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 after nasal or paranasal sinus surgery and in acute rhinitis – SeptaNazal® DOUBLE clinical study

Final report synopsis

Protocol ID: KCT09/2015-SeptaNazal®-DOUBLE
EudraCT Number: 2015-005155-27

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September 2018

1 INTEGRATED CLINICAL STUDY REPORT (TITLE PAGE)

1. Title of clinical study:

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 after nasal or paranasal sinus surgery and in acute rhinitis – **SeptaNazal DOUBLE clinical study**

2. Investigational medicinal products (IMPs):

PZ 1: a medicine containing xylometazoline: 1 ml of nasal spray solution contains 1 mg xylometazoline hydrochloride

PZ 2: a medicine containing xylometazoline and dexpanthenol (Septanazal): 1 ml of nasal spray solution contains 1 mg xylometazoline hydrochloride and 50 mg dexpanthenol

3. Indication:

Nasal congestion in patients undergoing nasal or paranasal sinus surgery and patients with acute rhinitis

4. Study design:

International, randomised, comparative, double-blind, prospective study
Duration of the study: 7-day active treatment
Dosage:
IMP 1: one spray (1 mg xylometazoline chloride) into each nostril three times daily
IMP 2: one spray (1 mg xylometazoline chloride and 50 mg dexpanthenol) into each nostril three times daily

5. Sponsor:

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

6. Protocol ID:

KCT09/2015-SeptaNazal®-DOUBLE

7. EudraCT number:

2015-005155-27

8. Study phase:

Phase IV

9. Starting date (first patient enrolled):

23.1.2017

10. Ending date (last patient completing the study):

6.3.2018

11. Principal investigators' contact details:

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13. Declaration:

This clinical study was conducted according to the study protocol and good clinical practice (ICH GCP) and in compliance with relevant directives and decisions and the Declaration of Helsinki, taking account of the following documents:

1. CPMP/ICH/135/95, Good Clinical Practice: Consolidated guideline, revised 1997
2. EU Commission document ENTR/F2/BL D (2003), Revision 2. Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.
3. CHMP/EWP/240/95 Rev. 1 Guideline on clinical development of fixed combination medicinal products

14. Final report writers:

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- Danijel Rojc, Krka, d.d., Novo mesto, Slovenia

15. Date of the final report:

September 2018

CLINICAL STUDY SUMMARY

Sponsor name:

Krka d.d., Novo mesto, Slovenia

Investigational medicinal products (IMPs):

IMP 1: a medicine containing xylometazoline: 1 ml of nasal spray solution contains 1 mg xylometazoline hydrochloride
IMP 2: a medicine containing xylometazoline and dexpanthenol (Septanazal): 1 ml of nasal spray solution contains 1 mg xylometazoline hydrochloride and 50 mg dexpanthenol

Active substances:

Xylometazoline or xylometazoline/dexpanthenol

Title of clinical study:

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 after nasal or paranasal sinus surgery and in acute rhinitis – **SeptaNazal® DOUBLE clinical study**

Principal investigator:
Prof. dr. Irena Hočevar-Boltežar, dr. med., Councillor, Department of Otorhinolaryngology and Cervicofacial Surgery Ljubljana

Clinical study duration:

Patients undergoing nasal or paranasal sinus surgery:

- Date of first patient enrolment: 8 March 2017
- Date of last patient completing the study: 6 March 2018

Patients with acute rhinitis:

- Date of first patient enrolment: 23 January 2017
- Date of last patient completing the study: 26 December 2017

Study phase: *IV*

Purpose of clinical study:

The purpose of this double-blind randomised clinical study was to compare the efficacy and safety of a fixed-dose combination of xylometazoline and dexpanthenol (Septanazal) with those of xylometazoline alone in nasal congestion and to establish the effect of added dexpanthenol on healing in patients who undergo nasal or paranasal sinus surgery and in patients diagnosed with acute rhinitis.

Study design and methods:

International, randomised, comparative, double-blind, prospective study

Three study visits were scheduled during the 7-day study period.

Patients who underwent nasal or paranasal sinus surgery were included in the study the next day after surgery (Visit 1). Visit 2 was on the third day after inclusion and Visit 3 was on the seventh day after inclusion.
Patients diagnosed with acute rhinitis were included in the study on the day the diagnosis of acute rhinitis was made (Visit 1). Visit 2 was on the third day after inclusion and Visit 3 was on the seventh day after inclusion.
Patients in both groups were randomly allocated to two arms. They were randomised to treatment with one of the following medicinal products:

- **Primary arm:** patients treated with xylometazoline (IMP 1)
- **Secondary arm:** patients treated with fixed-dose combination of xylometazoline and dexpanthenol (IMP 2)

All patients included in the study underwent rhinoscopy (the primary outcome measure in the assessment of treatment efficacy was global patency of nasal passages). The patients self-assessed on a VAS the effect of the IMP on nasal congestion, and other measured variables, and time to onset of effect. In addition, they self-assessed treatment efficacy by filling out the Sino-Nasal Outcome Test (SNOT-22 REV 2) questionnaires and by assessing treatment efficacy as related to the addition of dexpanthenol to therapy, and to other, secondary variables.
At Visit 2, three days after inclusion, the patients had rhinoscopy performed by the investigator. The investigator entered into the Case Report Form (CRF) the Global Assessment of Improvement score for of signs and symptoms during treatment (GAIB). The patients used questionnaires (to assess the efficacy of the therapy on VAS and the efficacy of added dexpanthenol and other secondary variables). The investigator collected information on possible adverse reactions.
At the final visit, Visit 3, after seven days of active treatment, the patients had rhinoscopy and the investigator entered information on the improvement of the signs and symptoms (GAIB) into the CRF. The patients self-assessed the efficacy of the therapy (VAS score, SNOT-22 REV 2 score, added dexpanthenol efficacy score, and other secondary variables). The investigator collected information on the occurrence of possible adverse reactions.

