



AMERICAN BOTANICAL COUNCIL

PROPRIETARY BOTANICAL PRODUCT

CLINICAL OVERVIEW 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.

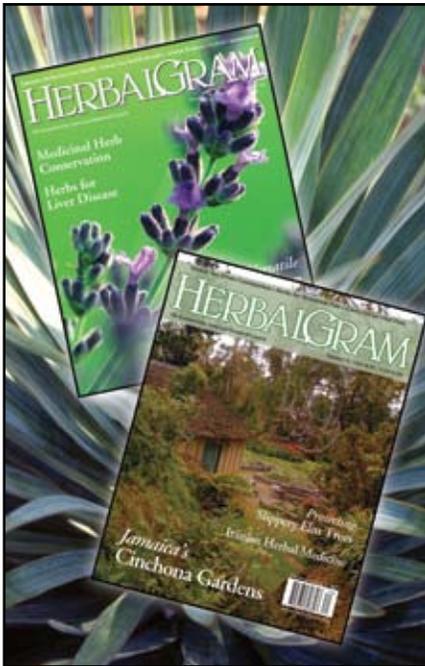
Studies included in the text of the Clinical Review section of the full monograph include a total of 4 clinical trials on the efficacy of Sinupret preparations for treating acute sinusitis. One study was in children and only 2 of the 4 studies have been published in their entirety in English (the other 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 phytomedicinal 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.

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