Family Medicine & Primary Care Review 2023; 25(3): 339–348, https://doi.org/10.5114/fmpcr.2023.131271

ISSN 1734-3402, eISSN 2449-8580

REVIEWS

Herbal medicinal products in RESPIRATORY diseases – STANce of the Polish PHYTOtherapy Association – STANPHYTO RESPIRATORY II

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary The paper reviews herbal medicinal products used in infectious diseases of the respiratory tract. Due to the multidirectional effects of the biological action of the contained herbal active substances (anti-inflammatory, antioxidant, antimicrobial, antitussive, diuretic and others), they have the properties that alleviate the severity of symptoms, reduce their frequency and, consequently, shorten the duration of the disease, as well as reduce the risk of complications. Some of them have additional immunomodulatory properties, supporting natural immune mechanisms.

Key words: respiratory system infections, phytotherapy, plant preparations.

Doniec Z, Krauze-Baranowska M, Czerwionka-Szaflarska M, Kuchar E, Fecka I, Sybilski A, Woroń J, Mastalerz-Migas A. Herbal medicinal products in RESPIRATORY diseases – STANce of the Polish PHYTOtherapy Association – STANPHYTO RESPIRATORY II. *Fam Med Prim Care Rev* 2023; 25(3): 339–348, doi: https://doi.org/10.5114/fmpcr.2023.131271.

Herbal medicinal products indicated for respiratory tract infections

J.00 – Acute nasopharyngitis (common cold)

Plant raw materials and derived preparations, due to the wide spectrum of confirmed biological activities, are particularly useful in the treatment of common colds, and their use allows for shorter duration of the disease and reduces the development of bacterial infections as a complication of a viral infection. Herbal medicinal products that belong to this group are single-constituent/component products, as well as multi-constituent/component products. The anti-cold activity of plant raw materials is mainly associated with the presence of polyphenolic compounds – flavonoids (especially from the flavonol group), proanthocyanidins, anthocyanidins, phenolic acids responsible for inhibitory and inflammation-limiting effects (anti-inflammatory and antioxidant effects), tannins with antimicrobial activity and a number of compounds determining immunomodulatory and diuretic effects (including flavonoids). Moreover, salicylic compounds found in some plant raw materials (willow bark) are responsible for antipyretic effects.

Herbal substances used in the treatment of acute rhinosinusitis (common cold):

1. **Geranium root** (*Pelargonii radix*).
2. **Onion bulb** (*Allii cepae bulbus*).
3. **Herbal active substances in a multi-component medicinal product: plantain leaf** (fluid extract) (*Plantaginis lanceolatae folii extractum fluidum*), **purple coneflower** (thick extract) (*Echinaceae purpureae extractum spissum*).
4. **Herbal active substances in a multi-component medicinal product: purple coneflower herb** (juice) (*Echinaceae purpureae herbae recentis succus*), **chokeberry fruit** (juice) (*Aroniae fructus succus*), **burdock root** (juice) (*Bardanae radicis recentis succus*), **camomile flower** (fluid extract) (*Chamomillae extractum fluidum*), common nettle (juice) (*Urticae herbae recentis succus*).
5. **Herbal active substances in a multi-component medicinal product:** (powdered active substances or fluid extract from active substances): **horsetail herb** (*Equi-*

setum arvense L., *herba*), **milfoil herb** (*Achillea millefolium* L., *herba*), **valerian root** (*Althaea officinalis* L., *radix*), **walnut leaves** (*Juglans regia* L., *folium*), **dandelion herb** (*Taraxacum officinale* F. H. Wigg., *herba*), **camomile flower** (*Matricaria recutita* L., *flos*), **oak bark** (*Quercus robur* L., Q. *petraea* (Matt.). Liebl. and *Quercus pubescens* Willd., *cortex*).

6. **Herbal active substances in a multi-component medicinal product**: **eucalyptus essential oil** *(Eucalyptus globulus* Labill. *aetheroleum*), **sweet orange essential oil** (*Citrus sinensis* L. *aetheroleum*), **myrtle essential oil** (*Myrtus communis* L. *aetheroleum*), **lemon essential oil** (*Citrus limon* L. *aetheroleum*).
7. **Herbal active substances in a multi-component medicinal product:** (extract of plant substances), **wild indigo root** (*Baptisiae tinctoriae radix*), **purple coneflower root** (*Echinaceae purpurae radix*), **white-cedar herb** (*Thujae occidentalis herba*).

African geranium root (*Pelargonii radix*)

Active constituents: The root of African geranium (*Pelargonium sidoides* DC, *P. reniforme* (Andrews) Curtis) contains a complex of biologically active compounds – a group of C-glycosylflavones, characteristic for this plant raw material, often in ester form with gallic acid, oligomeric proanthocyanidins: epigallo-and gallocatechin derivatives, and sulfonated oxidised coumarins. Important evidence for the efficacy of EPs® 7630 in URI infections is shown by the results of foregoing studies on the mechanisms of immunomodulatory and antiviral as well as antimicrobial activity [1]. African geranium root preparations exhibit antimicrobial effects, including antiviral activities, by inhibiting virus entry into host cells and inhibiting virus replication (proanthocyanidins) [2, 3]. In addition, studies have shown immunomodulatory, spasmolytic and expectorant effects within respiratory tracts as a result of improved ciliary epithelium function and secretory effects [4]. **Clinical studies:** For *Pelargonium sidoides* root preparation (EPs® 7630), numerous clinical studies have demonstrated its efficacy and safety in the common cold, which was confirmed by meta-analyses and systematic reviews [5]. Based on previous clinical studies on the extract, it has been shown to be therapeutically effective in upper respiratory tract infections of viral origin (sinusitis, tonsillitis and pharyngitis), as well as in acute bronchitis (not requiring antibiotic therapy) [6–8]. Relevant to the importance of EPs® 7630 in the treatment of these infections is the fact that it has been seen to have beneficial effects in patients with asthma – children and adults whose symptoms exacerbate in viral infections [9]. Studies have shown that the use of *Pelargonium sidoides* root preparations, as well as other herbal medicines at the moment of first symptoms of respiratory infections, reduces the use of antibiotics and the period of inability to work [10]. Despite the controlled clinical trials conducted to date, the positive results of meta-analyses and systematic reviews, geranium root preparations [liquid extract obtained with 11% (m/m) ethanol (DER 1: 8–10) and dry extract obtained with 11% (m/m) ethanol (DER 4–25: 1)] are still considered traditional herbal medicinal products [1]. **Indications for use:** Traditional medicinal products made of African geranium root are indicated for the symptomatic treatment of the common cold, from 6 yearsof age. **Detailed information** on selected medicinal products,such as: Pelafen Med, syrup (Phytopharm Klęka S.A.), Pelafen Med, tablets (PhytopharmKlęka S.A.), Pelavo Med, oral solution (US Pharmacia Sp. z o.o.), is available in the Summary of Product Characteristics.