Number of patients:

Sample size per protocol:

- Patients who underwent nasal or paranasal sinus surgery
  - Randomised: 70
  - Completing the study per protocol: 60
- Patients diagnosed with acute rhinitis (ITT analysis):
  - Randomised: 200
  - Completing the study per protocol: 160

Sample size at study conclusion:

- Patients who underwent nasal or paranasal sinus surgery
  - Randomised: 40
  - Completing the study per protocol: 40
- Patients diagnosed with acute rhinitis (ITT analysis):
  - Randomised: 154
  - Completing the study per protocol: 130

Diagnosis:

Nasal congestion following nasal or paranasal sinus surgery and nasal congestion related to acute rhinitis

Inclusion criteria:

Patients who underwent nasal or paranasal sinus surgery (Group 1):

- Age 18-60 years
- Nasal or paranasal sinus surgery (chronic sinusitis patients with nasal polyps (CRSwNP) and chronic rhinosinusitis patients without nasal polyps (CRSsNP)
- Patients tolerating intranasal administration of the IMP
- Signed informed consent form

Patients diagnosed with acute rhinitis (Group 2):

- Age 18–60 years
- Diagnosis of acute rhinitis
- Patients tolerating intranasal administration of the IMP
- Signed Informed Consent Form

Investigational medicinal products (IMPs):

- IMP 1: a medicine containing xylometazoline: 1 ml of nasal spray solution contains 1 mg xylometazoline hydrochloride
- IMP 2: a medicine containing xylometazoline and dexpanthenol (Septanazal): 1 ml of nasal spray solution contains 1 mg xylometazoline hydrochloride and 50 mg dexpanthenol

Dose and method of administration:

The IMPs were administered as nasal spray (solution).

Dosage was the same in both groups: one spray into each nostril three times daily (in the morning, in the afternoon and in the evening).

Efficacy of the treatment was monitored on days 1, 3 and 7 after inclusion.

IMPs batch numbers:

IMP 1: R41944, R42875

IMP 2: A61721, A65242

Study duration:

- 7 days of active treatment
- Study visits:
  - Patients who underwent nasal or paranasal sinus surgery (patients with CRSwNP and patients with CRSsNP):
    - Starting day of active treatment (inclusion in the study – Visit 1): on day 2 after surgery
    - Visit 2: on day 3 after inclusion
    - Conclusion of the study (Visit 3): on day 7 after inclusion
  - Patients diagnosed with acute rhinitis:
    - Starting day of active treatment (Visit 1): on the day acute rhinitis was diagnosed by the investigator
    - Visit 2: on day 3 after inclusion
    - Conclusion of the study (Visit 3): on day 7 after inclusion

Study objectives:

Primary objective:

Comparison of the efficacy of a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal) and a nasal spray containing xylometazoline alone in two groups of patients with nasal congestion:

- Group 1 – patients who underwent nasal or paranasal sinus surgery (patients with CRSwNP and patients with CRSsNP)
- Group 2 – patients diagnosed with acute rhinitis

Secondary objectives:

Comparison of the efficacy of a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal) and a nasal spray containing xylometazoline alone in two groups of patients based on the following clinical variables:

- Swelling of nasal mucosa
- Dryness of nasal mucosa
- Burning sensation in nasal passages
- Crust formation
- Bleeding of nasal mucosa
- Redness of nasal mucosa and the skin around the nostrils
- Sneezing
- Nasal discharge
- Nasal irritation

Comparison of treatment duration and occurrence of rebound nasal congestion between treatment with a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal) and a nasal spray containing xylometazoline alone in two groups of patients.

Comparison of time to onset of action between treatment with a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal) and treatment with a nasal spray containing xylometazoline alone in two groups of patients.

Safety evaluation:

- Overall incidence of adverse reactions (treatment-related adverse events)
- Frequency of adverse reactions by outcome
- Number or percentage of patients discontinuing the study due to clinically significant adverse reactions

Statistical analysis:

Arithmetic means, with standard deviations and asymptotic 95%-confidence intervals for expected values (depending on the anticipated sample size), were calculated for ratio variables and, where relevant, for interval random variables. Proportions and frequencies were calculated for ordinal random variables.

The following tests were used for comparisons of results between the groups: unpaired homoscedastic or heteroscedastic Student's test and corresponding 95%-confidence intervals for differences in expected values for continuous random variables, and if data indicated that using the normal model was reasonable, two-sample Wilcoxon-Mann-Whitney test for continuous random variables in case of too large deviations from the normal model, or chi-square homogeneity test for discrete random variables. Comparisons of different proportions between the groups were done with the exact confidence intervals for the difference of proportions by Shan and Wang. Statistical significance of differences was set at $p<0.05$.

Summary of the results and conclusions:

EFFICACY RESULTS:

Primary objective

- Comparison of the efficacy of a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal) and a nasal spray containing xylometazoline alone in two groups of patients with nasal congestion:

I. Group 1 – patients undergoing nasal or paranasal sinus surgery (patients with CRSwNP and patients with CRSsNP)

II. Group 2 – patients diagnosed with acute rhinitis

Group 1: patients undergoing nasal or paranasal sinus surgery

1. Results of front rhinoscopy

The investigator performed rhinoscopy of the right and left nasal passages in all patients and assessed 15 parameters that were used as outcome measures. The main IMP efficacy outcome measure was **global patency of nasal passages**, as assessed on VAS (0=completely open and 10=completely blocked).

The mean global patency score was 4.7 for the right nasal passages and 3.9 for the left nasal passages in the group treated with Septanazal, compared with 5.5 for the right and 5.6 for the left nasal passage in the group treated with xylometazoline. Global patency improved in both groups during the treatment, as demonstrated by a mean score of 3.4 for the right nasal passages and 2.6 for the left nasal passages in the Septanazal group, and of 4.8 and 4.9, respectively, in the comparative group at Visit 2. A further improvement in the global patency score for the right and left nasal passages was found at the final visit. In the Septanazal group, the final patency score for the right nasal passages was 2.0 and that for the left nasal passages 2.0 and 3.2 for the right and 3.5 for the left nasal passages in the comparative group, on a 0–10 scale.

In all patients (both groups) left and right nasal passage patency improved during the treatment. This provides direct evidence of a reduction in nasal congestion between the first and the final visit.

