



AMERICAN BOTANICAL COUNCIL
PROPRIETARY BOTANICAL PRODUCT
**SCIENTIFIC AND CLINICAL
MONOGRAPH**
FOR
SINUPRET[®]



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SINUPRET®

OVERVIEW

This Clinical Overview is based on the full monograph covering the published scientific and clinical research on Sinupret® (manufactured by Bionorica, Neumarkt, Germany), a unique herbal combination used to treat sinusitis or acute and chronic bronchitis. Sinupret contains extracts of five herbs: elder (*Sambucus nigra*, Caprifoliaceae) flowers, primrose (*Primula veris*, Primulaceae) flowers with calyx, common sorrel (*Rumex acetosa*, Polygonaceae) herb, European vervain (*Verbena officinalis*, Verbenaceae) herb, and gentian (*Gentiana lutea*, Gentianaceae) root. Sinupret has been sold in the German and European market for more than 70 years. In Europe the liquid dosage form (Sinupret Drops) has been available since 1934, tablets (Sinupret Sugar Coated Tablets) have been available since 1968, and a tablet containing a higher concentration of the herbs (Sinupret Forte Sugar Coated Tablets) has been available since 1997. Sinupret tablets have been available to a limited extent in the United States since about 2003, primarily via mail order and professional sales. As of fall 2008 the products have been available in the United States in mainstream retail outlets, sold under the trade names Sinupret Plus/Sinupret Adult Strength and Sinupret Syrup for Kids. Sinupret Plus/Sinupret Adult Strength has the same formulation as Sinupret Forte Sugar Coated Tablets and Sinupret Syrup for Kids is similar to the Sinupret Drops except that the Syrup has much lower (ethanol) content (see Dosage section below). Alcohol (ethanol) is used as a solvent in the manufacturing process to make the extract from the 5 botanical ingredients, in a quantity sufficient to extract the pharmacologically active volatile essential oils from the respective herbal constituents.

Sinupret has enjoyed a long history of popular use in Germany and has been a high-selling phytomedicine by physician prescription as well as by self-selection and self-medication by consumers. Sinupret was ranked as the second most prescribed phytotherapeutic agent used for cough and cold in Germany in 2006, 2007, and 2008. It was also ranked #1 as the most popular cough and cold remedy chosen by self-selection and self-medication in Germany in 2006, 2007, and 2008. Sinupret was ranked #10 of all prescribed products, including all prescription medicines, in Germany in 2003. In Germany in 2003, Sinupret Forte was prescribed for acute sinusitis (40.0% of the Sinupret prescriptions), chronic sinusitis (18.4% of the Sinupret prescriptions), acute infection of the upper respiratory tract (9.2%), acute bronchitis (7.2%), bronchitis not classified as acute or chronic (5.7%), acute rhinopharyngitis (3.4%), infections of the middle ear (2.8%), influenza (1.0%), acute infection of the lower respiratory tract (0.8%), chronic bronchitis (0.6%), and other causes (10.9% of the prescriptions).

PRIMARY USE

Sinusitis and related conditions: Manufacturer's literature states that Sinupret liquid or tablets are indicated for acute and chronic inflammation of the paranasal sinuses and the upper respiratory tract. There are numerous studies published in German and English supporting this use.

PHARMACOLOGICAL ACTIONS

Pharmacological studies employing *in vitro* and animal models have found that Sinupret has antimicrobial and antiviral effects, secretolytic activity (breaks down secretions, reduces the viscosity of mucus) and anti-inflammatory activity. All of these actions are important for treating respiratory infections.

Clinical trials on Sinupret were conducted on the commercial products available in Europe. The American products contain the same herbs and concentrations of those herbs, but the American products have different names. Also, the European liquid preparation for children contains alcohol (ethanol, 19% alcohol by volume) and the American syrup contains a reduced amount (8% by volume or 0.56 mL per 7.0 mL serving). The manufacturer claims that there should be absolutely no effect on the blood alcohol content after taking Sinupret Syrup at the recommended doses. The company draws this conclusion from the fact that most common fruit juices contain naturally occurring ethanol (< 0.1-0.5% by volume) and that the intake of alcohol associated with Sinupret Syrup is comparable, or smaller, than the intake with fruit juice. Also, there are reports that show that blood alcohol concentrations after intake of very small amounts of alcohol are insignificant or irrelevant.

DOSAGE AND DURATION OF USE

Daily Dose in Clinical Trials:

The doses used in the clinical trials and reported in the Table of Clinical Trials in the full monograph use the manufacturer's recommended dose. All of the studies use the European products, namely:

Sinupret Sugar Coated tablets:

- Adults—2 tablets, 3 times per day
- Children ages 12 and older—1 tablet, 3 times per day

Sinupret Forte Sugar Coated tablets (Sinupret Plus/Sinupret Adult Strength):

- Adults—1 tablet, 3 times per day

Sinupret Drops:

- Adults—50 drops, 3 times per day
- Children (6-12 years)—25 drops, 3 times per day
- Children (2-6 years)—15 drops, 3 times per day

In clinical trials the duration of treatment varied from 7 to 21 days.

Manufacturer Dose Recommendations:

According to the manufacturer the dosing for the US products are as follows:

Sinupret Plus/Sinupret Adult Strength:

- 1 tablet, 3 times per day

Sinupret Syrup for Children:

- 2 to 5 years old—½ teaspoon or 2.1 mL, 3 times per day
- 6 to 11 years old—¾ teaspoon or 3.5 mL, 3 times per day
- 12 years or older—1½ teaspoons or 7.0 mL, 3 times per day

CONTRAINDICATIONS AND PRECAUTIONS

Consumers and patients who know they are hypersensitive (allergic) to one of the ingredients in the Sinupret products should exercise caution before using Sinupret. Due to lack of clinical data, Sinupret Plus/Sinupret Adult Strength and Sinupret Forte Sugar Coated tablets should not be used by children younger than 12 years old. Children younger than 12 years old can use the liquid form.

Pregnancy and Lactation

Sinupret use in pregnancy and lactation has not been fully studied and should be used only after careful risk-benefit evaluation by a patient's physician or other appropriate healthcare provider.

The safety of Sinupret during pregnancy was evaluated in a retrospective surveillance study conducted from 1992-1997. Data was collected from 762 pregnant women who were treated with Sinupret Sugar Coated tablets or drops, as desired, for at least 24 hours during pregnancy. The patients were from 150 study centers in Germany. The data was compared to the data in the prospective population-based Mainz congenital birth registry for congenital malformations. The birth defect incidence rate in this study was 1.1%. This is lower than expected considering that the prevalence of malformation is 2-3% in passive registries and 6-7% in active registries. The authors concluded that a reasonable correlation between the intake of Sinupret and teratogenic or embryotoxic effects was not proven.

ADVERSE EFFECTS/SAFETY DATA

Sinupret has been safely used in millions of doses over 35 years. Reported adverse side effects include gastrointestinal (GI) disorders and hypersensitivity (allergy) reactions. In these cases, intake of Sinupret should be discontinued and a physician should be consulted. At the first sign of a hypersensitivity reaction Sinupret should not be taken again. According to the manufacturer, the incidence of total adverse drug reactions in clinical trials is 1%, based on 6849 patients. The incidence of spontaneous adverse drug reactions in the general population of Sinupret users during the period from 1973 to October 2008 is approximately 1 per 1,000,000 treatments, based on the sum of approximately 214 million treatments.

A post-marketing surveillance study of 3187 patients who were 1-94 years old reported that the adverse event (AE) rate was 0.8% (8/1013) for Sinupret (product type not specified), compared with the AE rate of 1.0% (3/313) for ambroxol, 4.3% (12/277) for N-acetylcysteine, and 5.8% (4/69) for myrtol. When a second medication was prescribed concomitantly the AE rate for all of the compounds increased. The rate of AEs was 3.4% (27/792) when Sinupret was taken with concomitant medication (medications not specified). In the post-surveillance study, 8 of the 1013 patients treated with Sinupret without concomitant medication reported GI symptoms (n = 7) or dizziness (n = 1) as AEs. Three of these cases were determined to be probably caused by Sinupret (it is unclear which cases), 1 was determined to be not caused by Sinupret (it is unclear which case), 1 case had a questionable association, and 3 cases did not have enough information for an assessment to be made.

Drug Interactions

To date there are no known drug interactions.

Smoking should be discontinued during the bronchial infection and treatment with Sinupret because smoking lowers the efficacy of treatment.

CLINICAL REVIEW

According to documentation provided by Bionorica, the manufacturer of Sinupret, from inception of the initial Sinupret product to January 2002 the efficacy of Sinupret has been evaluated in 5 placebo-controlled studies, 7 comparative trials, and 1 post-marketing surveillance study. Since then 2 systematic reviews of clinical trials, numerous abstracts, and several other studies have been published. Most of the scientific literature is published in German. This monograph reviews all of the studies that have been published in English or translated into English from inception to October 2008.