Onion bulb (*Allii cepae bulbus*)

The fluid extract of *Allium cepa,* onion (an oil extract according to the EMA), contains a number of sulfur (S)-containing as well as sulfur-free organic compounds. The main constituents of onion preparations are thiosulfinates, thiosulfonates, cepaenes, S-oxides, S, S'-dioxides, monosulfides, disulfides, trisulfides and zwiebanes only as degradation products of naturally occurring cysteine sulfoxides (e.g. (+)-S-propyl-L-cysteine sulfoxide) under the influence of the enzyme alliinase. An onion, depending on its variety, also contains the compounds that belong to flavonols (yellow variety), anthocyanins (red variety) and dihydroflavonols. The flavonol group is dominated by quercetin derivatives (spireoside, quercetin 3',4'-O-diglucoside), as well as kaempferol and isorhamnetin derivatives. In addition to sulfur compounds, selenium derivatives, such as *γ*-glutamyl-Se-methylselenocysteine, Se-methylselenocysteine, 'Se-alliin', Se-methionine, among others, have been detected. Specific fructans have also been demonstrated [11]. *In vitro* studies have revealed the inhibitory effect of organic sulfur compounds on the growth of certain bacteria and fungi, e.g. *Staphylococcus aureus, Helicobacter pylori* and of *Streptococcus*, *Candida albicans* and the *Fusarium oxysporum* genus [11]. A number of *in vitro* and *in vivo* studies and preclinical studies have evaluated the biological effects of onion preparations and compounds isolated from onions, demonstrating the anti-asthmatic effects of thiosulfinates [12, 13]. A number of onion components exert a significant effect on leukotriene metabolism, in particular cyclooxygenase and lipoxygenase-dependent reactions. Therefore, it is believed that onions may affect the respiratory system by modelling leukotriene-dependent reactions [11, 14]. The properties of onion bulb constituents, such as anti-allergic, anti-inflammatory, antimicrobial, antiviral, antifungal, antiglycaemic and antilipemic activities, have been confirmed in preclinical studies [11]. Active substances of an onion bulb show, among others, antioxidant, anti-inflammatory, anti-allergic, cholesterol-lowering, anti-lipemic andserum glucose-lowering effects, and they also affect coagulation [15]. **Clinical studies:** There have been no controlled clinical studies that could support the well-established use of medicinal products made from onions, *Allium cepa*, in respiratory tract diseases. The available data issufficient to support its traditional use. **Indications for use:** Traditional herbal medicinal product indicated for mild upper respiratory tract infections (common cold), from 6 years of age. **Detailed information** on the selected medicinal product: Syrop z cebuli (PPF Hasco-Lek S.A.) is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: plantain leaf (*Plantaginis lanceolatae folii extractum fluidum*), **purple coneflower** (*Echinaceae purpureae extractum spissum*).

Active constituents: fluid extract of plantain leaf (*Plantaginis lanceolatae folii extractum fluidum*), thick extract of purple coneflower (*Echinaceae purpureae extractum spissum*) – information on the active components is provided in the description of individual herbal substances. **Clinical studies:** There have been no controlled clinical studies to date to support the well-established use of the medicinal product. The available data issufficient to support its traditional use. **Indications for use:** Herbal medicinal product traditionally used as subsidiary therapy in common cold and inflammation of the nasal cavity and throat mucosa, from 6 years of age. **Detailed information** on the selected medicinal product: Syrop z babki lancetowatej i jeżówki (PPF Hasco-Lek S.A.) is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: purple coneflower herb (juice) (*Echinaceae purpureae herbae recentis succus*), **chokeberry fruit** (juice) (*Aroniae fructus succus*), **burdock root** (juice) (*Bardanae radicis recentis succus*), **camomile flower** (fluid extract) (*Chamomillae extractum fluidum*), **common nettle** (juice) (*Urticae herbae recentis succus*).

Active constituents: Multidirectional biological action of the active constituents of six herbal substances, which are natural antioxidants of the polyphenol group (flavonoids, anthocyanins, proanthocyanidins) and simple phenols (phenolic acids, mainly

caffeic acid derivatives). Polyphenols (nettle herb, chokeberry fruit juice, camomile flower) exhibit antioxidant and anti-inflammatory properties through inhibitory effects on the arachidonic acid cascade and cyclooxygenase and lipoxygenase [16–18]. The medicinal product shows anti-inflammatory (chokeberry fruit juice, camomile flower, burdock root), antioxidant (chokeberry fruit juice, nettle herb), diuretic (nettle herb, burdock root) and immunomodulatory (purple coneflower herb juice) effects. **Clinical studies:** There have been no controlled clinical studies to date to support its well-established use. The available data issufficient to support its traditional use. **Indications for use**: Traditional herbal medicinal product for the treatment of the common cold and as a preventive agent in case of susceptibility to frequent colds, adults and children 12 years of age or more. **Detailed information** on the selected medicinal product: Immunofort (PF Leki Natury Tadeusz Polański Sp. z o.o.) is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: (powdered active substances or fluid extract of active substances): **horsetail herb** (*Equisetum arvense* L., *herba*), **milfoil herb** (*Achillea millefolium* L., *herba*), **valerian root** (*Althaea officinalis* L., *radix*), **walnut leaves** (*Juglans regia* L., *folium*), **dandelion herb** (*Taraxacum officinale* F. H. Wigg., *herba*), **camomile flower** (*Matricaria recutita* L., *flos*), **oak bark** (*Quercus robur* L., *Q. petraea* (Matt.) Liebl. and *Quercus pubescens* Willd., *cortex*).