2. Assessment of nasal congestion on VAS

The patients self-assessed nasal congestion using a visual analogue scale (VAS) before and 1 min after IMP administration during all three study visits. During Visit 1 they also used VAS to assess nasal congestion 3 min, 6 min and 9 min after the first IMP dose. These additional data provided information on time to the onset of action of Septanazal and xylometazoline. A total number of 39 patients self-assessed their nasal congestion on VAS during all three study visits.

Severe nasal congestion or completely blocked nose before administration of one or the other IMP was found in 9 (22.5%) patients at Visit 1. The percentage of patients with severe congestion or completely blocked nose before IMP administration was reduced to 2.6% at Visit 3 (in all except for 1 out of 39 patients). While one minute after the IMP administration at Visit 1 five (12.5%) out of 40 patients assessed their nasal congestion as severe or completely blocked nose, there was only 1 such case out of 39 at 1 minute after IMP administration at Visit 3 (Table 1).

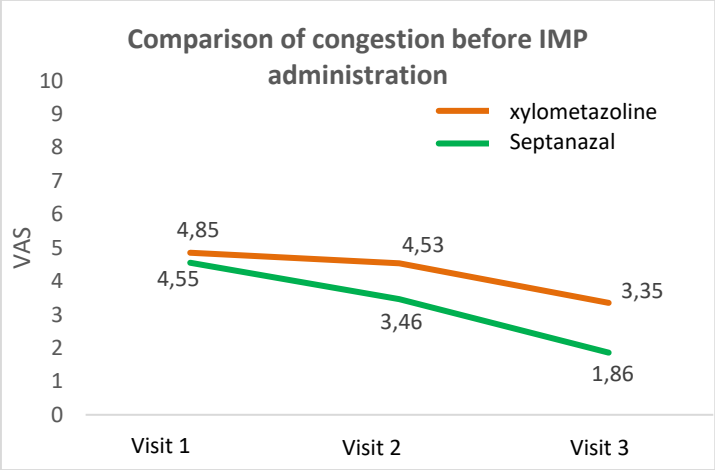
Table 1: Nasal congestion in all Group 1 patients before and 1 min after IMP administration

	Completely patent nasal passages 0 – 0.9	Mild congestion 1.0 – 3.9	Moderate congestion 4.0 – 6.9	Severe congestion 7.0 – 9.9	Completely blocked nasal passages 10	No data	Total	
	N	N	N	N	N	N	N	%
BEFORE IMP								
Visit 1	1	16	14	7	2	0	40	100%

Visit 2	1	19	12	7	0	0	39	98%
Visit 3	4	22	12	1	0	0	39	98%
1 MIN AFTER IMP								
Visit 1	2	22	11	5	0	0	40	100%
Visit 2	5	23	7	4	0	0	38	98%
Visit 3	15	18	5	1	0	0	38	98%

In both groups of patients nasal congestion was significantly reduced **before IMP administration** both between Visit 1 and Visit 2 and between Visit 2 and Visit 3. The mean VAS score in the xylometazoline group fell from 4.85 to 4.53 (7% reduction) at Visit 2 and to 3.35 (26% reduction) at Visit 3. Nasal congestion was reduced by 31% between Visit 1 and Visit 3. In patients treated with Septanazal, the mean VAS score of 4.55 at Visit 1 was reduced to 3.46 at Visit 2 and to 1.86 at Visit 3. Between Visit 1 and Visit 2 it was reduced by 24% and between Visit 2 and Visit 3 it was reduced by 46%. Over the whole study period nasal congestion was reduced by 59%. Nasal congestion was reduced statistically significantly in both groups at study visits. The mean nasal congestion scores at Visit 1 and Visit 2 did not differ statistically significantly. At Visit 3 the score was statistically significantly lower in the Septanazal group when compared to that in the xylometazoline group. The difference was 1.49, p<0.013. It can be concluded that Septanazal was more effective than xylometazoline in patients undergoing nasal and paranasal sinus surgery, as demonstrated by statistically significantly milder nasal congestion in patients treated with Septanazal (Figure 1).

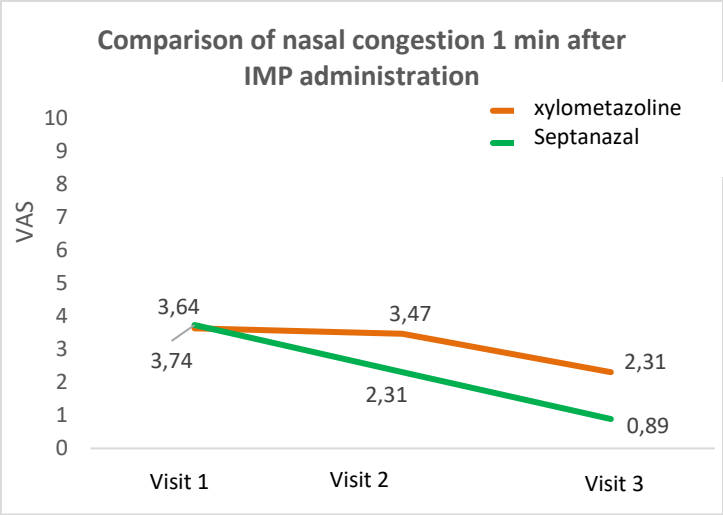
Figure 1: Comparison in nasal congestion before IMP administration between the xylometazoline and Septanazal group (Group 1)



NASAL CONGESTION BEFORE IMP	Xylometazoline	Septanazal
Visit 1	4.85	4.55
Visit 2	4.53	3.46
Visit 3	3.35	1.86

The mean VAS score **at 1 minute after IMP administration** in the xylometazoline group was 3.64 at Visit 1 and 3.47 at Visit 2 (5% reduction in nasal congestion). The mean VAS score at the final study visit was 2.31 (33% reduction compared with Visit 2). The total reduction in nasal congestion between Visit 1 and Visit 3 was 36%. In the Septanazal group, the mean VAS score at 1 minute after IMP administration at Visit 1 was 3.74 and at Visit 2 it was 2.31 (38% reduction in nasal congestion). At the final study visit, the mean VAS score was 0.89 (62% reduction compared with Visit 2). The total reduction in nasal congestion between Visit 1 and Visit 3 was 76% (Figure 2). The difference between nasal congestion at Visit 1 and Visit 2 was not statistically significant. The mean nasal congestion at Visit 3 was statistically significantly lower as that in the xylometazoline group. The difference was 1.42, p<0.017.