Studies included in the text of the Clinical Review section of the full monograph include a total of 4 clinical trials on the efficacy of Sinupret preparations for treating acute sinusitis. One study was in children and only 2 of the 4 studies have been published in their entirety in English (the other two were abstracts from conference proceedings). The studies included in the text of the Clinical Review section of the full monograph also include 2 clinical trials evaluating the efficacy of Sinupret for treating chronic sinusitis. Only one of these trials has been published in a peer-reviewed journal, the other is an abstract from a conference proceeding. One meta-analysis evaluating Sinupret for the treatment of sinusitis has also been included in the clinical review. The meta-analysis is interesting from the perspective that it includes 4 clinical trials, three of which are unpublished reports that have not been translated into English and as a consequence have not been reviewed in this monograph. The efficacy of Sinupret for treating bronchitis is reviewed in 2 clinical trials; unfortunately, these reviews are based solely on data presented at conference proceedings because peer-reviewed publications were not available in English. A post-marketing surveillance study of patients with bronchitis is also reviewed.

To summarize the clinical findings, based on the results of one placebo-controlled study and the meta-analysis of 2 placebo-controlled studies it appears that Sinupret is effective at augmenting the effects of standard pharmaceutical therapy. A small meta-analysis revealed that Sinupret is as effective as ambroxol. Additional studies are needed to confirm the findings and placebo or untreated control studies are needed to determine the efficacy of Sinupret as a monotherapy for the treatment of acute sinusitis. More methodologically rigorous studies in children are also needed. Preliminary results evaluating the efficacy of Sinupret for treating chronic sinusitis are equivocal—larger prospective studies are needed. In studies of bronchitis, Sinupret was equivalent or superior to pharmaceutical treatment.

This review of the pharmacological and clinical literature on Sinupret suggests that this phytochemical preparation has a relatively significant level of safety and efficacy data compared to many other botanical or otherwise natural medicinal preparations intended for use in maintaining the health of sinuses and the upper respiratory tract. The scientific and clinical literature on Sinupret supports pharmacological mechanisms of mucolytic, secretolytic, anti-inflammatory, antibacterial, antiviral, and immunological activity, some of which has been documented in open-label and randomized controlled human clinical trials. The overall safety of Sinupret has been extensively documented in pharmacovigilance data based on widespread and long-term use in Germany and other European countries, as well as other post-market surveillance safety data, including relative safety during pregnancy.

SINUPRET® Consumer/Patient Information Sheet

OVERVIEW

Sinupret® (manufactured by Bionorica, Neumarkt, Germany and imported into the United States by Bionorica, LLC) is a unique herbal combination used to treat sinusitis or acute and chronic bronchitis. Sinupret contains extracts of 5 herbs: elder (*Sambucus nigra*, Caprifoliaceae) flowers, primrose (*Primula veris*, Primulaceae) flowers with calyx, common sorrel (*Rumex acetosa*, Polygonaceae) herb, European vervain (*Verbena officinalis*, Verbenaceae) herb, and gentian (*Gentiana lutea*, Gentianaceae) root. Sinupret has been sold in the German and European market for more than 70 years. Sinupret was ranked as the second most prescribed phytotherapeutic agent used for cough and cold in Germany in 2006, 2007, and 2008. It was also ranked #1 as the most popular cough and cold remedy chosen by self-selection and self-medication in Germany in 2006, 2007, and 2008. Sinupret was ranked #10 of all products prescribed by physicians, including all prescription medicines, in Germany in 2003.

USES

Sinupret is used to treat sinusitis and related conditions. There are numerous studies published in German and English supporting this use.

DOSAGE AND DURATION OF USE

In Europe 3 products are available: Sinupret Drops, Sinupret Sugar Coated Tablets, and a tablet containing a higher concentration of the herbs called Sinupret Forte Sugar Coated Tablets. In fall 2008 the products have been available in the United States in mainstream retail outlets, sold under the trade names Sinupret Plus/Sinupret Adult Strength and Sinupret Syrup for Kids. Sinupret Plus/Sinupret Adult Strength has the same formulation as Sinupret Forte Sugar Coated Tablets and Sinupret Syrup for Kids is similar to the Sinupret Drops except that the Syrup has much lower alcohol (ethanol) content. Alcohol (ethanol) is used in the manufacturing process as a solvent to make the extract from the 5 botanical ingredients, in a quantity sufficient to extract the pharmacologically active volatile essential oils from the respective herbal constituents. The manufacturer claims that there should be no effect on the blood alcohol content after taking Sinupret Syrup at the recommended doses. They draw this conclusion from the fact that fruit juice contains naturally occurring ethanol (< 0.1-0.5% by volume) and that the intake of alcohol associated with Sinupret Syrup is comparable, or smaller, than the intake with fruit juice. Also, there are reports that show that blood alcohol concentrations after intake of very small amounts of alcohol are insignificant or irrelevant.

The doses used in the clinical trials use the manufacturer's recommended dose. All of the studies used the European products.

Sinupret Forte Sugar Coated Tablets:
Adults—1 tablet, 3 times per day

Sinupret Drops:
Adults—50 drops, 3 times per day
Children (6-12 years)—25 drops, 3 times per day
Children (2-6 years)—15 drops, 3 times per day

In clinical trials the duration of treatment varied from 7 to 21 days.

MANUFACTURER DOSE RECOMMENDATIONS:

According to the manufacturer the dosing for the US products are as follows:

Sinupret Plus/Sinupret Adult Strength: 1 tablet, 3 times per day

Sinupret Syrup for Children:

2 to 5 years old—½ teaspoon or 2.1 mL, 3 times per day

6 to 11 years old—¾ teaspoon or 3.5 mL, 3 times per day

12 years or older—1½ teaspoons or 7.0 mL, 3 times per day

CONTRAINDICATIONS AND PRECAUTIONS

Consumers and patients who know they are hypersensitive (allergic) to one of the ingredients in the Sinupret products should exercise caution before using Sinupret. Due to lack of clinical data, Sinupret Plus/Sinupret Adult Strength and Sinupret Forte Sugar Coated tablets should not be used by children younger than 12 years old. Children younger than 12 years old can use the liquid form, Sinupret Syrup for Kids.

PREGNANCY AND LACTATION

Sinupret use in pregnancy and lactation has not been fully studied and should be used only after careful risk-benefit evaluation by a patient's physician or other appropriate healthcare provider.

ADVERSE EFFECTS

Sinupret has been safely used in millions of doses over 35 years. Reported side effects include gastrointestinal (GI) disorders and allergy reactions. In these cases, intake of Sinupret should be discontinued and a physician should be consulted. At the first sign of an allergy reaction Sinupret should not be taken again. According to the manufacturer, the incidence of adverse drug reactions in clinical trials is 1%, based on 6849 patients. The incidence of spontaneous adverse drug reactions in the period from 1973 to October 2008 is approximately 1 per 1,000,000 treatments, based on the sum of approximately 214 million treatments.

DRUG INTERACTIONS

To date there are no known drug interactions with Sinupret.

Tobacco smoking should be discontinued during bronchial infection and use of Sinupret because smoking lowers its efficacy.

As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions. The information contained on this sheet has been excerpted from the full Scientific and Clinical Monograph on Sinupret®. ABC is an independent member-based educational organization focusing on the medicinal use of herbs. For more information visit the ABC website at www.herbalgram.org.



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PROPRIETARY BOTANICAL PRODUCT SCIENTIFIC AND CLINICAL MONOGRAPH

SINUPRET®

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PUBLISHER'S NOTE

The preparation and publication of this literature review and monograph on this proprietary botanical product has been conducted by the American Botanical Council (ABC) for educational purposes only. This publication reflects the state of the scientific and clinical literature on this specific commercial plant-based product up to a reasonable period of time prior to the initial publication (and/or any subsequent revisions). This publication has been peer reviewed for its accuracy by experts qualified in their formal training to assess the literature in various scientific disciplines and/or clinical medicine related to the information included in this document.

This publication should not be interpreted as a promotion or endorsement by the authors or ABC of the specific ingredients or any product containing the ingredients or of the commercial company or companies affiliated with their manufacture, importation, marketing, or sale. ABC has long recognized that much of the pharmacological and clinical literature on specific categories of herbs and phytomedicinal products are often based on one or several leading proprietary commercial preparations and, as such, this publication reflects and acknowledges the existence of such literature as having been conducted on one or more leading products in a particular category.

The American Botanical Council is an independent, nonprofit research and education organization, tax-exempt under section 501(c)(3) of the Internal Revenue Service code, dedicated to the rational and responsible use of herbs, medicinal plants, phytomedicines, teas, essential oils, and related plant-based ingredients.