Active constituents: Action and properties have been determined in preclinical studies. The components of the combination medicine exhibit immunomodulatory, anti-inflammatory, antiviral and antimicrobial properties. *In vitro* studies indicate inhibition of RSV replication and modulation of immune functions [19]. Medical findings also demonstrate an increased expression of the antiviral defensins HBD-1 and LL-37 [20]. An *in vitro* study on A549 lung epithelial cells notes a possible suppression of airway inflammation by inhibiting IL-8 and HBD-e production in epithelial cells [21]. In addition, the medicine increased phagocytosis capacity by 180%, which may enhance microbial elimination [19, 22]. Moreover, the immunomodulatory effects of the medicine have been shown, and these refer to stimulation of NK cell activity by 150%, increased cytolytic activity and interferon production, as demonstrated in an *in vitro* study of human tonsil cells [19]. **Clinical studies:** Clinical studies have confirmed the therapeutic efficacy of the medicine in relieving the course of infection, as well as shortening its duration [23–25]. The controlled clinical trials conducted to date are not sufficient to support the well-established use of the medicinal product. The available data issufficient to support its traditional use. **Indications for use:** The medicine is generally used at the moment of first signs of infection and during the duration of a common cold, from the age of 2 (oral drops) and from the age of 6(film-coated tablets). **Detailed information** on medicinal products, such as: Imupret N (oral drops) (Bionorica SE) and Imupret (film-coated tablets) (Bionorica SE), is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: **Eucalyptus essential oil** (*Eucalyptus globulus* Labill. *aetheroleum*), **sweet orange essential oil** (*Citrus sinensis* L. *aetheroleum*), **myrtle essential oil** (*Myrtus communis* L. *aetheroleum*), **lemon essential oil** (*Citrus limon* L. *aetheroleum*).

Active constituents: the active constituents of this medicinal product are essential oils and the monoterpenes that they contain (such as 1,8-cyneol, limonene, *α*-pinene, *β*-myrcene, and others), which exhibit secretolytic and secretomotor activity and have anti-inflammatory (as revealed in various experimental models) and antioxidant properties [26, 27]. Apart from secretolytic activity, further animal experiments and *in vitro* studies have demonstrated the antimicrobial activity of high doses [28]. Sweet orange essential oil has also demonstrated anxiolytic activity, and lemon essential oil has shown antidepressant effects. In preclinical trials, a decrease in central nervous system activity was observed following administration of very high doses, induced by inhibitory effects on CNS structures, and increased blood flow through kidneys caused an increase in glomerular filtration rate and a diuretic effect. Lower gastric juice production and gastrointestinal peristalsis have been also confirmed [29]. **Clinical studies:** Controlled clinical trials have been conducted in cases such as acute and chronic sinusitis, acute and chronic bronchitis and a chronic obstructive pulmonary disease [30, 31]. **Indications for use:** Relief of symptoms of acute upper respiratory tract inflammation. **Additional indications:** EPOS 2020 European document on the stance regarding sinusitis and nasal polyps: 1) acute viral sinusitis (common cold): category of evidence Ib:some herbal medicines, such as BNO1016 (Sinupret formulation) (may reduce symptoms of a runny nose, nasal discharge, headache, facial pain), cineole (may reduce a symptom index), have a beneficial effects on cold symptoms without causing side effects; 2) acute post-viral (bacterial) sinusitis: category of evidence Ib: certain herbal medicines, such as BNO1016 (Sinupret formulation) (significant effect on nasal obstruction and mucosal swelling), African geranium (drops) (*Pelargonium sidoides*) (moderate reduction in sinusitis severity), myrtol and other essential oils (significant improvement in a sinusitis symptom index), have a beneficial effects on common cold symptoms, without causing adverse effects [32]. **Detailed information** on the medicinal product: Respero Myrtol (G. Pohl-Boskamp GmbH & Co. KG) is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: (extract from herbal substances) **wild indigo root** (*Baptisiae tinctoriae radix)*, **purple coneflower root** (*Echinaceae purpureae radix)*, **white-cedar herb** (*Thujae occidentalis herba*).

Active constituents: The biologically active compounds are phenolic acids, polysaccharides of immunomodulatory properties and glycoproteins. Indigo root contains polysaccharides and glycoproteins, as well as flavonoids (isoflavones of estrogenic properties), tannins, coumarins and alkaloids. Various preclinical models show that this herbal medicine significantly and, dose-dependently manner, stimulates the immune system, which may be manifested *in vitro* and *in vivo* by increased production of various transmitters and cytokines, as well as increased antibody production [33]. **Clinical studies:** In clinical trials in humans, this product relieved symptoms and shortened the duration of illness of upper respiratory tract. There have been no controlled clinical trials to date to support its well-established use. The available data is sufficient to support its traditional use [34]. **Indications for use:** Herbal medicinal product used in the treatment of a common cold as subsidiary drug to shorten the duration of infection and alleviate its course, from the age of 4. **Additional information**: Experts recommend using the medicine for 4–8 days, at the beginning of the infection. **Detailed information** on the medicinal product: Esberitox N (Schaper & Brummer GmbH & Co) can be found in the Summary of Product Characteristics.

Herbal substances used in the treatment of acute inflammation of the nose and throat (cold) and with indications in subfebrile conditions:

1. **Linden flower** (*Tiliae inflorescentia*).
2. **Herbal substances in combination medicines: coltsfoot leaf** (*Tussilago farfara* L., *folium*), **elder flower** (*Sambucus nigra* L., *flos*), **linden flower** (*Tilia cordata* Miller, *Tilia platyphyllos* Scop, *Tilia vulgaris* Heyne, *flos*), **willow bark** (*Salix purpurea* L., *Salix daphnoides* Vill., *Salix fragilis* L., *cortex*).
3. **Herbal substances in combination medicine: lime flower** (*Tilia* spp.), **elder flower** (*Sambucus nigra* L.), **willow bark** (*Salix* spp.), **mullein flower** (*Verbascum* spp.).