Figure 2: Comparison of nasal congestion 1 min after IMP administration between xylometazoline and Septanazal group (Group 1)



NASAL CONGESTION 1 MIN AFTER IMP	Xylometazoline	Septanazal
Visit 1	3.64	3.74
Visit 2	3.47	2.31
Visit 3	2.31	0.89

3. SNOT-22 REV 2 questionnaire

The SNOT-22 REV 2 questionnaire contains 22 items, one of which assesses nose blockage. The severity of nose blockage symptoms was assessed on a 0–5 rating scale. From among the 22 items the patients had to mark 5 symptoms that most strongly affected their health.

Visit 1: 28 out of the total population of 40 patients marked nose blockage as one of the 5 symptoms that most strongly affected their health, which is 70% of all patients. Thirty-two out of 40 (80%) assessed nose blockage with a score of 3 or higher.

In the Septanazal group, 65% (11 out of 17) of the patients assessed nose blockage as one of the most disturbing symptoms of acute rhinitis. In the xylometazoline group, nose blockage was assessed as the most disturbing symptom by 74% (17 out of 23) of the patients. This symptom was assessed with a score of 3 or higher by 14 out of 17 patients in the Septanazal group, which is 82% of all patients. In the xylometazoline group, this symptom was assessed with a score of 3 by 18 out of 23 patients, which is 78%.

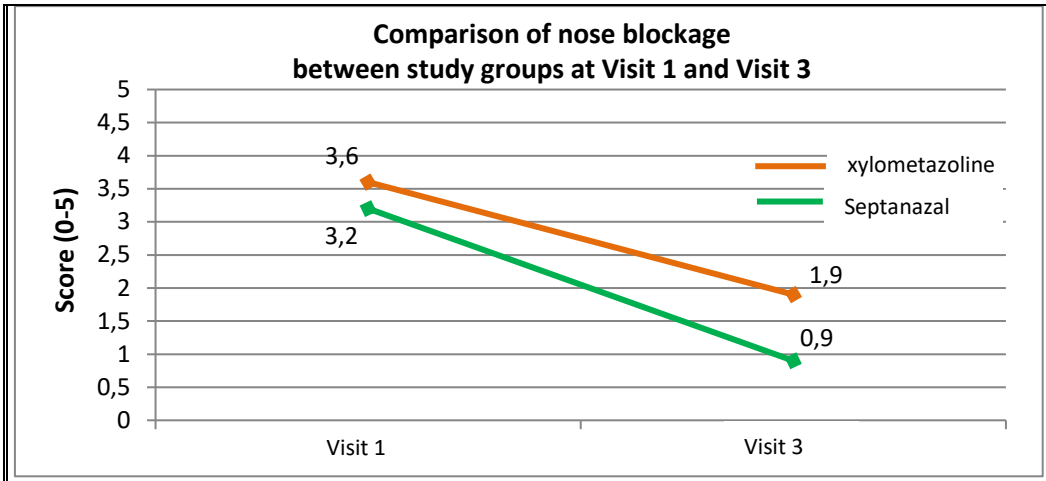
Visit 3: The percentage of patients who assessed nose blockage with a score of 3 or higher was significantly lower at Visit 3 in both groups. In the Septanazal group it was 12.5% (2 patients) and in the xylometazoline group it was 43.5% (10 patients).

There was an increase in the percentage of patients that assessed the symptom with a score of 0, 1 or 2. This percentage was 83% (14 patients) in the Septanazal group and 56.5% (13 out of 23) in the xylometazoline group.

A significant reduction in the mean score for nasal congestion was observed in both groups between Visit 1 and Visit 3. The mean score for nasal congestion in patients treated with xylometazoline was 3.6 (SD=1.24) on a 0–5 scale at Visit 1 and 3.2 (SD=1.13) in patients treated with Septanazal. At Visit 3 the mean score for nasal congestion was reduced to 1.9 in the xylometazoline group (46% reduction), which is by 1.7 units at the mean, and to 0.9 (70%) in the Septanazal group, whici is by 2.3 units at the mean.

The difference found in the mean score for nasal congestion between the patients treated with xylometazoline and the patients treated with Septanazal was statistically insignificant. A statistically significant difference in nasal congestion reduction between the groups in favour of Septanazal was found at Visit 3 (0.1, $p<0.020$). When differences in the reduction of nasal congestion were compared between the groups, statistical significance was not found (absolute difference in the xylometazoline group -1.7 and in the Septanazal group -2.3).

Figure 3 compares nasal congestion at Visit 1 and Visit 3 between study groups.



