milk. A risk to the suckling child cannot be excluded. Menopret® Film-coated tablets
should not be used during breast feeding.
Fertility
No studies on fertility have been performed.

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

The following frequency categories are used for the evaluation of undesirable effects:

Very common (≥1/10)	Common (≥1/100, <1/10)
Uncommon (≥1/1000, <1/100)	Rare (≥1/10000, <1/1,000)
Very rare (<1/10000)	Not known (frequency cannot be estimated from the available data)

Gastrointestinal disorders
Frequency not known: Gastrointestinal symptoms (i.e. dyspeptic disorders, diarrhoea)
Hepatobiliary disorders
Frequency is not known: Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests) is associated with the use of Cimicifuga containing products.
Skin and subcutaneous tissue disorders
Frequency not know: Skin reactions (urticaria, itching, exanthema), facial oedema.
General disorders and administration site conditions
Frequency not known: Peripheral oedema

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.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: other gynaecologicals
ATC code: G02CX04

Neither the mode of action nor the constituents relevant for the improvement of minor symptoms of menopausal complaints are known.
Clinical pharmacological studies indicate that menopausal complaints (such as hot flushes and profuse sweating) can improve under treatment with medicinal products from Cimicifuga racemosa root.

5.2 Pharmacokinetic properties

No data available.

5.3 Preclinical safety data

In a 28-days toxicity study in rats dose levels of 50, 200 and 1000 mg/kg body weight (human equivalent doses (HED) of 8,32 and 161 mg/kg; clinical dose = 0.11 mg/kg) were tested. Also in the low dosage group adverse effects on several organ systems (e.g. increased liver weights) were seen. In the lowest dosage group the effects on liver were reversible, while in the highest dosage group the liver weights were not completely decreased after 14 days of recovery. Electron microscopy investigations showed a dose-depending increase in the volume of hepatocellular mitochondria (mitochondrial swelling) and an enlargement of bile canaliculi in rats treated with an ethanolic Cimicifuga extract in doses from 10-1000 mg/kg b. w. (corresponding to the HEDs of 1.6-161 mg/kg).

Evidence from in vitro and in vivo pharmacological studies suggests that Cimicifuga extracts do not influence the latency or development of breast cancer. However, contradictory results have been obtained in other in vitro experiments.
In Cimicifuga-treated (isopropanolic black cohosh extract equivalent to 40 mg of root and rhizome), tumour-bearing, female transgenic mice, the percentage of mice with detectable metastatic lung tumours at necropsy was increased compared to those on the control diet. However, in the same

experimental model, no increase in primary breast tumour was seen. Influence on breast cancer or other hormone-depending tumours cannot be completely excluded.
Four studies performed with the ethanolic extract that investigated genotoxicity (*in vitro*: AMES test and mouse lymphoma assay, *in vivo*: unscheduled DNA synthesis test and oral mouse micronucleus test) showed no genotoxic risk potential.

There are no conclusive studies on carcinogenicity and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Potato starch
Magnesium stearate
Talc
Ammonio methacrylate copolymer, Type A, Dispersion 30% (Eudragit RL 30D)
Titanium dioxide (E 171)
Macrogol 6000
Iron oxide yellow (E 172)
Iron oxide red (E 172)
Sodium hydroxide
Sorbic acid

6.2 Incompatibilities

Not applicable.

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.
Keep the blisters in the outer carton.

6.5 Nature and contents of container

Menopret® Film-Coated Tablets are available in PVC/PVDC/aluminium blisters.
Package with 60 film-coated tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BIONORICA SE
Kerschensteinerstraße 11-15
92318 Neumarkt
Germany
Phone: +49 / (0)9181 / 231-90
Fax: +49 / (0)9181 / 231-265
e-mail: info@bionorica.de

8. ISRAELI MARKETING AUTHORIZATION HOLDER

Dr. Samuelov Importing & Marketing Ltd.
13 Hasadna st, POB 2486
Ra'anana 4365007
Israel
Phone: 09 7483769
Fax: 09 7889776
E-mail: info@drsamuelov.co.il

9 MARKETING AUTHORISATION NUMBER

165-11-34785-00

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