1.3.1	Herbion cowslip syrup
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Herbion® cowslip syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml of syrup (1 measuring spoon) contains:
- 3.08 g liquid aqueous extract of *Primula veris* L.or/and *Primula elatior* (L.) Hill, (Primulae radix), cowslip root and *Thymus vulgaris* L. or/and *Thymus zygis* L. (Thymi herba) garden thyme herb, equivalent to 0.22–0.51 g of Primula root and 0.62 g Thyme.
Extraction solvent: water.

Excipients with known effect: 5 ml of syrup (1 measuring spoon) contains 3.16 g sucrose and 8.75 mg methyl parahydroxybenzoate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.
Brown syrup with specific odour and taste. Slight sediment typical of natural substances can be noticed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Herbion cowslip syrup is a herbal drug recommended for easier expectoration in:
- respiratory inflammation (bronchitis, pharyngitis) in which expectoration of thick bronchial mucus is difficult,
- in common cold and flu accompanied by cough.

4.2 Posology and method of administration

Adults and children over 16 years of age should take 2 measuring spoons of syrup 3 to 4 times daily.
Children from 4 to 10 years of age should be given 1 measuring spoon of syrup 3 times daily, and children from 10 to 16 years of age 1 to 2 measuring spoons of syrup 3 times daily.
It is recommended that the syrup be taken with plenty of tea and warm beverages.
There is no experience in children under 4 years of age (see section 4.4).
Shake the bottle before use.

4.3 Contraindications

Hypersensitivity to the active substances or any of the excipients.
The syrup should not be taken in inflammation of the gastric mucosa and gastric ulcer.
A history of acute obstructive laryngitis in children.
Asthma.
Children under 4 years of age.

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4.4 Special warnings and special precautions for use

Herbion cowslip syrup contains sucrose and is therefore not recommended for diabetics.
The syrup is not recommended for children under 4 years of age due to lack of experience.

Special information about some of the ingredients
Herbion cowslip syrup contains sucrose. Patients with rare hereditary disorders of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take this drug.
Methyl parahydroxybenzoate (E218) may cause allergic reactions (which may be delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of medicines that suppress cough (antitussives) and reduce sputum production is not recommended because this makes expectoration of mucus difficult.
No interactions with food have been reported.

4.6 Pregnancy and lactation

The syrup should not be used during pregnancy and lactation since the data on safe use during pregnancy and lactation is limited.

4.7 Effects on ability to drive and use machines

The drug has not been reported to affect the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects that may occur during treatment with Herbion cowslip syrup are classified into the following groups in order of frequency:
- 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency of undesirable effects listed by individual organ systems:
Immune system disorders
- rare: hypersensitivity reactions to drug ingredients.

Gastrointestinal disorders
- very rare: gastric disorders, nausea and diarrhoea.

If severe undesirable effects occur, treatment should be discontinued.

4.9 Overdose

There are no reports of overdosage.
Excessive oral doses of saponin drugs or their extracts may cause gastrointestinal disorders manifested as nausea, vomiting and diarrhoea.

5. PHARMACOLOGICAL PROPERTIES

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations, Expectorants, excl. combinations with cough suppressants, ATC code: R05C.
The effect has not been established in clinical studies; it is based on pharmacological studies and many years of empirical experience (level of evidence for efficacy: IV).
Herbion cowslip syrup contains aqueous extracts of cowslip root (*Primula veris* L. and/or *Primula elatior* Hill) and garden thyme herb (*Thymus vulgaris* L.), and levomenthol. These active substances ease expectoration of thick bronchial mucus in respiratory inflammation, common cold and flu.
Due to its high saponin content, the drug Primulae radix is used as an expectorant. Saponins stimulate the gastric mucosa, which, via the vagus, induces a reflex increase in bronchial secretion and facilitates expectoration by thinning bronchial secretions. The surfactant activity of saponins, manifested as formation of a monomolecular film, makes it possible for them to spread from the throat to the surrounding respiratory tract mucosa and thus act locally on the thinning and secretion of thick bronchial mucus.
The drug Herba Thymi acts as an expectorant and bronchospasmolytic due to the content of essential oil, the major part of which is excreted through the lungs. On its way to the lungs, the drug promotes mucus secretion and facilitates expectoration, while also exerting a mild spasmolytic effect on the smooth muscles of the respiratory tract and thus relieving spasms. Thymol, the main component of the essential oil, also has an antiseptic effect.
Levomenthol has antiseptic and analgesic effects, and is often used in bronchitis and sinusitis.