OVERVIEW

Sinupret® (manufactured by Bionorica, Neumarkt, Germany) is the name for a unique herbal combination, available in several preparations and concentrations, used to maintain the normal function of the membranes of the sinus cavity. The name "Sinupret" is derived from the words *sinus* and *preti*, Latin for *price* or *value*, hence, *precious*. In Europe Sinupret preparations are prescribed by physicians and sold without prescription for the treatment of sinusitis or acute and chronic bronchitis.

Sinupret contains extracts of 5 herbs: elder (*Sambucus nigra*, Caprifoliaceae) flowers, primrose (*Primula veris*, Primulaceae) flowers with calyx, common sorrel (*Rumex acetosa*, Polygonaceae) herb, European vervain (*Verbena officinalis*, Verbenaceae) herb, and gentian (*Gentiana lutea*, Gentianaceae) root. [Note: Primrose, also known as cowslip, is not the same plant as the popular herb evening primrose (*Oenothera biennis*, Onagraceae).]

Sinupret has been sold in the German and European market for more than 70 years. In Europe the liquid dosage form (Sinupret Drops) has been available since 1934, tablets (Sinupret Sugar Coated Tablets) have been available since 1968, and a tablet containing a higher concentration of the herbs (Sinupret Forte Sugar Coated Tablets [imported into the United States as Sinupret® Adult Strength by Bionorica, LLC of San Clemente, CA]) has been available since 1997.¹ Sinupret tablets have been available to a limited extent in the United States since about 2003, primarily via mail order and sales to health professionals. In fall 2008 some of the Sinupret products have been available in the United States in mainstream retail outlets, sold under the trade names Sinupret® Plus/Sinupret® Adult Strength and Sinupret® Syrup for Kids. Sinupret Plus/Sinupret Adult Strength has the same formulation as Sinupret Forte Sugar Coated Tablets and Sinupret Syrup for Kids is similar to the Sinupret Drops except that the Syrup has much lower alcohol (ethanol) content (see Dosage section below). Sinupret Plus/Sinupret Adult Strength and Sinupret Syrup for Kids are available only in the United States.

Water and grain alcohol (ethanol) are used as a solvent in the manufacturing process to make the extract from the 5 botanical ingredients, in a quantity sufficient to extract the pharmacologically active constituents, including the volatile essential oils, from

the respective herbal ingredients.

Sinupret has enjoyed a long history of popular use in Germany and has been a high-selling phytomedicine by physician prescription as well as by self-selection and self-medication by consumers.² Sinupret was ranked as the second most-prescribed phytotherapeutic agent used for cough and cold in Germany in 2006, 2007, and 2008.² It was also ranked #1 as the most popular cough and cold remedy chosen by self-selection and self-medication in Germany in 2006, 2007, and 2008.² Sinupret was ranked 10th of all prescribed products, including all prescription medicines, in Germany in 2003.³ In Germany in 2003, Sinupret Forte was prescribed for acute sinusitis (40.0% of the prescriptions written by German physicians for Sinupret), chronic sinusitis (18.4% of the Sinupret prescriptions), acute infection of the upper respiratory tract (9.2%), acute bronchitis (7.2%), bronchitis not classified as acute or chronic (5.7%), acute rhinopharyngitis (3.4%), infections of the middle ear (2.8%), influenza (1.0%), acute infection of the lower respiratory tract (0.8%), chronic bronchitis (0.6%), and other causes (10.9% of the prescriptions).³

PRIMARY USE

Sinusitis and related conditions: Manufacturer's literature in Europe states that Sinupret liquid or tablets are indicated for acute and chronic inflammation of the paranasal sinuses and the upper and lower respiratory tract. There are numerous scientific and clinical studies published in German and English supporting this use (see Clinical Review section below).

DOSAGE AND DURATION OF ADMINISTRATION

Clinical trials on Sinupret were conducted on the commercial products available in Europe. The American products contain extracts of the same herbs in the same concentrations of those extracts, but the American products have different names, e.g., Sinupret® Plus/Sinupret® Adult Strength and Sinupret® Syrup for Kids. Also, the European liquid preparation for children contains alcohol (ethanol, 19% alcohol by volume) and the American syrup (Sinupret Syrup for Kids) contains a reduced amount (8% by volume or 0.56 mL per 7.0 mL serving). The manufacturer claims⁴ that there should be no effect on the blood alcohol content after

taking Sinupret Syrup at the recommended doses. The company draws this conclusion from the fact that many common fruit juices contain naturally occurring ethanol (< 0.1-0.5% by volume) and that the intake of alcohol associated with Sinupret Syrup is comparable, or smaller, than the intake with fruit juice. Also, there are reports that show that blood alcohol concentrations after intake of very small amounts of alcohol are insignificant or irrelevant.⁵

Daily Dose in Clinical Trials:

The doses used in the clinical trials and reported in the Table of Clinical Trials (below) use the manufacturer's recommended dose. All of the studies use the European products, namely:

Sinupret Sugar Coated tablets:

Adults—2 tablets, 3 times per day

Children ages 12 and older—1 tablet, 3 times per day

Sinupret Forte Sugar Coated tablets (Sinupret Plus/Sinupret Adult Strength):

Adults—1 tablet, 3 times per day

Sinupret Drops:

Adults—50 drops, 3 times per day

Children (6-12 years)—25 drops, 3 times per day

Children (2-6 years) —15 drops, 3 times per day

In clinical trials the duration of treatment varied from 7 to 21 days.

Manufacturer Dose Recommendations:

According to the manufacturer the dosing for the US products are as follows.

Sinupret Plus/Sinupret Adult Strength:

1 tablet, 3 times per day

Sinupret Syrup for Children:

2 to 5 years old—½ teaspoon or 2.1 mL, 3 times per day

6 to 11 years old—¾ teaspoon or 3.5 mL, 3 times per day

12 years or older—1½ teaspoons or 7.0 mL, 3 times per day

CHEMISTRY

Sinupret is an herbal preparation made from 5 herb extracts.

Sinupret Sugar Coated tablets contain elder flowers (powdered, 18 mg), primrose flowers with calyx (powdered, 18 mg), common sorrel herb (powdered, 18 mg), European vervain herb (powdered, 18 mg), and gentian root (powdered, 6 mg).

Sinupret Forte Sugar Coated tablets contain twice the concentration of Sinupret Sugar Coated tablets; specifically it contains the hydroethanolic extract of elder flowers (powdered, 36 mg), primrose flowers with calyx (powdered, 36 mg), common sorrel herb (powdered, 36 mg), European vervain herb (powdered, 36 mg), and gentian root (powdered, 12 mg).

Sinupret drops contain 29 g hydroethanolic extract (drug/extract ratio 1:11) from gentian root (cut), primrose flowers with calyx (cut), common sorrel herb (cut), elder flowers (cut), and European vervain herb (cut) in a 1:3:3:3:3 proportion. The extraction solution is 59% v/v ethanol, and the drops contain 19% of alcohol by volume.

Sinupret Plus/Sinupret Adult Strength contains hydroethanolic extracts of elder flowers (powdered, 36 mg), primrose flowers with calyx (powdered, 36 mg), common sorrel herb (powdered, 36 mg), European vervain herb (powdered, 36 mg), and gentian root (powdered, 12 mg).

Sinupret Syrup for Kids contains 10 g of a hydroethanolic extract (drug/extract ratio 1:11) from gentian root (cut), primrose flowers

with calyx (cut), common sorrel herb (cut), elder flowers (cut), and vervain herb (cut) in a 1:3:3:3:3 proportion. The extraction solution is 59% v/v ethanol, and the drops contain 8% of alcohol by volume.