4. Patient self-assessment of symptoms (IMP efficacy assessment form)

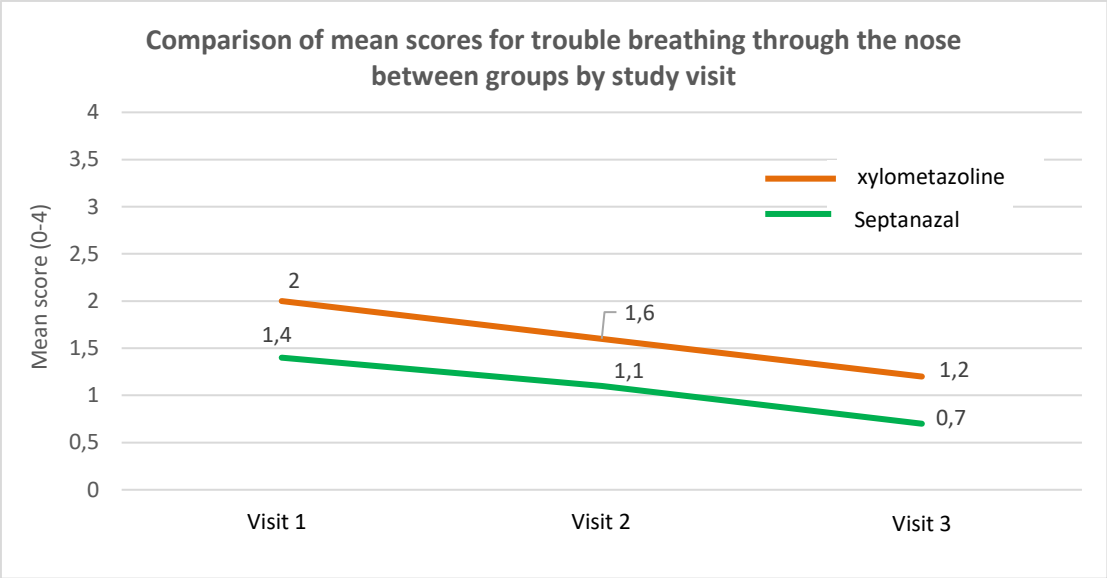
After IMP administration the patients assessed the severity of 11 problems/symptoms on a 0–4 scale. One of the items was trouble breathing through the nose which is a direct indicator of nasal congestion. This assessment was carried out during all three study visits.

The results demonstrated a reduction in the mean score for trouble breathing through the nose at all three study visits in both study groups (Figure 4).

The symptom trouble breathing through the nose was assessed with a score of 2 or higher by 21 (54%) of the patients at Visit 1, 65% (15/23) in the xylometazoline group and 36% (6/17) in the Septanazal group. The mean score for this symptom was 2.0 in the xylometazoline group and 1.4 in the Septanazal group. The patients assessed it at Visit 2 as less serious than at Visit 1. Only 47% (11/23) of the patients in the xylometazoline group assessed it with a score of 2 or higher. In the Septanazal group, the percentage of these patients was 24% (4/16) and thus somewhat lower. While in the xylometazoline group the mean score in this item was statistically significantly lower compared to that at Visit 1, 2.0 vs 1.6 (by 22%, p=0.021), no statistically significant reduction was found in the Septanazal group, 1.4 vs 1.1. After the end of the treatment the number of patients assessing the symptom with a score of 2 or higher was even smaller. The mean score in the xylometazoline group at that time point was 1.2 and in the Septanazal group it was 0.7. The mean score was significantly reduced in both study groups if compared with that at Visit 2. The percentage reduction was 25% (p<0.0020) in the xylometazoline group and 35% (p<0.0078) in the Septanazal group.

The results demonstrated that the above parameter improved in both study groups during the 7-day treatment. Its reduction was statistically significant between Visit 1 and Visit 3 (41% reduction in the xylometazoline group (p=0.031) and 49% reduction in the Septanazal group (p=0.004)) and demonstrates that the IMP provided an effective therapy.

Figure 4: Comparison of mean scores for trouble breathing through the nose between study groups during treatment (Group 1)

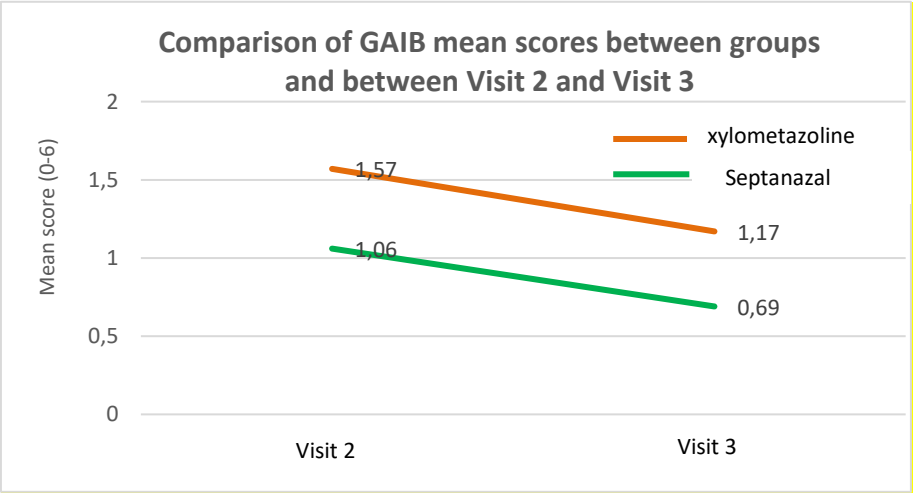


5. Global assessment of improvement of signs and symptoms during treatment (GAIB)

The investigator used the GAIB scale to assess improvement in the signs and symptoms during treatment. The GAIB scale uses a 7-point score and was used to assess active treatment with the IMP and to compare the severity of the condition at the end of the treatment with that at baseline.

The results (Figure 5) demonstrated a significant improvement in the global assessment of improvement score for signs and symptom during treatment in both study groups. In patients treated with Septanazal, the mean GAIB score was reduced by 0.4 (absolute value); this is by 35% if comparing the mean scores at Visit 2 and Visit 3. In patients treated with xylometazoline the mean score was reduced by 0.37 (absolute value); this is by 25% if comparing the mean scores at Visit 2 and Visit 3.

Figure 5: Comparison of GAIB mean scores between groups by study visit



Study visits	P, significance	
#2:#3	0.936	Insignificant difference

Group 2: patients diagnosed with acute rhinitis

1. Results of front rhinoscopy

The investigator performed a rhinoscopy of the right and left nasal passages in all patients and assessed 15 parameters that were used as outcome measures. The main IMP efficacy outcome measure was **global patency of nasal passages**, as assessed on VAS (0=completely open and 10=completely blocked).

The mean global patency VAS score was 7.2 for the right nasal passages and 6.9 for the left nasal passages in the group treated with Septanazal, and 7.0 for both right and left nasal passages in the group treated with xylometazoline. Global nasal patency improved in both groups during the treatment, as demonstrated by a mean score of 4.9 for the right nasal passages and 4.8 for the left nasal passages, and 4.6 and 4.7, respectively, in the comparative group at Visit 2. A further improvement in the global patency score for the right and left nasal passages was found at Visit 3. In the Septanazal group, the final patency score for the right nasal passages was 2.3 and that for the left nasal passages 2.1, and 2.2 for the right and 2.1 for the left nasal passages in the comparative group, on a 0–10 scale.