Lime flower (***Tiliae inflorescentia***)

Active constituents: The dry extract of linden flower contains flavonoids (kaempferol derivatives), including tiliroside – a glycosidic flavonoid ester, quercetin and myricetin derivatives, 0.02% to 0.1% of essential oils, including farnesol, terpineol, limonene, nerol and eugenol. Also present are mucilage (approx. 3%), phenolic acids (caffeic acid, p-coumaric acid, chlorogenic acid), proanthocyanidins, triterpenes, amino acids and mineral compounds. They have the anti-inflammatory, antioxidant, diaphoretic, diuretic, throat mucous coating (antitussive), antispasmodic and soothing effects [35]. For kaempferol, as the main component of the flavonoid complex in linden flower, anti-inflammatory effects have been confirmed in many *in vitro* and *in vivo* studies, among the others, by suppressing NF*κ*-B, a transcription factor, inhibiting the expression of adhesion proteins (ICAM-1, VCAM-1, selectins, integrins), modulating the gene expression of proteins active during inflammation (e.g. MAPK, PKC C, PI3K or NF*κ*-Bi AP-1), eliminating free radicals, blocking their formation [36]. **Clinical studies:** One study has demonstrated a perspiratory effect. An antipyretic effect, not related to the diaphoretic action, has not been confirmed in clinical studies. There have been no controlled clinical studies that could support the well-established use of medicinal products made from linden flower. The available data is sufficient to support its traditional use [35]. **Indications for use:** Lime flower herbal medicinal products are traditional medicines used as a mild diaphoretic agent in moderate febrile conditions. According to the EMA, lime flower preparations are exclusively used to treat symptoms of the common cold and to relieve mild symptoms of mental stress. It is not recommended in monotherapy as an antipyretic medicine but only in sub-febrile states as a primary treatment or ancillary treatment. It is not recommended for use in children under 3 years of age (according to the EMA, under 4 years of age). **Detailed information** on selected medicinal products, such as: Lipomal (Aflofarm Farmacja Polska Sp. z o.o.) is available in the Summary of Product Characteristics.

Substances in combination medicines: coltsfoot leaf (*Tussilago farfara* L., *folium*), **elder flower** (*Sambucus nigra* L., *flos*), **lime flower** (*Tilia cordata* Miller, *Tilia platyphyllos* Scop, *Tilia vulgaris* Heyne, *flos*), **willow bark** (*Salix purpurea* L. (*Salix daphnoides* Vill., *Salix fragilis* L.), *cortex*).

Active constituents: The biological activity of willow bark *Salicis cortex* (*Salix purpurea* L., *Salix daphnoides* Vill, *Salix fragilis* L.), lime flower *Tiliae flos* (*Tilia cordata* Miller, *Tilia platyphyllos* Scop, *Tilia vulgaris* Heyne, *flos*) have been described for single herbal substances. Furthermore, for the flavonoid compounds present in the linden flower, mainly kaempferol derivatives (tiliroside), a protective effect for liver cells has been demonstrated *in vitro* [36]. Coltsfoot leaf *Farfarae folium* (*Tussilago farfara* L.) contains mucilage (6–10%), phenolic acids – derivatives of caffeic acid, flavonoids – mainly quercetin and kaempferol derivatives (about 1%), tannins (about 5%), phytosterols and essential oils containing, among others, bisabolene epoxide (anti-inflammatory effects in an *in vitro* model) [37]. Mucilage substances relieve irritation of the pharyngeal mucosa and inhibit dry cough. Due to its rich complex of phenolic compounds, extracts from coltsfoot leaf have antioxidant and related anti-inflammatory actions [38]. Elder flower *Sambuci flos* contains flavonoids, kaempferol and quercetin derivatives, including rutoside (approx. 3%), caffeic acid derivatives, including chlorogenic acid (3%), triterpenes *α*- and *ß*-amyrin (oleanolic and ursolic acids), essential oils, phytosterols, mucilage, tannins and mineral compounds, especially K salts [39]. Elder flower exhibits a diaphoretic and diuretic effect (K salts and flavonoids), in addition to anti-inflammatory and antioxidant activity related to the presence of polyphenols. The anti-inflammatory effect is associated, among others, with the inhibition of interleukin-1*α*, interleukin-1*ß* and TNF-*α* (moderate effect). In addition, immunomodulatory effects were found for the polysaccharide fraction. Literature data also indicates an antiviral effect, though weaker than that of the fruit [40]. Medicines composed of the above-discussed herbal substances (preparations) exhibit anti-inflammatory, antioxidant, diaphoretic, diuretic, throat mucosa coating (cough suppressant) and antipyretic effects as a result of the activity of the individual herbal active substances and their synergistic interactions. Medicines composed of the above-discussed herbal substances exhibits anti-inflammatory, antioxidant, diaphoretic, diuretic, throat mucosa coating (cough suppressant) effects as a result of the activity of the individual herbal active substances and their synergistic interactions [41]. **Clinical studies:** For a drug composed of test herbal substances, observational studies were conducted on small groups to assess the clinical efficacy in children in the treatment of common conditions, and the duration of subfebrile conditions, cough and runny nose was monitored. There was a reduction in the duration of subfebrile conditions and cough after comparison to the control group. In addition, the need to include antibiotics was lower in the study group compared to the control group. However, the studies performed are not sufficient to confirm the well-established use of the combined medicinal product [42]. The available data are sufficient to support traditional use. **Indications for use:** Herbal medicinal product of the class of traditional products used as an subsidiary agent in subfebrile states in the course of inflammatory conditions, mainly of the upper airways, in children 3 years of age or more. **Detailed information** on the medicinal product Pyrosal (Wrocławskie Zakłady Zielarskie Herbapol S.A.) is available in the Summary of Product Characteristics.

Herbal substances in complex medicines: lime flower (*Tilia* spp.), **elder flower** (*Sambucus nigra* L.), **willow bark** (*Salix* spp.), **mullein flower** (*Verbascum* spp.).