Elder flower (*Sambucus nigra*) contains flavonoids (up to 3%) composed mainly of flavonol glycosides (astragalol, hyperoside, isoquercitrin, and rutin up to 1.9%) and free aglycones (quercetin and kaempferol); minerals (8-9%), mainly potassium; phenolic compounds (approximately 3% chlorogenic acid); triterpenes (approximately 1%) including α - and β -amyrin; triterpene acids (approximately 0.85% ursolic and oleanolic acids); sterols (approximately 0.11%); volatile oils (0.03-0.3%) composed of approximately 66% free fatty acids (linoleic, linolenic, and palmitic acids) and approximately 7% alkanes; mucilage; pectin; plastocyanin (protein); sugar; tannins.⁶⁻¹⁰

Primrose (*Primula officinalis*) flowers with calyx contains numerous flavonoids (i.e. rutin and quercetin), carotenoids, and salicylic acid derivatives.¹ The calyces also contain saponins.¹¹

Common sorrel (*Rumex acetosa*) contains polysaccharides, ascorbic acid, oxalates (including calcium oxalate), tannins, anthra-noids, aglycones, physcion, aloe-emodin, aloe-emodin acetate, emodin, rhein, quinoids, flavonoids (i.e. quercetin and glycosides), hydroxycinnamic acid derivatives (i.e. ferulic acids), and phenylpropanoid.^{1,12-14} All of the active compounds have not been identified.¹⁴ The leaves may contain 0.3% oxalate (oxalic acid) and 7-15% tannins.¹⁴

European vervain (*Verbena officinalis*) herb contains iridoid glycosides (i.e. verbenalin and hastatoside), triterpenic acids, sterols, caffeoyl derivatives (i.e. chlorogenic acid and verbascoside), hydroxycinnamic acid derivatives, bitter substances, and flavonoids.^{1,15-17} The aerial parts contain high amounts of ursolic acid and oleanolic acid and its derivatives.¹⁶ Vervain also contains volatile oil with citral, terpenes, and terpene alcohols.¹

Gentian (*Gentiana lutea*) root contains secoiridoid bitter principles gentiopicroside (2-4%) and amarogentin (0.025-0.084%) [bitterness value=58,000,000]; oligosaccharides gentianose and gentiobiose (2.5-8.0%); (gentisic, caffeic, and protocathechuic) phenolic acids; phytosterols; polysaccharides inulin and pectin; tannin; lupiol and β -amyrin triterpenes; xanthones (approximately 0.1%), mainly gentisin, isogentisin, gentisein, and gentioside; and traces of volatile oil.^{6-10,18,19}

PHARMACOLOGICAL ACTIONS/MECHANISM OF ACTION

Antimicrobial and Antiviral Effects

In vitro

The antimicrobial effects of Sinupret were evaluated in sinusitis-relevant microbes.²⁰ Gram-positive bacteria (*Staphylococcus aureus*, methicillin resistant *Staph. aureus* [MRSA], and *Streptococcus pyogenes*) and gram-negative bacteria (*Escherichia coli* and *Haemophilus influenzae*) were exposed to Sinupret and the killing action was assessed. Sinupret caused relevant bacteriocidal effects on gram positive and negative bacteria.²⁰ It was most potent against MRSA, *Staph. aureus*, and *Strep. pyogenes*. It was not effective against *E. coli*.

The antiviral activity of Sinupret drops were evaluated *in vitro*.²¹ Sinupret drops 0.1 mg/mL produced a 46% inhibition against human parainfluenza virus type 1; 0.01 - 0.025 mg/mL of Sinupret produced a 50% inhibition against human respiratory syncytial virus. Sinupret produced a synergistic effect against respiratory syncytial virus compared to its individual components primrose and European vervain.²¹

Animal

Mice were inoculated with *Strep. pneumoniae* to induce bacterial rhinosinusitis and then treated with Sinupret, ampicillin, dexamethasone, or sham treatment.²² All treatments (except sham) caused a reduction in bacterial growth after 4 days, which reached statistical significance after 8 days. The study was repeated in rabbits and the outcome was similar.²²

The ability of Sinupret to protect against a Sendai virus (*Parainfluenza viridae*) respiratory tract infection was studied in mice.²³ The mice were treated with Sinupret or 2 active controls (ambroxol and muramyldipeptide) several days prior to being infected with the Sendai virus. Sinupret significantly prolonged the mouse survival time compared with placebo ($p < 0.05$). The 2 positive controls were not as effective as Sinupret. Sinupret may be producing this effect by modulating cytokines and increasing antigen-specific CD4+ and CD8+ T-cells.²³

Secretolytic Activity

Animal

The secretolytic activity (process of breaking down secretions and reducing the viscosity of mucus) of Sinupret was evaluated with a classical model for determining pharmacological effects on the production of tracheal secretion in rabbits.²⁴ Sinupret, the individual herbs that are in Sinupret, and sodium chloride (control) were administered to rabbits for several days before their tracheal sections were collected. Sinupret and the individual herbs all statistically significantly increased the fluidity of respiratory tract secretions compared with baseline ($p < 0.05$ for all).²⁴ Doses of Sinupret that were 50-fold and 15-fold greater than the human dose did not cause any safety problems.²⁴

A second secretolytic study evaluated the effects of Sinupret and its individual components on secretion activity of rat respiratory epithelium.²⁴ The method, which uses phenol red, has been used to evaluate standard secretolytics. Sinupret had a dose-dependent effect on tracheobronchial secretion.^{24,25} Of the individual components, European vervain and gentian root extracts (dry extracts of an ethanol-water extract) displayed the most secretolytic effects. However, secretion produced by Sinupret (also a dry extract of an ethanol-water extract) was greater than that produced by the individual components, indicating a synergistic effect.²⁴ Saline had no secretolytic effect.

Anti-inflammatory Activity

In vitro

The immunological activity of Sinupret and its individual components were evaluated *in vitro* in human leukocytes isolated from peripheral blood.²⁶ Phagocytotic activity of the plant extracts were evaluated in isolated human neutrophil granulocytes (a type of leukocyte). Gentian root extract and vervain extract (type of extract not reported) increased phagocytic activity of neutrophils. Sorrel inhibited phagocytosis at high concentrations.²⁶ At low concentrations Sinupret only marginally increased phagocytosis. Sorrel extract (type of extract not reported) stimulated proliferation of lymphocytes. High concentrations of Sinupret marginally stimulated proliferation of lymphocytes *in vitro*. The authors concluded that human immune cells respond to the herbal extracts.²⁶

Neutrophils are part of the first-line innate immune response.²⁷ They can act as phagocytic cells and release reactive oxygen species (ROS) and proteases to attack bacteria and parasites. However, neutrophils can also cause inflammation—ROS is involved in the pathogenesis of some inflammatory diseases.²⁸ Neutrophils are activated after they adhere to the endothelium. Subsequently, superoxides can be produced in a process called respiratory burst. Sinupret (water and hydroethanolic extracts) was assayed for its ability to

influence the adhesion and superoxide production of ovine (sheep) neutrophils activated by phorbol 12-myristate 13-acetate (PMA).²⁷ PMA triggers neutrophil adhesion. The hydroethanolic extract strongly blocked neutrophil adhesion and superoxide production in a dose-dependent manner. Low concentrations increased superoxide production and the high concentration inhibited superoxide production. The aqueous extract did not influence neutrophil function, indicating that the most active molecules are not water soluble. The authors hypothesized that the flavonoid content in Sinupret may be responsible for the effect on neutrophils.²⁷ The aqueous extract stimulated cell viability, which may be related to the carotenoid content. The authors concluded that Sinupret has anti-inflammatory activity in this system.²⁷

Animal

Respiratory infections are inflammatory processes of the respiratory epithelium, so it is not unusual to test treatments for respiratory infection in standard *in vivo* models of inflammation.²⁴ Hence, Sinupret was evaluated in a rat hind paw model of inflammation. Inflammation was induced in the rat hind paw and the ability of oral Sinupret, phenylbutazone (positive control), and placebo to reduce swelling was measured.²⁴ Sinupret reduced swelling and the highest dose tested was as effective as phenylbutazone.²⁴ The authors attribute the anti-inflammatory effect to the polysaccharides and tannins in sorrel and the iridoids in vervain.^{12,15,24}

Bacterial infections of the upper respiratory tract can be treated with antibiotics, which target the bacteria, or can be treated with anti-inflammatory substances, which target the host response reaction.²⁹ This is because the initiation and persistence of rhinosinusitis involves a complex interaction between local inflammation and microbial colonization. The efficacy of Sinupret, dexamethasone (an anti-inflammatory agent), ampicillin (an antibiotic), and sham control were tested in mice inoculated intranasally with *Strep. pneumoniae* to induce bacterial rhinosinusitis.^{29,30} Sinupret significantly reduced bacterial growth ($p < 0.01$), the number of goblet cells (cells that secrete mucous) ($p < 0.05$), and the character of secretion compared with control ($p < 0.01$).³⁰ The reduction in bacterial growth was similar to the positive controls. The authors stated that Sinupret is working through an anti-inflammatory mechanism.^{29,30}

CONTRAINDICATIONS AND PRECAUTIONS

Consumers and patients who know they are hypersensitive (allergic) to one of the ingredients in the Sinupret products should exercise caution before using Sinupret (see Chemistry section above).³¹ Due to lack of clinical data on children, Sinupret Plus/Sinupret Adult Strength and Sinupret Forte Sugar Coated tablets should not be used by children younger than 12 years old.¹ Children younger than 12 years old can use the liquid form, Sinupret Syrup for Kids, according to the manufacturer's information.¹

Pregnancy and Lactation

Sinupret use during pregnancy and lactation has not been fully studied and should be used only after careful risk-benefit evaluation by a patient's physician or other appropriate healthcare provider.³¹

The safety of Sinupret during pregnancy was evaluated in a retrospective surveillance study conducted from 1992-1997.³² Data was collected from 762 pregnant women who were treated with Sinupret Sugar Coated tablets or drops, as desired, for at least 24 hours during pregnancy. The patients were from 150 study centers in Germany. The data was compared to the data in the prospective population-based Mainz congenital birth registry for congenital malformations. This birth registry includes 94.8% of all births in Rheinhessen, Germany. The pregnant women in the study were treated with Sinupret Sugar Coated tablets or drops for sinusitis

(59.4%), bronchitis (20.2%), or both (20.2%). The mean duration of treatment for sinusitis was 10.4 days, for bronchitis 11.8 days, and for the combination 11.9 days.