5.2 Pharmacokinetic properties

Studies on absorption, distribution and metabolism of the active substances in the syrup have not been performed because it is not known which active substances and to what extent contribute to the effect.
No data are available on pharmacokinetics of cowslip root saponins. It has been established that only a negligible amount of saponins is absorbed.
Following oral intake of thyme extract, the main active substance of the essential oil, thymol, is rapidly absorbed. Peak plasma levels are achieved after 1.97 hours. In the body, thymol is metabolized Primarily sulphate, not free thymol, is present in the plasma. A part of thyme essential oil or thymol is excreted in the urine in the form of glucuronide and sulphate.
Levomenthol is readily soluble in fats and is therefore easily absorbed through the intestinal mucosa into the blood, from where it reaches the liver. In the liver, it first undergoes hydroxylation and then binds to glucuronic acid. It is excreted in the bile and through the kidneys. Within 24 hours, 35 to 50% of an oral dose of menthol is excreted in the urine.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
Preclinical data on toxicity of the syrup and individual drugs are not available; however, toxicity studies have been performed with some isolated active substances.
Oral toxicity of **saponins** is relatively low due to extremely poor absorption from the gastrointestinal tract. The LD_{50} of different saponins following oral administration to rats ranges from 50 to 960 mg/kg. The LD_{50} of cowslip saponins administered intraperitoneally to mice ranges from 10.5 to 56 mg/kg. Cowslip root has been used for a long time as an ingredient of preparations for the treatment of the common cold. However, no toxic effects have been observed so far during long-term treatment nor any harmful effects on reproduction, teratogenicity, mutagenicity and carcinogenicity.
The oral LD_{50} of **garden thyme** essential oil in rats is 4.7 g/kg, and that of thymol 980 mg/kg. In mice, the LD_{50} of thymol is about 600 mg/kg. In a 3-month study in mice, thyme ethanol extract in a dose of 100 mg/kg caused a significant increase in the liver and testis size, but had no spermatotoxic effect. *In*

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vitro, thymol potentiated secondary gonadotropin activity, which was manifested as increased uterus weight in immature rats. Safety of use of thyme preparations during pregnancy and lactation has not been confirmed, but the widely spread use of thyme indicates that its use is safe. On the basis of some *in vitro* tests with thymol and the long-term use of thyme, it can be concluded that thyme has no mutagenic and carcinogenic effects.
The oral LD_{50} of **menthol** in mice ranges between 2974 and 3577 mg/kg while in rats it is up to 3300 mg/kg. In mice which died during the 21-day long observation period, gastrointestinal lesions were registered. Menthol in oral doses of 200 to 800 mg/kg administered to rats for 28 days caused a significant increase in liver weight and vacuolization of hepatocytes. With daily doses below 200 mg/kg, no toxic effects were observed. Menthol administered to pregnant mice, rats, hamsters and rabbits had no harmful effects on reproduction nor did it have any teratogenic effects. Studies in rats and mice gave no convincing evidence of carcinogenicity of menthol after oral intake. In i*n vitro* and *in vivo* tests, menthol had no mutagenic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

levomenthol
sucrose
methyl parahydroxybenzoate (E218)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
The syrup should be used within 3 months after opening the bottle.

6.4 Special precautions for storage

Before opening the bottle:
This medicinal product does not require any special storage conditions.
After opening the bottle:
Do not store above 25°C.

6.5 Nature and contents of container

Bottle (glass type III, in accordance with the Ph. Eur.), plastic closure, measuring spoon: 150 ml of syrup, in a box.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT