Comparison of the Efficacy and Safety of the Fixed-Dose Combination of Xylometazoline and Dexpanthenol Contained in the Medicinal Product Septanazal® and Xylometazoline Alone in Nasal Congestion in Patients with Acute Rhinitis

Nataša Uranič

Published in Med Razgl. 2018; 57 (4): 613–22

Key words
acute rhinitis, nasal congestion, xylometazoline, dexpanthenol, nasal spray, fixed-dose combination

Abstract

Acute rhinitis is an inflammation of the nasal mucosa. With adults it normally occurs 2–5 times per year. Nasal obstruction is the most inconvenient symptom, occurring due to the nasal mucosa congestion in response to inflammation. For this reason, nasal alpha sympathomimetic topical decongestants are the first in the line of choice in treatment of acute rhinitis. Several double-blind, randomised, controlled clinical studies demonstrated the benefit of nasal decongestants when used in a combination with a topical dexpanthenol. The goal of this study was to compare the efficacy of treatment of both sprays, i.e. nasal spray with a fixed-dose combination of xylometazoline and dexpanthenol (used in Septanazal® nasal spray, Krka, d. d., Novo mesto) and xylometazoline used as a monotherapy in reducing nasal congestion, and the effect of an addition of dexpanthenol on the healing of nasal mucosa inflammation in patients with acute rhinitis. At the start of the clinical study, 88% of patients evaluated nasal congestion as one of the most disturbing symptoms of acute rhinitis. This study showed that the fixed-dose combination of a decongestant and dexpanthenol, or the decongestant used independently, may have a positive effect on nasal congestion. However, a significantly greater effect in reducing nasal congestion was shown between Day 3 and Day 7 of active treatment with the use of a fixed-dose combination of xylometazoline and dexpanthenol. Dexpanthenol's positive effect was demonstrated after three days of treatment with a fixed-dose combination of xylometazoline and dexpanthenol. Apart from treating nasal congestion, the fixed-dose combination of a decongestant and dexpanthenol improves other symptoms of acute rhinitis during treatment such as: nasal discharge, dry nasal mucosa, burning sensation and tickling in the nose, sneezing and skin redness at the entrance to the nasal cavity. The study also demonstrated safety of the fixed-dose combination of xylometazoline and dexpanthenol, since a high percentage of patients did not experience adverse effects, and none of them had a serious adverse effect. The fixed-dose combination of two active ingredients, xylometazoline and dexpanthenol, in Septanazal® has been demonstrated to be effective and safe in the treatment of nasal congestion in patients with acute rhinitis.

Introduction

Viral infections of the upper respiratory tract are the main cause of acute rhinitis, which may affect people of all ages and which has a profound impact on the quality of their lives.[1] Acute rhinitis is a time-dependent disease, occurring 2–5 times per year in adults.[2, 3] Though mostly of a viral origin, acute bacterial rhino sinusitis may, however, develop in 0.5–2% of patients.[4] Nasal congestion is the most inconvenient symptom of acute rhinitis for most patients.

Nasal congestion is a subjective issue manifested as a sensation of getting inadequate air flow through the nose. It is most commonly due to nasal mucosa inflammation, which is why nasal decongestants, namely α-sympathomimetic topical products, are the main choice for symptomatic local treatment of acute rhinitis symptoms.[5]

Several double-blind randomized controlled clinical studies have demonstrated greater therapeutic efficacy of nasal decongestants when used in a combination with topical dexpanthenol.[3, 6, 7] It is assumed that the protective effect of dexpanthenol on the nasal mucosa epithelium and the impact on mucociliary transport are the main factors that lead to better treatment results with decongestants, which also includes dexpanthenol. A double-blind controlled clinical study in 152 patients with acute rhinitis demonstrated better efficacy of the fixed-dose combination (xylometazoline and dexpanthenol) compared to the mono-product (xylometazoline) on parameters such as rhinorea, nasal obstruction, nasal swelling and nasal mucosal hyperaemia.[6]

Goal of the clinical study with Septanazal® was to compare treatment efficacy (nasal congestion reduction) with a nasal spray containing a fixed-dose combination of xylometazoline and dexpanthenol and monotherapy with xylometazoline, and to determine the effect of the addition of dexpanthenol on the healing of nasal mucosa inflammation in patients with acute rhinitis.

Septanazal® contains a fixed-dose combination of α-sympathomimetic compounds (xylometazoline) and vitamin-like compounds for topical use on the nasal mucosa (dexpanthenol). Xylometazoline hydrochloride is an imidazole derivative and α-adrenergic sympathomimetic. It has a vasoconstrictor action and thus reduces mucosa swelling. The effect usually occurs within five to ten minutes, shown as easier breathing through the nose due to reduced mucosa swelling and improved secretion drainage.[8-10] Dexpanthenol is an alcoholic analogue of the pantothenic acid, which protects the epithelium and facilitates wound healing.[8, 11, 12] It has been demonstrated to reduce nasal mucosa inflammation and irritation, as well as moistens nasal mucosa.[13] It is well worth combining xylometazoline and dexpanthenol, since the two active ingredients exhibit a synergistic action.[6]

Methods

This international, randomised, comparative double blind prospective clinical study was conducted in Slovenia and Croatia in the period from January 2017 to February 2018.

There were 154 patients with acute rhinitis aged 18–60 years that were included in the study. Patients who complied with the inclusion criteria were treated with one of the two investigational medicinal products (IMPs) – with a product containing xylometazoline (1 ml of nasal spray contains 1 mg of xylometazoline hydrochloride) or with a fixed-dose combination of xylometazoline and dexpanthenol (Septanazal® – 1 ml of nasal spray contains 1 mg of xylometazoline hydrochloride and 50 mg of dexpanthenol).
Patients were not included in the clinical study if they were hypersensitive to the active substances or to any of the excipients, if they had dry nasal inflammation, if they received local or systemic flu treatment, sympathomimetics or if they concomitantly received another nasal decongestant. Also excluded from

the study were patients with asthma, medication or chronic rhinitis, phaeochromocytoma, elevated intraocular pressure, and patients treated with monoamine oxidase inhibitors or other medicinal products that could increase blood pressure.
The clinical study did not include patients with a respiratory infection (including middle ear infection) within two weeks prior to Visit 1 that required them to take antibiotics. The study also excluded patients with a history of transsphenoidal hypophysectomy or other surgical procedures in which dura mater was exposed. Men or women with a nose injury suffered less than three months before the study, as well as smokers or former smokers (if they stopped smoking less than six months before the study) were also not included. We excluded pregnant women and nursing mothers and patients who took part in another clinical study 30 days prior to our clinical study.

Patients came in for three visits over a seven-day period. They were included into the clinical study on the day of being diagnosed with acute rhinitis. Visit 2 was done on the third day after inclusion, and Visit 3 on the seventh day after inclusion. The course of the clinical study and the methods used are presented in Table 1.

	Visit 1 (diagnosis of acute rhinitis and inclusion)	Visit 2 (third day after inclusion)	Visit 3 (seventh day after inclusion)
Approval of inclusion criteria	x		
Patient's medical history	x		
Randomisation	x		
Signed voluntary consent	x		
Rhinoscopy	x	x	x
Efficacy assessment on VAS	x	x	x
Efficacy assessment with SNOT-22si	x		x
Efficacy assessment of the addition of dexpanthenol and other secondary parameters	x	x	x
Overall assessment of the improvement of signs and symptoms during treatment (GAIB)		x	x
Adverse effect monitoring	x	x	x

VAS – visual analogue scale, SNOT-22si – sino-nasal outcome test

Table 1. Course of the 7-day clinical trial according to visits and the methods used for demonstrating the efficacy and safety of IMPs

Efficacy and safety assessment

The standard procedures for checking compliance with inclusion and exclusion criteria were general medical history, standard systematic medical examination and a pregnancy test.
All observed efficacy events were identified at Visits 1, 2 and 3. The investigator examined the right and left nasal cavities with a rhinoscopy and assessed the global passage of the nasal cavity with a scale from 0 to 10 (0 – complete passage of the nose, 10 – completely blocked nose). The patients assessed the rate of nasal passage and the onset of action after IMP was administered on a visual analogue scale (VAS).
Efficacy assessment of the addition of dexpanthenol and other secondary parameters (swelling and dryness of the nasal mucosa, burning sensation in the nose, formation of crusts, bleeding, redness of the nasal mucosa and skin redness at the entrance of the nose, sneezing, nasal discharge, nose

irritation) was assessed by the patients on a scale from 0 to 4 (0 – no problems/symptoms, 4 – very serious problems/symptoms).
The patients also filled in the SNOT-22si (sino-nasal outcome test) questionnaire containing 22 questions related to the symptoms of rhinosinusitis and their social/emotional consequences.[14] The questions were related to how the treatment influenced the quality of their lives – how the disease affected their sleep, the general daily feeling, and the senses of smell and taste. Each response was evaluated with a score from 0 to 5, depending on the severity of the symptoms/consequences (0 – the symptom/consequence does not cause problems, 5 – the symptom/consequence presents the worst possible problems). In the questionnaire the patients had to select five symptoms/consequences that had the greatest impact on their health. In order to obtain information on the efficacy of the medicine, the researcher also assessed the overall improvement of the Global Assessment of Improvement from Baseline (GAIB). GAIB contains seven marks (0 – completely improved condition, 6 – worse state than at baseline). GAIB was used to track active IMP treatment and compare the final status with the severity of the baseline condition. The GAIB score was also used to monitor the recurrence of congestion.
In order to assess the safety profile, adverse effects were monitored throughout the clinical study. On Visits 2 and 3, IMP safety was also assessed on the basis of the data obtained in patient interviews. The assessed and analysed observed adverse events were the overall incidence of adverse effects and the frequency of adverse drug reactions according to their type or the percentage of patients who did not discontinue treatment due to adverse effects. All adverse events were classified according to drug relation, intensity, severity, time to onset, frequency, need for treatment and degree of adverse effect expectation.

Results

The clinical study included 154 patients diagnosed with acute rhinitis, of which 80 patients were given xylometazoline, and 74 a fixed-dose combination of xylometazoline and dexpanthenol (Septanazal®). Among the included patients there were 100 women (65%) and 52 men (34%). In two patients, gender data was not recorded. The average age of patients was 39.2 years. The average weight was 73.5 kg, the average height was 172.3 cm and the average body mass index was 24.6 kg/m^2.

Efficacy

At the beginning of the clinical study, 88% of the patients involved estimated that nasal congestion was one of the most disturbing symptoms affecting their health. In all patients, regardless of whether they were treated with a fixed-dose combination of xylometazoline and dexpanthenol (Septanazal®) or only with xylometazoline alone, it was the investigator's assessment that the overall passage in both nasal cavities decreased statistically significantly, which clearly shows that nasal obstruction decreased from Visit 1 to Visit 3.
After IMP administration, the patient assessed the feeling of being unable to breathe through the nose at each visit on a scale from 0 to 4 (Figure 1), which directly implicates nasal congestion.

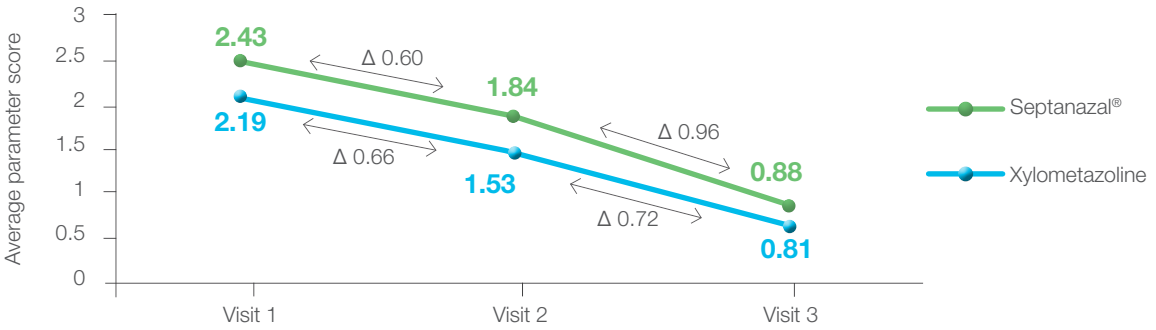
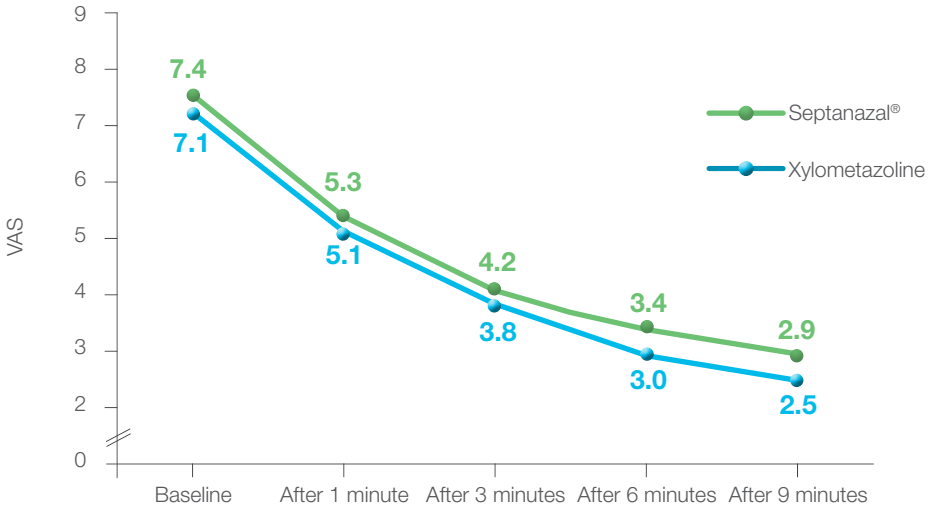


Figure 1. Average assessment comparison of the feeling of being unable to breathe through the nose between the two groups over the seven-day treatment period.

In both investigated groups, the observed parameter improved during treatment. The average subjective assessment decreased significantly from Visit 1 to Visit 3 (by 63% in the group treated with xylometazoline and by 64% in the group treated with Septanazal®), indicating the efficacy of treatment with IMP. The comparison of the average assessments of this symptom showed a difference between the groups at Visit 2. The estimated difference was 0.31 (Septanazal® 1.84, xylometazoline 1.53), which was statistically significant ($p < 0.027$). A comparison of the decrease in average estimates of the observed parameter during visits showed that the decrease in value between Visits 2 and 3 was statistically more significant in the group of patients treated with a fixed-dose combination of xylometazoline and dexpanthenol (Septanazal® by 0.96, xylometazoline by 0.72; $p < 0.028$). The differences between the groups between Visits 1 and 2, and Visits 1 and 3 were statistically insignificant.

In the treatment with both medicinal products it was shown that the subjective perception of nasal obstruction, also assessed by VAS, was significantly improved in comparison with the baseline condition. In both groups of patients, nasal congestion was significantly decreased within the first, three, six, and nine minutes after the first dose of IMP, as shown in Figure 2. There were no statistically significant differences between the two groups in the observed periods.



VAS – visual analogue scale, IMP – investigational medicinal product.

Figure 2. Nasal obstruction results prior to administration and one, three, six, and nine minutes after the IMP was administered at Visit 1.

The fixed-dose combination of xylometazoline and dexpanthenol as well as xylometazoline alone start to work already one minute after administration. The average estimated value of nasal obstruction in patients using a fixed-dose combination of xylometazoline and dexpanthenol was decreased by 28.2% in the first minute after administration, an additional 22% after three minutes, an additional 17.4% after six minutes and for an additional 15.8% after nine minutes. The final average nasal obstruction value after nine minutes was 2.9 according to VAS, which meant a 60.8% reduction in congestion versus the state before the first administration of the medicine.
In all patients, nasal congestion just prior to the first dose administration was assessed as strong and intense, significantly limiting the ability of patients to perform daily activities and maintain social relations. It also caused sleep disorders. All patients had only a mild congestion nine minutes after IMP was administered. Although congestion was still annoying, it did not disturb daily activities. The quality of life improved significantly.

The researchers assessed the response to treatment with an IMP in the two investigated groups as very good, since a considerable degree of progress was shown. In all patients there was a statistically significant improvement in the global assessment of signs and symptoms during treatment. In the group where patients were treated with a fixed-dose combination of xylometazoline and dexpanthenol the average score decreased by 52%, while in the group treated with xylometazoline it decreased by 47%, if we compare the average scores at Visits 2 and 3.

Comparing the average overall improvement of signs and symptoms among the two groups (Figure 3) shows a statistically significant difference at Visit 2; a higher grade was obtained in the group treated with a fixed-dose combination of xylometazoline and dexpanthenol ($p < 0.027$).

Figure 3. Global Assessment of Improvement from Baseline (GAIB) between the two groups (*$p < 0.027$) and between visits (**$p < 0.028$).

At Visit 3 the difference between the groups was not statistically significant. In the group treated with a fixed-dose combination of xylometazoline and dexpanthenol, the assessment, despite its higher value at Visit 2, decreased to the level of the group treated with xylometazoline. The reduction in average assessments at Visits 2 and 3 showed that the assessment decreased more in the group treated with a fixed-dose combination of xylometazoline and dexpanthenol (the difference between the groups was 0.24, and $p < 0.028$), indicating a statistically significant improvement in the symptoms and signs of the disease.

The improvement in the signs and symptoms of acute rhinitis, assessed by GAIB during the third and seventh day of treatment confirmed the notion that an addition of a dexpanthenol to a decongestant was a reasonable thing to do. The use of a fixed-dose combination of xylometazoline and dexpanthenol seems to be justified for the treatment of patients with nasal obstruction due to acute rhinitis.

The recurrence of nasal congestion for both IMPs in patients with acute rhinitis was tracked with the help of a GAIB questionnaire. Nasal congestion did not recur in any of the investigated groups, as the signs and symptoms of acute rhinitis improved in both groups.

The clinical study also demonstrated the effect of a fixed-dose combination of xylometazoline and dexpanthenol on nasal discharge, dryness of nasal mucosa, burning sensation in the nose, irritation in the nose, sneezing and redness of the skin at the entrance of the nose. All these parameters were statistically significantly reduced during the treatment of acute rhinitis, as shown in Figure 4.

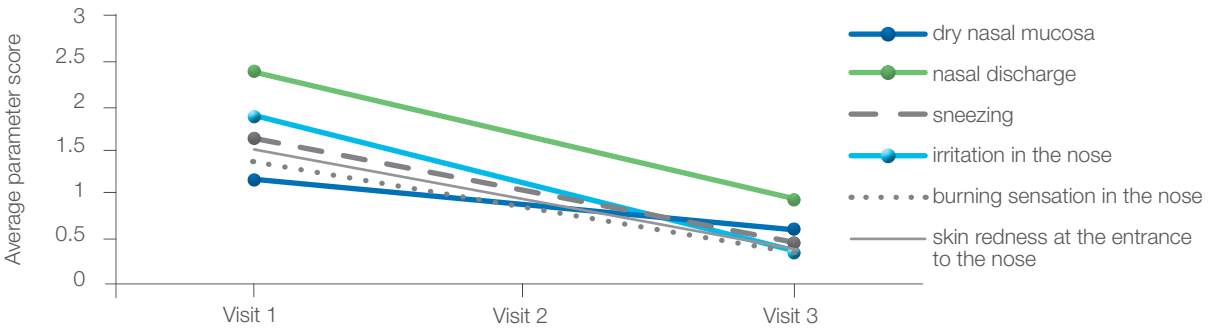


Figure 4. Monitoring of the symptoms of acute rhinitis (dry nasal mucosa, burning sensation in the nose, nasal discharge, nose irritation, sneezing and redness of the skin at the entrance of the nose) in patients treated with a fixed-dose combination of xylometazoline and dexpanthenol.

Nasal discharge is one of the symptoms that can affect the patient with acute rhinitis. The average assessed value was statistically significantly decreased during treatment with a fixed-dose combination of xylometazoline and dexpanthenol – at Visit 1 it was 2.32, at Visit 2 it was 1.62, and at Visit 3 the value was 0.96. During treatment, nasal discharge decreased by 59%.

In patients treated with a fixed-dose combination of xylometazoline and dexpanthenol, the dryness of nasal mucosa also decreased in a statistically significant manner. The average assessment at Visit 2 decreased by 22% in comparison with Visit 1. On Visit 3, the score dropped to 0.6 on a scale from 0–4, which meant an additional reduction of 36%. This parameter decreased by 50% during treatment.

Some decongestants may cause a burning sensation in the nose due to their composition. In this clinical study, this symptom statistically significantly decreased in the patients treated with a fixed-dose combination of xylometazoline and dexpanthenol. The initial average score decreased by 37% at Visit 2. At the last visit it dropped by 61% and finally reached 0.35 at the end on the scale from 0 to 4. During treatment, the estimated parameter in this group of patients decreased by 76%. At the end of the seven-day treatment period, patients hardly complained of a burning sensation in their noses.

In the group treated with a fixed-dose combination of xylometazoline and dexpanthenol, irritation in the nose was also statistically significantly reduced. The average assessed value at Visit 2 decreased by 37% compared to baseline, with a further reduction by 61% at Visit 3. The estimated parameter decreased by 75% during treatment.

In addition, both sneezing and redness of the skin at the entrance of the nose statistically significantly decreased. At the end of treatment, sneezing decreased by 82%, and skin redness at the entrance to the nose by 83%.

Acute rhinitis reduces the patient's quality of life, as besides its typical symptoms such as a blocked nose and a runny nose, it significantly interferes with the normal function of the nose. The clinical study also assessed the decreased perception of odour and taste, as well as the impact of a blocked nose on sleep. It has been shown that after treatment with a fixed-dose combination of a decongestant and dexpanthenol, odour and taste improve in a statistically significant manner. The assessed parameter improved by 73% compared to the value at Visit 1. What is more, on the seventh day of treatment patients were shown to fall asleep in a statistically significantly easier manner than on Day 1, as this parameter improved by 75%.

Patients treated with a fixed-dose combination of xylometazoline and dexpanthenol experienced a significant improvement in the quality of their lives. This is also reflected in the results, as the average of the sum of individual parameters in the SNOT-22si questionnaire (perception of smells and flavours, difficulty falling asleep, waking up in the middle of the night, lack of sleep, fatigue, decreased productivity, decreased concentration, irritability and agitation, sadness, shame, etc.) greatly reduced from Visit 1 to Visit 3. At Visit 1, the sum of the average of 22 parameters was 42.8, while at Visit 3 it was only 11.7.

Safety

The safety of the investigational medicinal products was evaluated in all 154 patients. None of the patients experienced a severe adverse effect; they only had mild and moderate adverse effects. There were also no permanent adverse effects recorded in any patient. In the group treated with a fixed-dose combination as many as 89.2% of patients did not experience any adverse effects. There were no differences in the rate of adverse effects among the two investigated groups.

Conclusions

Nasal obstruction is one of the most severe symptoms affecting the patient with acute rhinitis. The clinical study demonstrated that both the fixed-dose combination of a decongestant with a dexpanthenol and a decongestant alone can improve this symptom. Significantly greater progress in improving nasal obstruction was demonstrated between the third and the seventh day of active treatment with a fixed-dose combination of xylometazoline and dexpanthenol (Septanazal®). The clinical study also showed the beneficial effect of adding dexpanthenol to a decongestant, since treatment progress was visible already after three days. On the basis of these results we can conclude, or rather concur with an understanding that already exists in the medical literature: dexpanthenol strengthens the effects of xylometazoline since it accelerates wound healing, thus reducing inflammation of the nasal mucosa and improving breathing through the nose.[6, 15, 16] The clinical study demonstrated that the fixed-dose combination of a decongestant and dexpanthenol, in addition to nasal obstruction, in seven days of treatment significantly improves other symptoms of acute rhinitis such as nasal discharge, burning sensation in the nose, irritation in the nose, sneezing and skin redness at the entrance of the nose. The safety of the combination of these two agents was also demonstrated – a large proportion of patients experienced no adverse effects, and none of the patients experienced a severe adverse effect. A fixed-dose combination of xylometazoline and dexpanthenol in Septanazal® is thus proven to be an effective and safe choice in the treatment of nasal obstruction in patients with acute rhinitis.

Reference

[1] Nyenhuis S, Mathur SK. Rhinitis in older adults. Curr Allergy Asthma Rep 2013; 13 (2): 171–7.

[2] Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis 2005; 5 (11): 718–25.

[3] Mösges R, Shah-Hosseini K, Hucke HP, et al. Dexpanthenol: An overview of its contribution to symptom relief in acute rhinitis treated with decongestant nasal sprays. Adv Ther 2017; 34 (8): 1850–8.

[4] Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. Rhinology 2012; 50 (1): 1–12.

[5] Passàli D, Salerni L, Passàli GC, et al. Nasal decongestants in the treatment of chronic nasal obstruction: efficacy and safety of use. Expert Opin Drug Saf 2006; 5 (6): 783–90.

[6] Kehrl W, Sonnemann U, Dethlefsen U. Advance in therapy of acute rhinitis–comparison of efficacy and safety of xylometazoline in combination xylometazoline-dexpanthenol in patients with acute rhinitis. Laryngorhinootologie 2003; 82 (4): 266–71.

[7] Jagade MV, Langade DG, Pophale RR, et al. Oxymetazoline plus dexpanthenol in nasal congestion. Indian J Otolaryngol Head Neck Surg 2008; 60 (4): 393–7.

[8] Krka, tovarna zdravil, d. d., Novo mesto [internet]. Novo mesto: Krka, tovarna zdravil, d. d., Novo mesto; 2018 [cited 2018 Jun 7]. Available from: https://www.krka.biz/sl/zdravila-in-izdelki/izdelki-brez-recepta/septanazal/8597/

[9] Drugdex Evaluations: Xylometazoline hydrochloride, DRUGDEX System [internet]. Greenwood Village, Colorado, USA: Thomson Reuters (Healthcare) Inc.; 2018 [cited 2018 Apr 17]. Available from: http://www.micromedexsolutions.com/

[10] Cateholamines, sympathomimetic drugs, and adrenergic receptor antagonists: Nasal decongestion. In: Hardman JG, Limbird LE, Gilman AG. Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill; 2001. p. 240.

[11] MedicinesComplete: AHFS Drug information [internet]. Bethesda, MD: American Society of Health-System Pharmacists; 2012 [cited 2018 May 15]. Available from: www.medicinescomplete.com

[12] Gering W, Gloor M. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydratation. Results of human in vivo study. Arzneimittelforshung 2000; 50 (7): 659–63.

[13] Antienna Wollina U, Nissen H-P, Kubicki J. Antientzündliche Wirkungen von Dexpanthenol. Akt Dermatol 2004; 30: 478–82.

[14] Urbančič J, Soklič Košak T, Jenko K, et al. SNOT-22: Questionnaire Validation and Evaluation of Treatment of Patients with Chronic Rhinosinusitis. Med Razgl 2016; 55 (2): 39–45.

[15] Hauptmann S, Schäfer H, Fritz A, et al. The growth modifying effect of wound ointments on cell cultures. Hautartzt 1992; 43 (7): 432–5.

[16] Hosemann W, Göde U, Länger F, et al. Experimental studies of wound healing in the paranasal sinuses. II. Spontaneous wound healing and drug effects in a standardized wound model. HNO 1991; 39 (2): 48–54.

Author

Nataša Uranič, MPharm
Krka, d. d., Novo mesto, Dunajska cesta 65, 1000 Ljubljana, Slovenia

Krka's medicines are marketed in different countries under different brand names.

Some products may not be available in all countries due to still valid patent protection.

For complete information on the products please refer to the Summary of Product Characteristics. You can obtain it from Krka's medical representatives.