The study population and Mainz population were similar in mean age, percent of first and second pregnancies, and duration of pregnancy.³² The study population had significantly (p values not reported) more patients with obesity (BMI > 30), multiple pregnancies (twins), premature labor, and nicotine abuse. From the 762 pregnancies, there were 782 live births, 3 miscarriages, and 1 still birth.³² Compared with the Mainz birth registry and the standard references for West-European infants, there were no differences in birth weight, body length, or head circumference. In the study population there were 5 congenital malformations: Talipes equinovarus (clubfoot), renal duplication, cleft lip, single umbilical artery, and aplasia of corpus-callosum (absence of the corpus-callosum of the brain plus laryngo-tracheomalacia—cartilage in airway too soft and collapses during breathing). There were also 1 chromosome aberration (Trisomy 21) and 3 deformities: 2 cases of talipes calcaneus (weakness or absence of calf muscle so toes point up and person walks on heels) and 1 case of talipes adductus (inversion of foot with only the outer side of sole touching the ground).

In 8 of the 9 newborns with birth defects, a causal relationship with Sinupret was completely ruled out.³² In the case of single umbilical artery, it was determined that Sinupret could have theoretically caused the adverse event (AE) but not likely because Sinupret was taken at the 21st week of gestation and single umbilical artery deformity rarely occurs late in pregnancy.^{32,33} Also the patient had other risk factors for birth defects. One case of miscarriage was ruled to be theoretically possibly caused by Sinupret because the miscarriage occurred shortly after ingestion of Sinupret.³² However, the patient also had other risk factors that could have contributed to the miscarriage. The birth defect incidence rate in this study was 1.1%. This is lower than expected considering that the prevalence of malformation is 2-3% in passive registries and 6-7% in active registries.^{34,35} The authors concluded that a reasonable correlation between the intake of Sinupret and teratogenic or embryotoxic effects was not proven.³²

ADVERSE EFFECTS/SAFETY DATA

Pre-clinical Toxicology

The toxicity of Sinupret is regarded as very low. The acute toxicity is low after administration in rats and rabbits, the no-effect level was 60-100 times the recommended human dose.¹

In chronic toxicity tests, oral administration of up to 1000 mg/kg/day in rats did not produce clinical, macroscopic, ophthalmic, weight, or food intake changes. No animals died during the study.³⁶

In reproductive toxicity tests, there were no Sinupret-induced negative effects on breeding rats or their off-spring. Mating behavior, fertility, litter size, and developmental body weight were normal.³⁷ High doses of Sinupret during organogenesis did not cause any toxicity to the embryo or fetus.³⁸

The non-mutagenicity of Sinupret was verified with the Ames test, the micronucleus assay *in vivo*, and with the unscheduled DNA synthesis test *in vivo*.^{1,39} The results demonstrate that Sinupret is non-mutagenic and does not contain any carcinogenic substances.^{1,40}

Human Safety Data

According to information from the manufacturer, Sinupret has been safely used in millions of doses over 35 years.⁴¹ Reported side effects include gastrointestinal (GI) disorders and hypersensitivity (allergic) reactions. In these cases, intake of Sinupret should be discontinued and a physician should be consulted. At the first sign

of a hypersensitivity reaction Sinupret should not be taken again. According to the manufacturer, the incidence of adverse drug reactions in clinical trials is 1%, based on 6849 patients.³¹ The incidence of spontaneous adverse drug reactions in the period from 1973 to October 2008 is approximately 1 per 1,000,000 treatments, based on the sum of approximately 214 million treatments.³¹

A post-marketing surveillance study of 3187 patients who were 1–94 years old reported that the AE rate was 0.8% (8/1013) for Sinupret (product type not specified), compared with the AE rate of 1.0% (3/313) for ambroxol, 4.3% (12/277) for N-acetylcysteine, and 5.8% (4/69) for myrtilol.^{42,43} When a second medication was prescribed concomitantly, the AE rate for all of the compounds increased.⁴³ The rate of AEs was 3.4% (27/792) when Sinupret was taken with concomitant medication (medications not specified).⁴³ In the post-surveillance study, 8 of the 1013 patients treated with Sinupret without concomitant medication reported GI symptoms (n = 7) or dizziness (n = 1) as AEs.⁴³ Three of these cases were determined to be probably caused by Sinupret (it is unclear which cases), 1 was determined to be not caused by Sinupret (it is unclear which case), 1 case had a questionable association, and 3 cases did not have enough information for an assessment to be made.⁴³

DRUG INTERACTIONS

To date there are no known drug interactions.^{1,41}

Smoking should be discontinued during the bronchial infection and treatment with Sinupret because smoking lowers the efficacy of treatment.⁴²

REGULATORY STATUS IN VARIOUS COUNTRIES

ASIA: Sinupret is registered as an herbal drug (China, Hong Kong, Indonesia, Korea, Malaysia, Mongolia, Philippines, Thailand).

EASTERN EUROPE/EURASIA: Herbal drug (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Macedonia, Moldavia, Ukraine, Uzbekistan).

EUROPEAN UNION: Herbal drug (Austria, Czech Republic, Denmark, Germany, Hungary, Latvia, Lithuania, Luxembourg, Poland, Romania, Slovakia, Slovenia, Sweden).

LATIN AMERICA: Herbal drug (Mexico).

MIDDLE EAST: Herbal drug (United Arab Emirates, Egypt).

RUSSIA: Herbal drug.

SINGAPORE: Sanitary Registration, sold as a health supplement.

SWITZERLAND: Herbal drug.

USA: Dietary supplement through notification under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

PATENTS

There are currently no international Sinupret patents.

CLINICAL REVIEW

According to documentation provided by Bionorica, the manufacturer, from inception of Sinupret to January 2002, the efficacy of Sinupret has been evaluated in 5 placebo-controlled studies, 7 comparative trials, and 1 post-marketing surveillance study. Since then, 2 systematic reviews of clinical trials, numerous abstracts, and several other studies have been published. Most of the scientific literature is published in German. This monograph reviews all of the studies that have been published in English or translated into English from inception to October 2008.

The studies reviewed here include a total of 4 clinical trials on the efficacy of Sinupret preparations for treating acute sinusitis. One study was in children and only 2 of the 4 studies have been published in their entirety in English (the other two were abstracts

from conference proceedings). The studies reviewed here also include 2 clinical trials evaluating the efficacy of Sinupret for treating chronic sinusitis. Only one of these trials has been published in a peer-reviewed journal, the other is an abstract from a conference proceeding. One meta-analysis evaluating Sinupret for the treatment of sinusitis has also been included in the clinical review. The meta-analysis is interesting from the perspective that it includes 4 clinical trials, three of which are unpublished reports that have not been translated into English and as a consequence have not been reviewed in this monograph. The efficacy of Sinupret for treating bronchitis is reviewed in 2 clinical trials; unfortunately, these reviews are based solely on data presented at conference proceedings; peer-reviewed publications were not available in English. A post-marketing surveillance study of patients with bronchitis is also reviewed.

A systematic review of various botanical products used for acute or chronic sinusitis identified 4 randomized controlled trials on Sinupret.⁴⁴ The authors conclude, "There is some evidence that Sinupret and bromelain [an enzyme from pineapple (*Ananas comosus*, Anonaceae)] may be effective adjunctive treatments in acute rhinosinusitis."

Acute Sinusitis

Neubauer & Marz, 1994.⁴⁵ A randomized, placebo-controlled, double-blind trial was conducted in men (mean age: 24.5 years) with acute bacterial sinusitis who were receiving antimicrobial (Vibramycin, Pfizer, United States) and decongestant (Otriven, Novartis, Germany) therapy. The purpose was to determine whether the response rates could be improved by adding Sinupret to the therapeutic regimen. Patients were treated 3 times per day with 2 Sinupret Sugar Coated tablets (n = 81) or placebo (n = 79) for 2 weeks in addition to the standard pharmaceutical therapy. Patients were randomized to treatment groups via a computer generated sequence. The primary outcome measure was sinus radiographic findings (rated as completely opaque, shadowed, or nothing abnormal). Entry criteria ensured that all patients had opaque sinus radiograms at baseline. Compared with placebo-treated patients, significantly more patients in the Sinupret group had improvements from baseline on their radiograms (p = 0.008). Changes in clinical signs showed good correlation with the radiographic findings, with significantly more Sinupret-treated patients having improvement in mucosal swelling, nasal obstruction, and headache (p-value not provided). According to the patient assessment, significantly more Sinupret-treated patients found treatment favorable than placebo-treatment (p < 0.001). Tolerability (i.e., safety profile) was good. There were no drug-herb interactions. The authors conclude that Sinupret can enhance basic (i.e., conventional drug) therapy.⁴⁵

The authors' conclusions, however, appear to be too broad. Rather than concluding that Sinupret can enhance basic therapy, the evidence from this trial suggests that the authors should have concluded that Sinupret can enhance the specific therapy evaluated in the study. That is, a more accurate conclusion would be that Sinupret enhances Vibramycin and Otriven treatment of acute sinusitis, or that Sinupret appears to act as an adjunct with Vibramycin and Otriven.