Active constituents: The biological activity of the constituents of the extracts of lime flower (*Tilia* spp.), elder flower (*Sambucus nigra* L.), willow bark (*Salix* spp.) and mullein flower (*Verbascum* spp.) is provided in the characteristics of individual herbal substances. **Clinical studies:** There have been no controlled clinical studies to date to support the well-established use of combined medicinal products. The available data is sufficient to support its traditional use [34, 41]. **Indications for use:** The syrup of linden, elder flower, willow and mullein is traditionally used as a mild diaphoretic agent in non-high fevers occurring in the course of a common cold. **Additional indications:** As an subsidiary therapy in the course of upper respiratory tract inflammations accompanied by cough, fever or sore throat. **Detailed information** on selected medicinal products, such as: Syrop z lipy, bzu czarnego, wierzby i dziewanny (PPF Hasco-Lek S.A., combination medicine, adults and children 6 of age or more) is available in the Summary of Product Characteristics.

Herbal substances used in the treatment of acute rhinosinusitis (common cold) and in prophylaxis of respiratory tract infections:

1. **Herb and root of purple coneflower** (*Echinaceaeherba, Echinaceae radix*).
2. **Candelabra aloe leaf** (*Aloe arborescens folium*).
3. **Garlic bulb** (*Alli sativi bulbus*).
4. **Herbal active substances in a multi-component medicinal product**: **complex extract of plantain leaf** (*Plantaginis lanceolatae folium*), **grindelia herb** (*Grindeliae herba*) **and rosehip** (*Rosae fructus*), **fluid extract of thyme herb** (*Thymi herbae extractum*), **juice of purple coneflower herb** (*Echinaceae purpureae herba erecentis succus*).

Herb and root of purple coneflower (*Echinaceaeherba, Echinaceae radix*)

Active constituents: The herb contains alkamides, including dodecatetraenoic acid isobutylamide, caffeic acid derivatives [chlorogenic acid, 1.5-dicaffeoylquinic acid, 2-*O*-dicaffeoylquinic

acid (caftaric acid), 2,3-*O*-dicaffeoylquinic acid (chicoric acid)] and polysaccharides. The pressed juice (from the aboveground parts) contains heteropolysaccharides and glycoproteins. The root contains the afore-mentioned caffeic acid derivatives and alkamides. *In vitro* studies confirm the modulation effects of the non-specific immune response of coneflower preparations [43]. In *in vitro* conditions, the ethanol extract of the coneflower herb inhibited the secretion of IL-6 and IL-8 cytokines from epithelial cells (lung and bronchial epithelium) infected with rhinoviruses, showed virucidal activity against viruses of influenza, HSV and RSV, while the aqueous extract of the fresh herb stimulated the secretion of IL-2, triggering the proliferation of lymphocytes and the production of INF-*γ*. The specific immune response involves the activation of the alternative complement pathway by a coneflower (associated with the neutralisation of pathogens) and anincrease in the level and activity of T lymphocytes and natural killer cells [44]. Alkamides interact with the CB2 cannabinoid receptor, which confirms the modulation of the immune system by coneflower andstimulate IL-10, an anti-inflammatory cytokine that inhibits the release of pro-inflammatory cytokines, such as IL-2 and INF-*γ* that inhibit the release of pro-inflammatory TNF-α *in vitro*. Coneflower hinders the activity of COX-1, COX-2 and LOX-5, exhibiting anti-inflammatory effects [45]. Administration of coneflower preparation in a clinical study on sixvolunteers was shown to decrease the levels of pro-inflammatory cytokines IL-8, IL-6 and TNF-*α*. Coneflower deactivates reactive oxygen species formed in the process of a developing inflammation, deactivates hyaluronidase, which causes the degradation of hyaluronic acid – a component of blood walls, limiting the spread of inflammation [46]. Studies confirm that coneflower preparations have immunomodulatory, anti-inflammatory and antiviral effects, which is likely to be the result of synergistic interactions. **Clinical studies:** The efficacy and safety of coneflower have been evaluated in numerous clinical trials, as well as systematic reviews and meta-analyses [46–48]. The available data issufficient to support its traditional use. **Indications for use:** Herbal medicinal products are intended for traditional subsidiary use in common cold and in short-term prophylaxisin order to reduce susceptibility to common colds, from 12 years of age. **Detailed information** on medicinal products, such as: Alchinal (PPF GEMI Grzegorz Nowakowski), Echinerba (Laboratorium Farmaceutyczne Labofarm Sp. z o.o., Sp.K.), Echinacea-Ratiopharm MAX (Ratiopharm GmbH, Teva Pharmaceuticals Polska Sp. z o.o), Echinapur (Poznańskie Zakłady Zielarskie Herbapol S.A.), Immunofort (PF Leki Natury Tadeusz Polański Sp. z o.o), Succus echinaceae (Phytopharm Klęka S.A.), is available in the Summary of Product Characteristics.

Candelabra aloe leaf (*Aloe arborescens folium*)