In all patients (both those treated with Septanazal and those treated with xylometazoline) left and right nasal patency improved during the treatment. This provides direct evidence of a reduction in nasal congestion between the first and the final visit.

2. Assessment of nasal congestion on VAS

The patients self-assessed nasal congestion using the visual analogue scale (VAS) before and 1 min after IMP administration during all three study visits. During Visit 1 they also used VAS to assess nasal congestion 3 min, 6 min and 9 min after the first IMP dose. These additional data provided information on time to the onset of action of Septanazal and xylometazoline. The resukts are in Table 2.

A total number of 151 patients self-assessed their nasal congestion on VAS during all three study visits.

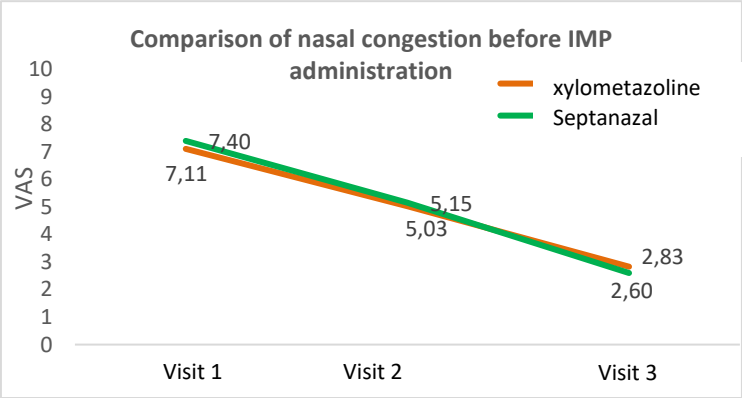
Severe nasal congestion or completely blocked nose before administration of one or the other IMP was found in 107 (69.5%) patients at Visit 1. The percentage of patients with severe congestion or completely blocked nose before administration of IMP was reduced to 3% at Visit 3 (only 5 out of 154 patients). While at Visit 1, one minute after IMP administration 35 (22.7%) out of 154 patients assessed their nasal congestion as severe or completely blocked nose, there were no such cases 1 minute after the administration of the IMP at Visit 3.

Table 2: Nasal congestion in all patients (Group 2) before and 1 minute after IMP administration during 7-day treatment

	Completely patent nasal passages 0 – 0.9	Mild congestion 1.0 – 3.9	Moderate congestion 4.0 – 6.9	Severe congestion 7.0 – 9.9	Completely blocked nasal passages 10.0	No data	Total	
	N	N	N	N	N	N	N	%
BEFORE IMP								
Visit 1	0	4	43	103	4	0	154	100%
Visit 2	3	33	82	35	0	1	154	100%
Visit 3	14	101	31	5	0	3	154	100%
1 MIN AFTER IMP								
Visit 1	1	37	81	34	1	0	154	100%
Visit 2	13	87	46	6	0	2	154	100%
Visit 3	64	78	9	0	0	3	154	100%

In both groups of patients nasal congestion was significantly reduced **before IMP administration**, both between Visit 1 and Visit 2 and Visit 2 and Visit 3 (Figure 6). The reduction of the mean nasal patency VAS score in the xylometazoline group was from 7.11 to 5.03 (29% reduction) at Visit 2 and to 2.83 (44% reduction) at the final visit. The total reduction in nasal congestion between Visit 1 and Visit 3 was 60%. In patients treated with Septanazal, the mean VAS scores were 7.40 at Visit 1, 5.15 at Visit 2 and 2.60 at Visit 3. The percentage reduction in nasal congestion was 30% between Visit 1 and Visit 2 and 49% between Visit 2 and Visit 3. The mean nasal congestion VAS score was reduced by 65% during the treatment. Nasal congestion was reduced significantly after the study visits in both groups. A between-group comparison showed that there were no statistically significant differences between the study groups in the mean VAS scores after the study visits. **Similar results were observed at 1 minute after IMP administration**. While nasal congestion was significantly reduced between the study visits in both groups, there were no statistically significant differences in the reduction of nasal congestion between the groups. It can be concluded that Septanazal and xylometazoline were equally effective in unblocking the nose at 1 minute after IMP administration.

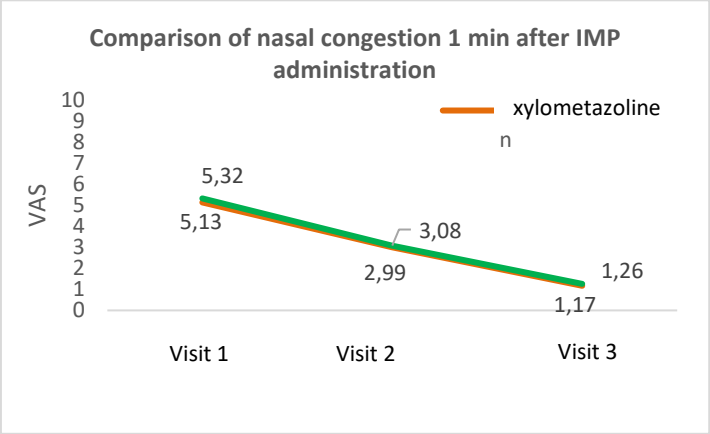
Figure 6: Comparison of nasal congestion before IMP administration between the study groups (Group 2)



NASAL CONGESTION BEFORE IMP	Xylometazoline	Septanazal
Visit 1	7.11	7.40
Visit 2	5.03	5.15
Visit 3	2.83	2.60

The mean VAS score **at 1 minute after IMP administration** in the xylometazoline group was 5.13 at Visit 1 and 2.99 at Visit 2 (42% reduction in nasal congestion). The mean VAS score at the final study visit was 1.17 (61% reduction compared with Visit 2). The total reduction in nasal congestion between Visit 1 and Visit 3 was 77%. In the Septanazal group, the mean VAS score at 1 minute after IMP administration at Visit 1 was 5.32 and at Visit 2 it was 3.08 (42% reduction in nasal congestion). At the final study visit, the mean VAS score was 1.26 (59% reduction compared with Visit 2). The total reduction in nasal congestion between Visit 1 and Visit 3 was 76%. The results are shown in Figure 7.

Figure 7: Comparison of nasal congestion at 1 minute after IMP administration between the study groups



NASAL CONGESTION 1 MIN AFTER IMP ADMINISTRATION	Xylometazoline	Septanazal
Visit 1	5.13	5.32
Visit 2	2.99	3.08
Visit 3	1.17	1.26

3. SNOT-22 REV 2 questionnaire

The SNOT-22 REV 2 questionnaire contains 22 items, one of which assesses nose blockage. The severity of nose blockage symptoms was assessed on a 0–5 rating scale. From among the 22 items the patients had to mark 5 that most strongly affected their health.

Visit 1: 136 out of 154 included patients marked nose blockage as one of the 5 symptoms that most strongly affected their health, which is 88% of all patients. One hundred and forty-three (93%) of them assessed nose blockage with a score of 3 or higher.

In the Septanazal group, 91% (67 out of 74 patients) assessed nose blockage as one of the most disturbing symptoms of acute rhinitis. In the xylometazoline group, nose blockage was assessed as the most disturbing symptom by 86% (69 out of 80 patients). This symptom was assessed with a score of 3 or higher by 72 out of 74 patients in the Septanazal group, which is 97% of all patients. In the xylometazoline group, this symptom was assessed with a score of 3 by 71 out of 80 patients, which is 89%.

Visit 3: The percentage of patients who assessed nose blockage with a score of 3 or higher was significantly lower at Visit 3 in both groups. In the Septanazal group it was 18% (13 patients) and in the xylometazoline group it was 10% (8 patients).

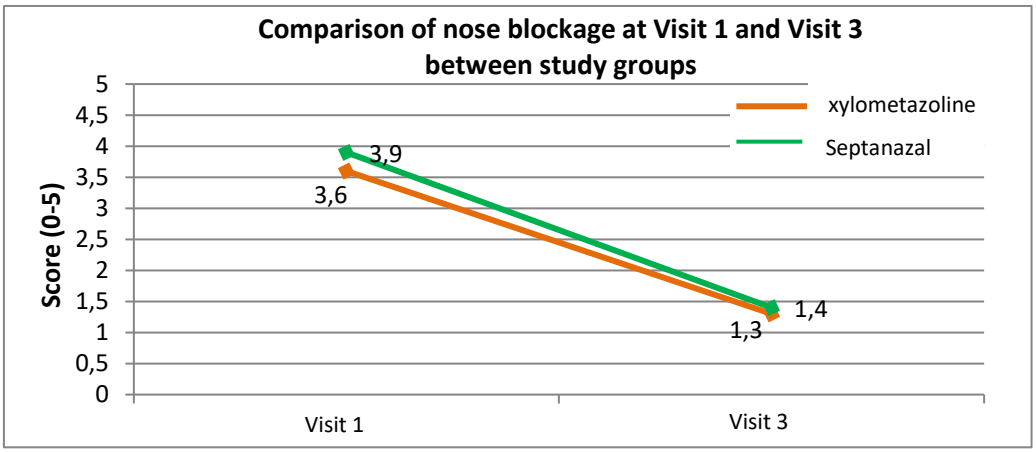
There was an increase in the percentage of patients assessing the symptom with a score of 0, 1 or 2. This percentage was 80% (59 patients) in the Septanazal group and 89% (71 out of 80 patients) in the xylometazoline group.

A significant reduction in the mean score for nose blockage was observed in both groups between Visit 1 and Visit 3. The mean score for nose blockage in patients treated with xylometazoline was 3.6 (SD=0.91) on a 0–5 scale at Visit 1 and 3.9 (SD=0.87) in patients treated with Septanazal. At Visit 3 the mean score for nasal congestion was reduced to 1.3, by 2.3 units, in the xylometazoline group (64% reduction) and to 1.4, by 2.5 units, (63% reduction) in the Septanazal group.

No significant differences were found in the mean scores for nasal congestion after study visits between the study groups. The difference between the groups in nasal blockage reduction was also insignificant (absolute difference in the xylometazoline group -2.3, absolute difference in the Septanazal group -2.5).

Figure 8 shows a comparison in nose blockage at Visit 1 and Visit 3 between study groups

Figure 8: Comparison of nose blockage at Visit 1 and Visit 3 between study groups



4. Patient self-assessment of symptoms (IMP efficacy assessment form)

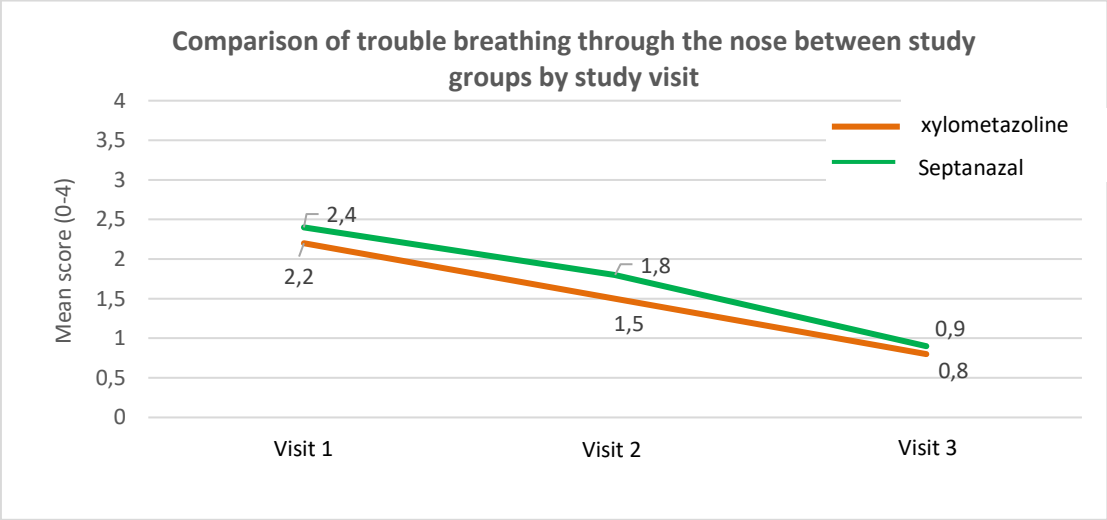
After IMP administration the patients assessed the severity of 11 problems/symptoms on a 0–4 scale. One of the items was trouble breathing through the nose which is a direct indicator of nasal congestion. This assessment was carried out during all three study visits.
The results demonstrated a reduction in the mean score for trouble breathing through the nose at all three study visits in both study groups (Figure 9).

