This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in May 2019

1. NAME OF THE MEDICINAL PRODUCT

Tesalin, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
P. hybridus leaf native extract Ze 339 corresponding to 8.0mg petasins

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of symptoms of allergic rhinitis (hay-fever) as well as related symptoms in eyes, nose and throat.

4.2 Posology and method of administration

Adults and adolescents from 12 years of age: 2 film coated tablets distributed over the day. In cases of high pollen exposure the dosage may be increased to 3 times 1 film coated tablet per day if needed. The film coated tablet should be swallowed unchewed with some water. The tablet intake does not depend on day-time or meals.

The safety and efficacy have not been established in children younger than 12 years.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Very rare cases of liver damage, including some serious cases, have been observed in association with preparations containing a CO_2-extract made from roots of *Petasites hybridus*. However, a liver damaging effect cannot be excluded for the CO_2-extract made from leaves of *Petasites hybridus* (Ze 339), which is contained in Tesalin. During treatment, doctors and patients should therefore look at early signs of liver damage such as upper abdominal pain, loss of appetite, jaundice, ocular icterus et al.

There are no own clinical trial results available with patients having a reduced liver or kidney function. For these patients it is therefore advised that the preparation should be taken with caution and under medical supervision.

The safety and efficacy have not been established yet in children younger than 12 years. Therefore, Tesalin must not be taken by this age group.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with other medicinal products and also with foods or stimulants are not known. Pharmacological *in vitro* studies with intestinal test systems (CaCo-2 cells) demonstrated that the used extract from the leaves of *Petasites hybridus* (Ze 339) does not induce MDR1 and CYP3A4 gene expression. Also, liver enzymes activity remains unchanged, i.e. neither induced nor inhibited. The following enzymes were tested so far: CYP2E1, CYP1A2, CYP2D6, CYP2C19, CYP3A4 and CYP2C9. The results of these studies show that interactions with other drugs are not to be expected.

4.6 Fertility, pregnancy and lactation

There are no clinical data on the use during pregnancy and lactation.

Scientific investigations with animals did not show any direct or indirect effect on pregnancy or embryonic development with administrations of up to 30 times the usual dosage. The potential risk for humans is not known.

Therefore, the intake of Tesalin during pregnancy and lactation is not recommended.

4.7 Effects on ability to drive and use machines

No corresponding studies were conducted.

4.8 Undesirable effects

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

No differences were observed in the frequency of adverse reactions between Tesalin and placebo in clinical trials.

Gastrointestinal tract:

Common: gastrointestinal discomfort such as nausea, diarrhoea and abdominal pain.

Skin:

Uncommon: hypersensitivity reactions of the skin with erythema, oedema, and pruritus.

Nervous system:

Unknown: headache

Immune system:

Unknown: hypersensitivity reactions

Liver damage:

Very rare cases of liver damage, including some serious cases, have been observed in association with preparations containing a CO_2-extract made from roots of *Petasites hybridus*. However, a liver damaging effect cannot be excluded for the CO_2-extract made from leaves of *Petasites hybridus* (Ze 339), which is contained in Tesalin. Please refer to « *Special warnings and precautions for use* ».

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

Acute intoxications with Tesalin are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products, ATC code: R07AX.

In an explorative study with 18 symptom-free adult patients with a history of allergic rhinitis caused by grass pollen, a faster reduction of nasal obstruction after targeted provocation with grass pollen could be shown under treatment with Tesalin compared to placebo and desloratadine.

Clinical efficacy:

The efficacy of Tesalin in allergic rhinitis has been studied so far in 3 clinical trials.

In a three-arm study, the superiority of 2 and 3 film coated tablets Tesalin versus placebo was demonstrated for the TSS (total sum score) as well as for the improvement of individual symptoms, such as sneezing, itchy nose and eyes, rhinorrhoea and nasal obstruction. When using 3 film coated tablets Tesalin, 91% responders (≥ 25% improvement of TSS) and with 2 film coated tablets 71% responders were observed.

In an additional trial Tesalin and fexofenadine were tested for their efficacy in comparison to placebo. Both active ingredients significantly improved the TSS, as well as the individual symptoms sneezing, itchy nose, itchy/reddened eyes and rhinorrhoea.

In a third trial the effects of Tesalin and cetirizine with respect to the patients' quality of life were determined. An equivalent efficacy (non-inferiority) of Tesalin and cetirizine resulted.

5.2 Pharmacokinetic properties

In a kinetic phase-I-study with crossover design, 24 male healthy volunteers were treated with single administration of either 2 or 4 tablets containing P. hybridus extract (CO_2 extract Ze 339 from leaves of *Petasites hybridus* (L.) Gaertn., B. Mey. et Scherb.). The average dosage of measured petasin corresponded to 0.20 mg/ kg body weight for 2 tablets or 0.41 mg/ kg body weight for 4 tablets.

Absorption

No corresponding studies were conducted.

Distribution

The following data are available for the ingredient petasin, but no conclusions can be drawn for distribution of the total extract, i.e. the active substance.

Maximal plasma concentrations (c_{max}) were reached after approx. 1.6 hours (t_{max}) dose-independently for both dosages (SD ± 0.499 or ± 0.926, respectively) and were dose-dependend at 25.5 ± 14.8 ng/ ml after administration of 2 tablets and at 58.1 ± 26.7 ng/ ml after administration of 4 tablets; the AUC was proportional to the dose at 65.3 ± 35.61 ng/ ml*h after administration of 2 tablets and at 151.2 ± 68.21 ng/ ml*h after administration of 4 tablets.

Metabolism

No corresponding studies were conducted.

Elimination

Elimination of petasin was comparable between the two doses, with a half life time of 7.155 ± 4.611 h (2 tablets) and 7.618 ± 3.338 h (4 tablets).

5.3 Preclinical safety data

Pre-clinical data do not indicate any specific danger for humans based on conventional studies with respect to safety pharmacology toxicity after acute and repeated oral administration, reproductive toxicity and mutagenicity. Carcinogenicity was not examined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal anhydrous, cellulose microcrystalline, sodium starch glycolate type A, hypromellose, magnesium stearate, , titanium dioxide (E 171), stearic acid, macrogol 20,000.

The product contains less than 0.2 mg digestible carbohydrates per single dose.

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 25 °C in the original package.

6.5 Nature and contents of container

Blisters

20 tablets per box.

60 tablets per box.

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. MANUFACTURER

Max Zeller Söhne AG, Switzerland

8. REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

9. REGISTRATION NUMBER

162-17-35348