Active constituents: Candelabra aloe leaves contain polypeptides of lectin-like properties that have the ability to hemagglutinate, activate cell mitosis and inhibit fungal growth. Polysaccharides buffer the activities of acids and bases, exhibit detoxifying and laxative properties, activate the C3 component of human serum that stimulates B lymphocytes to produce antibodies, induce serum opsonins that improve the absorption of bacteria by leukocytes and stimulate the course of lymphocyte mitosis [49]. Aloctin-A and aloctin-B in *in vitro* studies have revealed immunochemical, haemagglutination and mitosis-stimulating properties and an increase in the absolute number of lymphocytes. *In vivo* and *in vitro* studies have confirmed the role of aloctin-A as an immunomodulator. Aloe vera is a rich source of plant enzymes (biostimulants); the most important arethe isoenzyme superoxide dismutase, which neutralises superoxide anion radical, and carboxypeptidases. Carboxypeptidase, a bradykinase, inhibits cell membrane permeability and hydrolyses bradykinin, which is a mediator of inflammation and allergic reaction [50]. Aloe pulp also contains large quantities of water-soluble vitamins (C, B_1, B_2, B_3, B_6, B_{12}, folic acid, biotin) and fat-soluble vitamins (E, *β*-carotene), minerals, including macronutrients (sodium, potassium, calcium, magnesium, phosphorus) and microelements (zinc, iron, manganese, copper, cobalt). Macro-elements are also present in bound form, i.e. magnesium lactate, which has the ability to inhibit the activity of histidine decarboxylase, the enzyme responsible for the formation of histamine, and calcium lactate, with its known antimicrobial properties [50]. Anthraquinones are characterised by strong antibacterial, fungicidal and antiviral properties [51]. Based on pharmacological studies, it has been concluded that the aqueous extract of fresh candelabra aloe leaves increases the number of T and B lymphocytes and circulating antibodies in the blood and stimulates the phagocytic activity of the immune system, as well as the humoral and cellular responses of the immune system [52, 53]. **Clinical studies:** a controlled study showed that children treated with Bioaron C containing candelabra aloe extract had a significantly lower incidence of recurrent bronchitis (17.4%); in the comparison group, recurrences were 2.6 times more frequent. The obtained results demonstrate a significant beneficial effect of BC on inflammatory parameters during the treatment of acute infection and a long-term effect of this preparation by reducing patients' susceptibility to develop infections (increase in immunity) [54]. An observational study of 6,764 children from 3–18 years of age from all over Poland diagnosed with upper respiratory tract infections showed that a preparation with aloe vera extract used in children in treatment of viral and bacterial upper respiratory tract infections produces positive therapeutic effects, leading to resolution of infection symptoms, as well as improved appetite in the case of its absence [56]. The available data from clinical trials (including randomised trials with a control group) are sufficient to support its traditional use. **Indications for use:** Indications for traditional use are upper respiratory tract infections of various aetiologies, subsidiary in the prevention of recurrent upper respiratory tract infections. **Detailed information** on medicinal products, such as: Biostymina (Phytopharm Klęka S.A., 5 years of age or more), Bioaron C (Phytopharm Klęka S.A., 3 years of age or more) and Bioaron system (Phytopharm Klęka S.A., 3 years of age or more), is available in the Summary of Product Characteristics.

Garlic bulb (*Alli sativi bulbus*)

Active constituents: Garlic bulb contains a number of organic sulphur derivatives [mostly alliin (S-allyl cysteine sulfoxide) and other cysteine sulfoxides as being predominant, as well as flavonoids (quercetin, myricetin, apigenin derivatives, including rutin) andcoumarins, present in very low concentrations. Moreover, there are saponins with antifungal (in *in vitro* tests) and cholesterol-lowering effects (in animal studies), selenium-containing compounds and fructosamines. The evidence from several studies suggests that the biological and therapeutic effects of garlic are related to the activity of various organic sulfur compounds as numerous degradation products, which are initially formed from alliin (converted to allicin by enzyme alliinase as a product of this reaction), which further undergoes the process of degradation (e.g. dialkylsulfinates). However, inhibition of the enzyme activity (by an appropriate technological process) leaves a high concentration of cysteine sulfoxides in the plant raw material. The composition and chemical nature of sulphur derivatives in garlic products (sulfoxides, sulfiniates, sulfides, ajoenes) depends on the processing method applied (crushed plant raw material, oil or ethanol extract, etc.) [56]. **Clinical studies:** Traditionally, this plant raw material is used in upper respiratory tract infections; however, there is no clinical evidence of its efficacy. Most studies are concerned with cholesterol- and triglyceride-lowering effects [56]. The available data issufficient to support its traditional use. **Indications for use:** The herbal medicinal products are intended for traditional use in the prevention and support of mild upper respiratory tract infections (common colds), 12 years of age or more. **Detailed information** on selected medicinal products, such as: Alliomint (Laboratorium Farmaceutyczne Labofarm Sp. z o.o., Sp. K.),

Alliofil (Poznańskie Zakłady Zielarskie Herbapol S.A.), is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: complex extract of plantain leaf (*Plantaginis lanceolatae folium*), **grindelia herb** (*Grindeliae herba*) **and rosehip** (*Rosae fructus*), **liquid extract of thyme herb** (*Thymi herbae extractum*), **purple coneflower herb juice** (*Echinaceae purpureae herbae succus*).

Active constituents: The compounds contained in the plantain leaf include phenylpropanoids, iridoids and flavonoid compounds and mucilage; in the grindelia herb – grindelic acids, polyphenolic compounds, triterpene saponins andessential oil; in the thyme herb – flavonoids, essential oil containing thymol, rosmarinic acid from the *Labiatae* group of tannins; in coneflower herb – alkamides, polysaccharides and caffeic acid derivatives; in rosehip – anti-inflammatory galactolipid (GOPO); galactopyranosylglycerol, vitamin C, phenols, lycopene, lutein, zeaxanthin and other carotenoids [34, 57]. The product exhibits anti-inflammatory, antioxidant (thyme herb, rosehip), immunomodulatory (coneflower herb) and expectorant effects due to the presence of the thyme herb preparation (secretolytic effect, antimicrobial effect) andgrindelia herb (secretolytic, spasmolytic, antimicrobial effect) and a protective effect for the upper respiratory tract mucosa (plantain leaf). Furthermore, the presence of vitamin C in the rosehip, an important agent in a common cold therapy, has a beneficial effect on the immune system [34]. **Clinical studies:** There have been no controlled clinical trials to date to confirm the well-established use of a multi-component medicinal product. The available data issufficient to support its traditional use. **Indications for use:** Traditionally used as a prophylactic agent during the periods of lower immunity, as an auxiliary agent in mild inflammations of the upper respiratory tract with cough symptoms (e.g. during cold), 7 years of age or more. **Detailed information** on the medicinal product: Echinasal (Wrocławskie Zakłady Zielarskie Herbapol S.A.) is available in the Summary of Product Characteristics.