Biebach & Kramer, 2004.⁴⁶ The efficacy and safety of Sinupret was evaluated in children (n = 3109) with acute sinusitis. Girls and boys (n = 1638 girls; n = 1471 boys; mean age 6.9 years) with typical symptoms of sinusitis participated in this open-label, multicenter study conducted at 967 medical practices in Germany. The dosage of Sinupret drops varied with the patients' age. Two-thirds (64%) of the children received an average of 20 Sinupret drops 3 times per

day. The number of drops was slightly reduced over the course of the study; specific details were not reported. In lieu of the drops, 10% of the children aged 2-6 years received 1 Sinupret Sugar Coated tablet 3 times per day and 26% children aged 7-12 years received 1 Sinupret Sugar Coated tablet 3 times per day. The authors did not report the duration of treatment. At baseline the most frequently documented symptoms were "much" and "viscous" nasopharyngeal discharge, impaired nasal breathing, and "moderately severe" cough. At the final check-up (average of 12 days after entering the study), 93% of the patients reported "little" nasal discharge or no discharge and 90% of the cases reported the discharge as "thin" and "clear." At study end only 0.3% of the children reported severe impairment of nasal breathing and 75% had no cough. The effects of the 2 dosage forms were similar in children 7-12 years old. However, in the children 2-6 years old the Sugar Coated tablets were slightly superior to the drops in treating stuffy nose and cough, while the drops were more effective at improving facial pain and headache. Most of the physicians (88%) judged Sinupret to be "very good" or "good." Approximately 74% of the patients were treated with concomitant medications, including rhinological agents and/or antibiotics. There were 25 AEs (0.8%), all classified as not severe and self-limiting. Most of the AEs were gastrointestinal complaints and skin reactions. The investigators attributed 50% of the AEs to the concomitant medications. The authors concluded that the study documents the efficacy and tolerability of Sinupret in children.⁴⁶

A limitation of this study was that there was no placebo group or no untreated control group. Acute rhinitis is often a self-limiting disease,⁴⁶ so a control group is necessary to prove efficacy. Without a control group there is no way to know definitively if Sinupret was producing an effect. Another limitation of the study was the flexible dosing and no report of the treatment duration, and a large percentage of the patients were taking concomitant cold/flu medication. Nevertheless, one conclusion from this trial is the high degree of safety of Sinupret, particularly since half of the AEs were observed in patients taking concomitant pharmaceutical preparations.

Kraus & Schwender, 1992.⁴⁷ A randomized, open-label, comparative study was conducted in patients at the Germany Army Hospital (Bundeswehrkrankenhaus) in Amberg, Germany. The patients (n = 134), who had radiologically certified acute sinusitis, were treated for 3 weeks with Sinupret Sugar Coated tablets (dose not reported) or GeloMyrtol[®] Forte (Gelomyrtol, Germany); a mucolytic agent containing volatile oils of myrtle (*Myrica gale*, Myricaceae), lime (*Citrus* spp., Rutaceae; species unreported), pine (*Pinus* spp., Pinaceae, species unreported), and eucalyptus (*Eucalyptus* spp., Myrtaceae; species unreported). After 3 weeks of treatment the percent of improvement was equivalent between the treatments, with 49% of patients in both groups classified as having "nothing abnormal detected" or "improved." Note that this review lacks some details because it is from an abstract presented at an international conference.⁴⁷ A peer-reviewed manuscript was not available.

A limitation of the study was that there was no untreated or placebo control group. It is unclear whether the 49% of patients who improved at 3 weeks responded to therapy or if the sinusitis resolved spontaneously.

Braun & Marz, 1990.⁴⁸ A randomized, open-label, comparative study was conducted in patients at the Germany Army Hospital (Bundeswehrkrankenhaus) in Amberg, Germany. The patients (n = 114), who had x-ray proven acute sinusitis, were treated for 21 days with Sinupret Sugar Coated tablets (2 tablets, 3 times per day) or N-acetylcysteine (manufacturer identity not reported; 200 mg, 3 times per day). Concomitant medication was permitted. After 21 days of treatment, as determined by x-ray, 12.3% (7/57) of Sinupret-treated patients improved and 56.1% (32/57) were without pathologic findings, which was similar to 13.7% (7/51) of N-acetylcysteine-treated

patients who improved and 43.1% (22/51) who were without pathologic findings. Approximately 85% of the Sinupret-treated patients and 86.8% of N-acetylcysteine-treated patients reported that they were “improved” or “cured.” The authors concluded that Sinupret was at least as effective as N-acetylcysteine. Note that this review lacks some details because it is from an internal report abstract.⁴⁸ A peer-reviewed manuscript was not available.

This study is limited by the need for an untreated or placebo control group. Also, the researchers permitted the use of concomitant medications, which could affect the outcome. The abstract did not detail the use of concomitant medications.

Melzer J et al, 2006.⁴⁹ A systematic review identified 2 placebo-controlled trials with almost identical design that could be examined by meta-analysis.^{45,50} These trials were considered to be “key” trials. In both of these studies Sinupret was used as an adjunct to standard care of acute and chronic sinusitis. Nearly all of the participants (98-99%) were treated with antibiotics and decongestants. The studies included a predominantly male population of young adults (mean \leq 29 years old). Patients received placebo (n = 160) or Sinupret (n = 159, 2 Sugar Coated tablets 3 times per day⁴⁵ or 50 drops 3 times per day⁵⁰) for 14 days. The pooled analysis showed that the patients’ global assessment was that Sinupret was significantly better than placebo (p < 0.001). Compared with placebo, Sinupret had significantly better rates of absence of any symptom (p < 0.05, 39% vs 51%, respectively) or objective sign (p < 0.05, 24% vs. 36%, respectively).⁴⁹ Sinupret was significantly better in reducing drain obstruction (p < 0.01) and headache (p < 0.05) compared with placebo. When the analysis was restricted to patients with acute sinusitis the results were similar to the total study population, with Sinupret producing a significantly better “cure” and “improvement” rate than placebo (p < 0.001). A multiple stepwise regression analysis confirmed that there was a highly significant difference between treatments (p-value not reported).⁴⁹ Sinupret was well tolerated and had an incidence of AEs that was comparable to placebo.

In the same systematic review, Melzer J et al⁴⁹ also identified 2 comparative trials with almost identical design that could be examined by meta-analysis.^{51,52} These trials were likewise considered to be “key” trials. The studies included only men, with a mean age of 23 years in one study⁵² and 40 years in the other study.⁵¹ Patients with sinusitis received ambroxol (n = 150, 100 drops 3 times per day) or Sinupret (n = 151, 50 drops 3 times per day) for 14 days. Antibiotics were co-prescribed in 12% of the Sinupret-treated patients and 15% of the ambroxol-treated patients, and 75% of both groups were treated with decongestants. The primary efficacy variable was the patients’ global assessment. There was no significant difference in the percent of Sinupret- or ambroxol-treated patients who were rated as “cured” or “improved.” Likewise, when only the patients with acute sinusitis were analyzed, there was no significant difference in the global assessment. When looking at the secondary variables (symptoms), pyorrhea (pus discharge) and headache were more frequently improved with Sinupret (p < 0.05).⁴⁹ A multiple stepwise regression analysis confirmed that there was no significant difference between treatments.⁴⁹

Three of the studies compared by Melzer J et al (described above) are not individually reviewed in this monograph because they are unpublished reports that have not been translated into English. One is a double-blind, placebo-controlled trial on patients with acute sinusitis by Berghorn et al (1990)⁵⁰ and two are double-blind clinical trials published in 1990 by Simm & Pape⁵¹ and in 1992 by Wahls⁵² that compared Sinupret against a nasal drop in cases of acute sinusitis.

Acute Sinusitis Summary

Aside from the one pediatric study, it is unusual that all of the studies included mostly men. There are no known gender differ-

ences in the incidence, clinical presentation, or clinical course of sinusitis.⁴⁹ Nonetheless, it might be preferable if the studies evaluated the general population and not just men. Based on the results of 1 placebo-controlled study and the meta-analysis of 2 placebo-controlled trials it appears that Sinupret is effective at augmenting the effects of standard pharmaceutical therapy. A small meta-analysis revealed that Sinupret is as effective as ambroxol. Additional studies are needed to confirm the findings, and placebo or untreated control studies are needed to determine the efficacy of Sinupret as a monotherapy for the treatment of acute sinusitis. More methodologically rigorous studies in children are also needed.

Chronic Sinusitis

Richstein & Mann, 1999.⁵³ A randomized, double-blind, placebo-controlled trial was conducted in patients (n = 31) with chronic sinusitis. The patients (age range: 6-73 years) were treated for 7 days with either placebo, 2 Sinupret Sugar Coated tablets 3 times per day, or 50 Sinupret drops 3 times per day. At baseline both the Sinupret-treated patients (n = 16) and placebo-treated patients (n = 15) had similar symptoms (headache, fever, nasal discharge). Radiologic and ultrasonographic findings of the paranasal sinuses revealed that 12 of 16 Sinupret-treated patients had considerable improvement or complete recovery compared with 6 of 15 placebo-treated patients (p-value not reported). Significantly more patients treated with Sinupret were headache-free after treatment compared with patients treated with placebo (p = 0.025). X-ray findings of the paranasal sinuses showed significantly greater improvement with Sinupret treatment than with placebo treatment (p = 0.001). There was no difference between the groups on posterior nasal secretion. The tablets and liquid formulations performed similarly. There were no adverse effects. The authors concluded that Sinupret had a positive effect on subjective and objective findings in patients with chronic sinusitis.⁵³

As with acute sinusitis, chronic sinusitis can also spontaneously recover. Nonetheless, this study showed that there was a benefit beyond that of placebo treatment. Although this study is limited by its small size, the objective measures provide credibility to support the conclusion that Sinupret is efficacious in treating chronic sinusitis.

Braum & Marz, 1990.⁴⁸ A randomized, open-label, comparative study was conducted in patients at the Germany Army Hospital (Bundeswehrkrankenhaus) in Amberg, Germany. The patients (n = 46), who had x-ray proven exacerbation of chronic sinusitis, were treated for 21 days with Sinupret Sugar Coated tablets (2 tablets, 3 times per day) or N-acetylcysteine (manufacturer identity not reported; 200 mg, 3 times per day). Concomitant medication was permitted. As determined by x-ray, 23.5% (4/17) of Sinupret-treated patients improved and 41.7% (10/24) were without pathologic findings compared with 41.7% (10/24) of N-acetylcysteine-treated patients who improved and 20.8% (5/24) who were without pathologic findings after treatment (it is not clear if the assessment was made after 7 days or 21 days). Approximately 65% of the Sinupret-treated patients and 61.9% of N-acetylcysteine-treated patients reported that they were “improved” or “cured.” The authors concluded that Sinupret was equivalent to N-acetylcysteine therapy. Note that this review lacks some details because it is from an internal report abstract.⁴⁸ A peer-reviewed manuscript was not available.

This study is limited by the size and the lack of an untreated or placebo control group. Also, the researchers permitted the use of concomitant medications, which could affect the clinical outcome. The abstract did not detail the use of concomitant medications.

Melzer J et al, 2006.⁴⁹ A systematic review identified 2 placebo-controlled trials and conducted a meta-analysis on the data.^{45,50} In both of these studies Sinupret was used as an adjunct to standard care of chronic sinusitis. Nearly all of the participants (98–99%) were treated with antibiotics and decongestants. The studies included a predominantly male population of young adults (mean \leq 29 years old). Patients with chronic sinusitis received placebo ($n = 30$) or Sinupret ($n = 24$, 2 Sugar Coated tablets 3 times per day⁴⁵ or 50 drops 3 times per day⁵⁰) for 14 days. In patients with chronic sinusitis there was no statistical difference between Sinupret treatment and placebo in the rate of “cure” or “improvement.”⁴⁹ Sinupret was well tolerated and had an incidence of AEs that was comparable to placebo.

In the same systematic review, Melzer J et al⁴⁹ also examined by meta-analysis 2 comparative trials with almost identical design.^{51,52} The studies included only men, and the mean age was 23 years in one study⁵² and 40 years in the other study.⁵¹ Patients with chronic sinusitis received ambroxol ($n = 26$, 100 drops 3 times per day) or Sinupret ($n = 36$, 50 drops 3 times per day) for 14 days. Some patients were co-prescribed antibiotics and/or decongestants to be taken with ambroxol or Sinupret (percent of patients not reported). However, the only baseline differences between the groups were duration of chronic sinusitis and body weight. The primary efficacy variable was the patient’s global assessment. Significantly more Sinupret-treated patients than ambroxol-treated patients were rated as “cured” or “improved” ($p = 0.036$). However, when looking at the secondary variables (symptoms) there were no significant differences between treatment groups.⁴⁹ The authors acknowledge that the findings require confirmation by larger studies.

Three of the studies compared by Melzer J et al (described above) are not individually reviewed in this monograph because they are unpublished reports that have not been translated into English. One study is a double-blind, placebo-controlled trial on 21 patients with chronic sinusitis (Berghorn et al 1990)⁵⁰ and the other 2 are comparative trials (Simm & Pape⁵¹ and Wahls⁵²).

Chronic Sinusitis Summary

A placebo-controlled study demonstrated that Sinupret may benefit patients with chronic sinusitis and a meta-analysis concluded that Sinupret is equal or better than ambroxol. However, a meta-analysis of 2 placebo-controlled studies concluded that Sinupret as adjunct therapy for chronic sinusitis is not significantly better than placebo. All of these studies were small and should be viewed as preliminary findings. A larger prospective trial is needed to confirm Sinupret’s efficacy in patients with chronic sinusitis.

Acute Bronchitis

Pinnow & Egenteinmaier, 1992.⁵⁴ A blinded, active-controlled study evaluated the efficacy of Sinupret compared with a mucolytic agent in patients with uncomplicated acute bronchitis. Patients ($n = 158$) were treated with either Sinupret Sugar Coated tablets (dose not reported) or N-acetylcysteine (Mucret[®], Astra Zeneca, sustained release tablets—dose not reported) for an unreported duration. The age and gender of the patients were not reported. The efficacy of Sinupret was statistically equivalent to the pharmaceutical treatment. Sinupret had good or better effects on frequency of cough, sensation of pain, expectoration, and auscultation (breathing sounds) (p -value not reported). Note that this review lacks specific details because it is from an abstract presented at an international conference.⁵⁴ A peer-reviewed manuscript was not available.

Egenteinmaier & Marz, 1991.⁵⁵ A double-blinded, active-controlled study evaluated the efficacy of Sinupret compared with a mucolytic agent in patients with uncomplicated acute bronchitis. Patients ($n = 80$) were treated with either Sinupret drops (dose not

reported) or ambroxol hydrochloride drops (Mucosolvan[®], Boehringer Ingelheim GmbH—dose not reported) for 14 days. The age and gender of the patients was not reported. After 14 days of treatment the efficacy of Sinupret was significantly better than the efficacy of ambroxol in well-matched patients ($p < 0.05$). Sinupret was superior to ambroxol in daytime coughing frequency and sputum/amount (p -values not reported). Note that this summary lacks specific details because it is from an abstract presented at an international conference and an internal report abstract.^{54,55} A peer-reviewed manuscript was not available.

Ernst et al, 1997.^{42,56} The efficacy and safety of Sinupret for treating acute bronchitis or exacerbated chronic bronchitis was evaluated in a post-marketing surveillance study. General and internal medicine test centers in Germany ($n = 330$) recruited 3187 patients who were 1–94 years old. The physicians were instructed to treat 5 patients with Sinupret (2 sugar coated tablets 3 times per day or 50 drops 3 times per day for adults) and 5 patients with an expectorant of their choice (dose recommended by manufacturer). Using a specially prepared form, physicians assessed clinical symptoms at baseline and at the end of the 10-day treatment period. A total of 72 different expectorants were used, classified into 7 categories: Sinupret (56.6%, 1805/3178), ambroxol (18.1%, 576/3178), N-acetylcysteine (17.1%, 544/3178), myrtol (3.5%, 111/3178), bromhexine (2.4%, 76/3178), carbocysteine (0.7%, 22/3178), and others (1.6%, 51/3178). The authors concluded that Sinupret was at least as effective as the other expectorants, if not superior.⁴² The adverse event rate was 0.8% (8/1013) for Sinupret, compared with the AE rate of 1.0% (3/313) for ambroxol, 4.3% (12/277) for N-acetylcysteine, and 5.8% (4/69) for myrtol.^{42,42,43} The rate of AEs was 3.4% (27/792) when Sinupret was taken with concomitant medication (medications not specified).⁴³

A limitation of this study was that there were no statistics reported. The authors state that the differences between treatments were small for body temperature, diurnal coughing, coughing pain, and cough quality but “marked for the remaining criteria” (nocturnal coughing, sputum quality, sputum viscosity, sputum type, patient criteria, and auscultation). However, there was no statistical analysis reported so it is unknown whether the differences were statistically or clinically relevant. Further, Sinupret appears to be superior to the other treatments when the data from all of the other expectorants are compiled. This compilation is not the preferred method because the 72 different expectorants can have vastly different effects. There is very little difference between treatments when the most popular treatment (ambroxol) is compared with Sinupret. Hence, the study might not actually prove superiority over other expectorants, but rather equivalency. It would appear that Sinupret is as effective as the other expectorants; however, concomitant medications were permitted. The authors report only that concomitant medications were used but do not elaborate. The impact of concomitant medications on study outcome is not known.