J01 – Acute sinusitis

Acute sinusitis (AS) is a common respiratory disease, with 6–15% of the population affected annually. The disease is most often of viral aetiology and self-limiting, but it can lead to life-threatening complications. AS is one of the most common reasons for taking antibiotics, and limiting the use of these medicines is extremely important due to their overuse and thegrowing problem of antibiotic resistance [58]. The disease is defined by the presence of two or more of the following symptoms, one of which should be either nasal obstruction or nasal cavity discharge (anterior or posterior rhinorrhoea): 1) nasal obstruction, 2) nasal cavity discharge (anterior or posterior rhinorrhoea), 3) facial pain/pressure, 4) impairment/loss of smell [32].

Herbal substances used in the treatment of acute sinusitis:

1. **Eucalyptus leaf** (*Eucalypti folium*), **Eucalyptus essential oil** (*Eucalypti aetheroleum*), **cineole** (*Cineolum*).
2. **Herbal active substances in a complex medicinal product: primrose flower with calyx** (*Primulaveris* L. and (or) *Primula elatior* L. Hill.), **gentian root** (*Gentiana lutea* L.), **sorrel herb** (from various species of the genus *Rumex*, including *R. acetosa* L., *R. acetosella* L., *R. obtusifolius* L., *R. patientia* L., *R. crispus* L., *R. thyrsiflorus Fingerh*.), **elder flower** (*Sambucus nigra* L.), **verbena herb** (*Verbena officinalis* L.).

Eucalyptus (*Eucalypti folium*), eucalyptus essential oil (*Eucalypti aetheroleum*), cineole (*Cineolum*)

Active constituents: The leaf contains an essential oil (1–3.5%), flavonoids, including rutin, and tannins, procyanidins and triterpenes (ursolic acid derivatives). The active component in the eucalyptus essential oil, obtained from eucalyptus leaves, is a bicyclic monoterpene ether – 1,8-cineole (*Cineolum*) (also referred to as eucalyptol), as the main constituent of this oil (54–95% content in the oil). Apart from this, *α*-terpineol (up to 28%), cymene, *α*-pinene, *β*-pinene and others are also present in the oil [59]. Eucalyptus essential oil and cineole, when administered orally or by inhalation, exhibit secretolytic and expectorant effects by increasing mucus secretion in the respiratory tract, influencing the function of the tonsillar epithelium and increasing ciliary movement, which improves airway mucosal clearance (cineole acts similarly to surfactant) and has a beneficial effect in the treatment of a productive cough. Clinical studies have confirmed the improved mucociliary transport for therapeutic doses. A mild diastolic effect was also noted. In *in vitro* tests, eucalyptus oil and cineole additionally exerted moderate anti-inflammatory and antimicrobial effects (against Gram (+) and Gram (-) bacteria, *Candida albicans*, *Fusarium* sp. – the oil proved to be more active than cineole) [60, 61]. Inhalations (breathing in) of eucalyptus oil are believed to stimulate the thermoreceptors of the nasal mucosa, resulting in a sensation of cold and increased airflow. Eucalyptus leaf extract, and the eucalyptus essential oil due to the presence of cineole, are used in acute and chronic URIs, both orally (often as an ingredient in combination products) and by inhalation, respectively [62]. **Clinical studies:** Clinical studies have shown a reduction in the severity of acute sinusitis symptoms, such as headache, trigeminal sensitivity to pressure, nasal congestion and excessive accumulation of secretion, as well as general malaise in acute sinusitis and acute bronchitis [61, 63]. The controlled clinical trials conducted to date have confirmed the well-established use of cineole in respiratory diseases. **Indications for use:** The medicinal product Soledum forte is used as an expectorant in a productive cough and ancillary treatment in acute non-purulent sinusitis, 12 years of age or more. Bronchosol MAXIPUREN has an auxiliary effect in common colds and inflammatory conditions of the upper respiratory tract accompanied by cough, runny nose and difficulty in expectorating sticky mucus, as a supportive agent in non-purulent inflammatory conditions of the paranasal sinuses, 12 years of age or more. **Additional indications:** EPOS 2020 European document on the stance regarding sinusitis and nasal polyps: 1) acute viral sinusitis (common cold): category of evidence Ib: some herbal medicines, such as BNO1016 (Sinupret formulation) (may reduce symptoms of a runny nose, nasal discharge, headache, facial pain), cineole (may reduce a symptom index), have beneficial effects on cold symptoms without causing side effects [32]. **Detailed information** on medicinal products, such as: Soledum and Soledum forte (MCM Klosterfrau Healtcare), Bronchosol MAXIPUREN (Phytopharm Klęka S.A.), is available in the Summary of Product Characteristics.

Herbal active substances in a multi-component medicinal product: primrose flower with calyx (*Primula veris* L. and (or) *Primula elatior* (L.) Hill. *flos*), **gentian root** (*Gentiana lutea* L. *radix*), **sorrel herb** (of various *Rumex* species, including *R. acetosa* L., *R. acetosella* L., *R. obtusifolius* L., *R. patientia* L., *R. crispus* L., *R. thyrsi florus* Fingerh. *herba*), **elder flower** (*Sambucus nigra* L. *flos*), **verbena herb** (*Verbena officinalis* L.).

Active constituents: The action and properties have been established for the complex extract in *in vivo*, *in vitro* and clinical tests. Its secretolytic, secretomotor, anti-inflammatory, virostatic and antimicrobial effects have been confirmed in pharmacological studies. In *in vitro* studies, the bioflavonoids contained in the medicine have been shown to increase chloride anion secretion and hydration of the ASL epithelium in a dose-dependent manner [64]. Other experimental models have demonstrated anti-inflammatory effects of the medicine [65, 66]. Virostatic properties have been confirmed in *in vitro* tests on cultures of human epithelial cells infected with influenza A virus and RSV when comparing with amantadine and ribavirin [67]. In an *in vivo* model of bacterial infection, a randomised trial showed

reduced bacterial growth, formation of polyps and a decrease in the number of inflammatory cells in the medicine-treated group [68]. **Clinical studies:** Clinical studies demonstrated the beneficial effects of treatment in infections of viral aetiology and combination therapy with an antibiotic in acute bacterial rhinosinusitis [69, 70]. Radiographic studies showed resolution of lesions in 50 patients (64%) and of symptoms in 60.3% of patients in the medicine-treated group [71]. Moreover, a reduction in nasal mucosal swelling and improvement in nasal patency were observed. A multi-centre study on a large group of 3,109 children with acute rhinosinusitis showed an alleviation of sinusitis symptoms, such as nasal congestion, headache, cough and hoarseness, in all age groups [69]. The controlled clinical trials conducted to date are not sufficient to confirm the well-established use of the medicinal products: Sinupret solution and Sinupret film-coated tablets. Controlled clinical trials have confirmed the well-established use of Sinupret extract. **Indications for use:** Herbal medicinal product for ancillary use in acute and chronic sinusitis, 6 years of age or more. **Additional indications:** EPOS 2020 European document on the stance regarding sinusitis and nasal polyps: 1) acute viral sinusitis (common cold): category of evidence Ib: some herbal medicines, such as BNO1016 (Sinupret formulation) (may reduce symptoms of a runny nose, nasal discharge, headache, facial pain), cineole (may reduce a symptom index), have beneficial effects on cold symptoms without causing side effects; 2) acute post-viral (bacterial) sinusitis: category of evidence Ib: certain herbal medicines, such as BNO1016 (Sinupret formulation) (significant effect on nasal obstruction and mucosal swelling), African geranium (drops) (*Pelargonium sidoides*) (moderate reduction in sinusitis severity), myrtol and other essential oils (significant improvement in a sinusitis symptom index), have a beneficial effects on common cold symptoms, without causing adverse effects [32]. **Detailed information** on medicinal products, such as: Sinupret, film-coated tablets (Bionorica SE), Sinupret oral drops, solution (Bionorica SE), Sinupret extract (Bionorica SE, adults 18 years of age or more, acute uncomplicated sinusitis) is available in the Summary of Product Characteristics.

J20 – Acute bronchitis

Bronchitis is a respiratory infection whose main symptom is a dry cough or productive cough, which may be accompanied by fever, and on physical examination, a doctor may find auscultatory symptoms, such as crackles or wheezes. When bronchitis is suspected, there is usually no need for additional blood tests or a chest X-ray. The most common causes of bronchitis are viruses, which is why the medications that are usually used are aimed at relieving symptoms, and the use of antibiotics is unnecessary and often even harmful.

Herbal substances used in the treatment of acute bronchitis:

1. **Herbal active substances in a compound medicinal product: thyme herb (fluid extract)** (*Thymi herbae extractum fluidum*), **ivy leaf (fluid extract)** (*Hederae helicis folii extractum fluidum*).

Active constituents: the biological activity of the components is presented in detail for individual herbal substances. The biological activity of the medicinal product has been determined in *in vitro* and *in vivo* studies. An *in vitro* study of human neutrophils stimulated with the A23187 ionophore (induction of leukotriene B4-LTB4) and monocytes (induction of leukotriene cysteinyl) showed inhibition of the enzymatic activity of 5-lipoxygenase (5-LOX) and the decreased production of LTB4 in neutrophils and leukotriene cysteinyl in monocytes. Inhibition of phosphodiesterase (PDE) 4 E2 activity was also determined [72]. In an inflammation model, the medicine was shown to stimulate mucociliary system activity by a concentration-dependent increase in ciliary beat frequency (CBF) in tracheal respiratory epithelial cells and a reduction in airway epithelial remodelling [73]. Reduced leukocyte counts in BALF and peripheral blood, mucosal goblet cell number and tissue inflammatory infiltration were also observed, which was indicated by a significant reduction in cough frequency, whichwas confirmed *in vivo* [74]. Studies confirmed muco-regulatory activity, inhibition of the inflammatory response and bronchial remodelling (goblet cells) and restoration of normal function of the mucociliary apparatus [75]. *In vitro* and *in vivo* studies also indicate bronchodilatory and antimicrobial activity [72]. **Clinical studies:** The study was conducted in a group of 182 patients with acute bronchitis; administration of the medicine reduced or suppressed cough in 50% of those treated two days earlier than in the placebo group and alleviated the course of the infection [76]. A clinical trial on 1,234 children from 2–17 years of ages showed a significant relief of bronchitis symptoms, including cough, in all age groups. The number of cough episodes the day before the scheduled visit was reduced, on average, by 81.3% [77]. The controlled clinical trials conducted to date are sufficient to support the well-established use of the medicinal product [78]. **Indications for use:** Well-established herbal medicinal product for symptoms of cough with persistent secretion in the course of mild to moderate infection and inflammation of the respiratory tract, such as acute bronchitis, from the age of 2. Detailed information on the medicinal product: Bronchipret TE (Bionorica SE) is available in the Summary of Product Characteristics.

Summary

Herbal medicinal products are an important component of the treatment armamentarium for acute respiratory infections. The multidirectional biological activity of the plant substances in medicines justifies their use in clinical indications (dry cough, wet cough, fever) and in defined respiratory diseases (acute rhinosinusitis, acute sinusitis, acute bronchitis). The activity demonstrated in the studies also allows them to be used in the prophylaxis of respiratory infections, particularly in the case of recurrent upper respiratory tract infections. The medicines have a high safety profile, which also justifies their wide use in the indications specified in the Summary of Product Characteristics of individual preparations.

Source of funding: This work was funded from the authors' own resources.
Description of a potential conflict of interest. Zbigniew Doniec – lectures for pharmaceutical companies: Wrocławskie Zakłady Zielarskie Herbapol S.A., PPF Hasco-Lek S.A., Phytopharm Klęka S.A., US Pharmacia Sp. z o.o., Bionorica Polska Sp. z o.o.; Ernest Kuchar – lectures for pharmaceutical companies: Wrocławskie Zakłady Zielarskie Herbapol S.A., PPF Hasco-Lek S.A., Bionorica Polska Sp. z o.o., Salveo Poland Sp. z o.o.; Mirosława Krauze-Baranowska – lectures for pharmaceutical companies: Wrocławskie Zakłady Zielarskie Herbapol S.A., Bionorica Polska Sp. z o.o. The other authors do not declare a conflict of interest.

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Tables: 0
Figures: 0
References: 78

Received: 21.08.2023
Reviewed: 04.09.2023
Accepted: 16.09.2023

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