Bronchitis Summary

The acute bronchitis studies available for review were all comparator studies; none were placebo controlled. Thus, efficacy cannot be concluded based solely on a claim of equivalence to other treatments. Placebo-controlled or untreated control studies are needed to confirm the efficacy of Sinupret for treating bronchitis.

SCIENTIFIC AND CLINICAL SUMMARY

This review of the pharmacological and clinical literature on Sinupret suggests that this phytochemical preparation has a relatively significant level of safety and efficacy data compared to many other botanical or otherwise natural medicinal preparations intended for use in maintaining the health of sinuses and the upper respiratory tract. The scientific and clinical literature on Sinupret

supports pharmacological mechanisms of mucolytic, secretolytic, anti-inflammatory, antibacterial, antiviral, and immunological activity, some of which has been documented in open-label and randomized controlled human clinical trials. The overall safety of Sinupret has been extensively documented in pharmacovigilance data based on widespread and long-term use in Germany and other European countries, as well as other post-market surveillance safety data, including relative safety during pregnancy.

MANUFACTURER INFORMATION

Manufacturer: Bionorica AG. International Division, P.O. Box 1851, 92308 Neumarkt, Germany. Tel: +49/(0)91 81/231-90, Fax: +49/(0)91 81/231-265. Sinupret products are imported into the United States by Bionorica LLC, 903 Calle Amanecer, Suite 110, San Clemente, CA 92673. Tel: (949) 361-4900. www.bionorica.com.

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CONFLICT OF INTEREST DISCLOSURE

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Table: Selected Clinical Trials on Sinupret®

Acute Sinusitis						
Author /Year	Subject	Design	Duration	Dosage	Preparation	Results
Neubauer & Marz, 1994	Acute sinusitis	R, PC, DB n=160 men w/ acute bacterial sinusitis who were receiving antimicro- bial (Vibramycin) & decongestant (Otriven) therapy (mean age 24.5 yrs)	2 wks	2 tablets 3x/d or placebo	Sinupret® Sugar Coated tablets	Patients in Sinupret group had greater improvement on their radiograms than those given placebo. Significantly more Sinupret-treated patients also showed improvement in mucosal swelling, nasal obstruction, & headache. According to patient assessment, significantly more Sinupret-treated patients found treatment favorable than those given placebo.
Biebach & Kramer, 2004	Acute sinusitis	OL, MC n=3109 children w/ typical symp- toms of sinusitis, including "much" and "viscous" nasopharyngeal discharge, impaired nasal breathing, & "moderately severe" cough. (n = 1638 girls and n = 1471 boys, mean age 6.9 years)	NR	64% of children received avg of 20 drops 3x/d. The number of drops was slightly reduced over course of study; specific details were NR. 10% of children (age 2-6 years) received 1 tablet 3x/d. 26% of chil- dren age 7-12 years received 1 tablet 3x/d. Concomitant medication was given to 74% of the children.	Sinupret drops & Sinupret Sugar Coated tablets	At final check-up, 93% of patients reported "little" nasal discharge or no discharge & 90% of cases reported discharge as "thin" & "clear." Only 0.3% of the children reported severe impairment of nasal breathing & 75% had no cough. The effects of 2 dosage forms were similar in children aged 7-12 years. However, in children age 2-6 years, tablets were slightly superior to drops in treating stuffy nose & cough, while drops were more effective at improving facial pain & headache.

Table: Selected Clinical Trials on Sinupret® Continued**Acute Sinusitis Continued**

Kraus & Schwender, 1992	Acute sinusitis	R, OL, Cm n=134 (gender NR but likely to be predominantly men since patients were at Germany Army Hospital, age NR)	3 wks	Sinupret dose NR or GeloMyrtol® forte dose NR	Sinupret Sugar Coated tablets, GeloMyrtol 300 mg capsules	Percent of improvement was equivalent between treatments, w/ 49% of patients in both groups classified as having “nothing abnormal detected” or “improved.”
Braum & Marz, 1990	Acute sinusitis	R, OL, Cm n=114 (gender NR but likely to be predominantly men since patients were at the Germany Army Hospital, age NR)	21 days	Sinupret: 2 tablets 3x/d or N-acetylcysteine: 200 mg 3x/d	Sinupret Sugar Coated tablets, N-acetylcysteine preparation NR	As determined by x-ray, 12.3% of Sinupret-treated patients improved & 56.1% were w/out pathologic findings, while 13.7% of N-acetylcysteine-treated patients improved & 43.1% were without pathologic findings. Approximately 85% of Sinupret-treated patients & 86.8% of N-acetylcysteine-treated patients reported that they were “improved” or “cured.”

Chronic Sinusitis

Richstein & Mann, 1999	Chronic sinusitis	R, DB, PC n=31 (gender NR, age range: 6-73 years)	7 days	2 tablets 3x/d, or 50 drops 3x/day, or placebo	Sinupret Sugar Coated tablets, Sinupret drops	Radiologic & ultrasonographic findings of paranasal sinuses revealed that 12 of 16 Sinupret-treated patients had considerable improvement or complete recovery compared w/ 6 of 15 placebo-treated patients. Significantly more patients treated w/ Sinupret were headache-free after treatment. X-ray findings showed that paranasal sinuses were improved significantly more w/ Sinupret treatment. There was no difference between groups on posterior nasal secretion.
Braum & Marz, 1990	Exacerbation of chronic sinusitis	R, OL, Cm n=46 (gender NR but likely to be predominantly men since the patients were at the Germany Army Hospital, age NR)	21 days	Sinupret: 2 tablets 3x/d or N-acetylcysteine: 200 mg 3x/d	Sinupret Sugar Coated tablets, N-acetylcysteine preparation NR	As determined by x-ray, 23.5% of Sinupret-treated patients improved & 41.7% were w/out pathologic findings, while 41.7% of N-acetylcysteine-treated patients improved & 20.8% were w/out pathologic findings (although it is not clear if assessment was made after 7 days or 21 days). Approximately 65% of Sinupret-treated patients & 61.9% of N-acetylcysteine-treated patients reported that they were “improved” or “cured.”

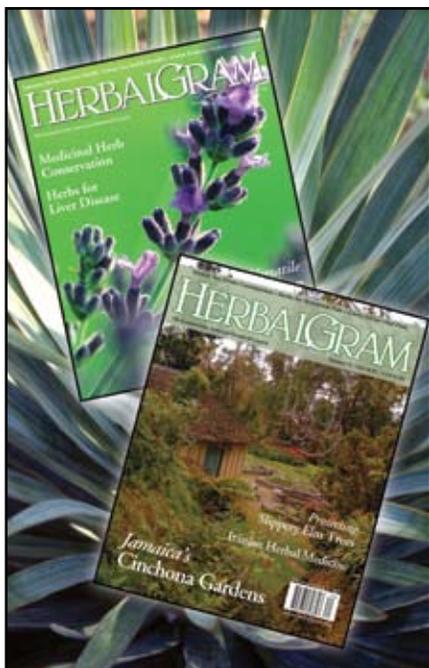
Acute Bronchitis

Pinnow & Egentmaier, 1992	Uncomplicated acute bronchitis	Cm, B n=158 (gender NR, age NR)	NR	Sinupret: dose NR or N-acetylcysteine: dose NR	Sinupret Sugar Coated tablets, N-acetylcysteine sustained release tablets	Efficacy of Sinupret was statistically equivalent to N-acetylcysteine. Sinupret had good or better effects on frequency of cough, sensation of pain, expectoration, & auscultation (breathing sounds).
Egentmaier & Marz, 1991	Uncomplicated acute bronchitis	DB, Cm n=80 (gender & age NR)	14 days	Sinupret: dose NR or ambroxol hydrochloride (Mucosolvan®): dose NR	Sinupret drops, ambroxol drops	Efficacy of Sinupret was significantly better than efficacy of ambroxol in well-matched patients. Sinupret was superior to ambroxol in daytime coughing frequency and sputum/amount.

Key: B: blinded, Cm: comparative, C: controlled, d: day, DB: double-blind, MC: multicenter, NR: not reported, OL: open-label, PC: placebo-controlled, PG: parallel group, R: randomized

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