The symptom trouble breathing through the nose was assessed with a score of 2 or higher by 124 (80%) of the patients at Visit 1, 77% (61/80) in the xylometazoline group and 85% (63/74) in the Septanazal group. The mean score for this symptom was 2.2 in the xylometazoline group and 2.4 in the Septanazal group. The patients assessed it at Visit 2 as less severe than at Visit 1. Only 51% (41/80) of the patients in the xylometazoline group assessed it with a score of 2 or higher. In the Septanazal group, the percentage of these patients was 70% (52/74) and thus somewhat higher. The mean score for the symptom was statistically significantly lower in both groups of patients if compared to the baseline score. The reduction was from 2.2 to 1.5 for xylometazoline (30% reduction) and from 2.4 to 1.8 for Septanazal (25% reduction, $p<0.0001$). After seven days of treatment the number of patients assessing the symptom with a score of 2 or higher was even smaller. The mean score in the xylometazoline group was 0.8 and in the Septanazal group it was 0.9. The mean score was significantly reduced in both study groups if compared with that at Visit 2. The percentage reduction was 47% ($p<0.0001$) in the xylometazoline group and 52% ($p<0.0001$) in the comparative group.
The results demonstrated that the observed parameter improved in both study groups during the 7-day treatment. Its reduction was statistically significant between Visit 1 and the final visit (63% reduction in the xylometazoline group, $p<0.0001$, and 64% reduction in the Septanazal group, $p<0.0001$) and demonstrates that the IMP provided an effective therapy.

A comparison of the mean scores for trouble breathing through the nose showed a significant difference between the study groups at Visit 2 of 0.3 (Septanazal 1.8 vs xylometazoline 1.5), which was of statistical significance ($p<0.027$).

A comparison of the mean score reductions in this item between the study visits demonstrated that the reduction in the mean score between Visit 2 and Visit 3 was statistically significantly greater in the Septanazal group (Septanazal -1.0 vs xylometazoline -0.7, $p<0.028$). Differences in score reductions between the groups were insignificant between Visit 1 and Visit 2 and between Visit 1 and Visit 3.

Figure 9: Comparison of mean scores for trouble breathing through the nose between study groups during treatment (Group 2)



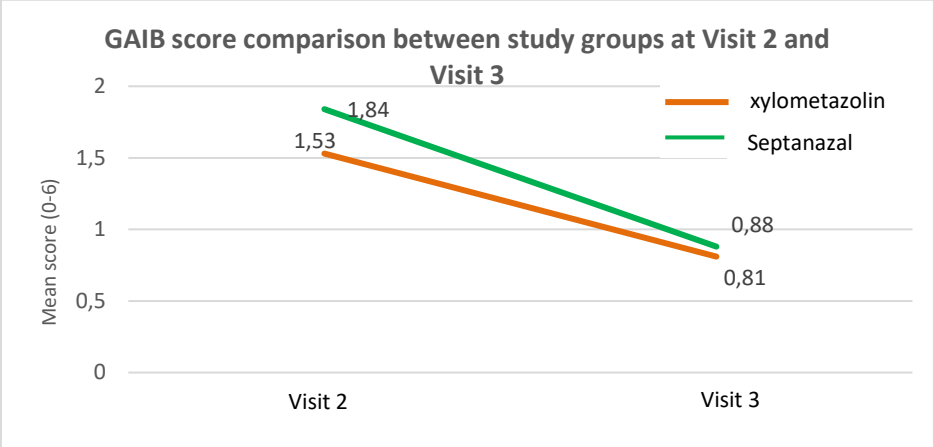
5. Global assessment of improvement of signs and symptoms from baseline (GAIB)

The investigator used the GAIB questionnaire to assess improvement in the signs and symptoms during treatment. GAIB uses a 7-point score and was used to monitor active treatment with the IMP and to compare the severity of the condition at the end of the treatment with that at baseline.

The results demonstrated a significant improvement in the global sign and symptom improvement score during treatment in both study groups (Figure 10). In patients treated with Septanazal, the mean score was reduced by 0.96 (absolute value), this is by 52% ($p<0.0001$) compared with the mean score at Visit 2 and Visit 3. In patients treated with xylometazoline the mean score was reduced by 0.72 (absolute value), this is by 47% ($p<0.0001$) if the mean scores at Visit 2 and Visit 3 are compared.

The investigators reported a very good response to the treatment with the IMP in both groups. A between-group comparison of the mean global sign and symptom improvement scores obtained during the treatment demonstrated a statistically significant difference at Visit 2, with a higher value in patients treated with Septanazal ($p<0.027$). No statistically significant differences were found between the study groups at Visit 3. It can be seen that, despite the higher value at Visit 2 in the Septanazal group, the score at Visit 3 was reduced to the level found in the xylometazoline group at this time point. A comparison of the mean score reductions between Visit 2 and Visit 3 shows that there was a greater reduction in the Septanazal group (difference between the study groups=0.24, $p<0.028$).

Figure 10: Mean GAIB score comparison between the study groups by study visit (Group 2)



Study visits	P, significance	
#2:#3	0.028	Significant difference

Secondary objectives:

- Comparison of the efficacy of a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal®) and a nasal spray containing xylometazoline alone in two groups of patients based on the following clinical variables:
  - Swelling of nasal mucosa
  - Dryness of nasal mucosa
  - Burning sensation in nasal passages
  - Crust formation
  - Bleeding of nasal mucosa
  - Redness of nasal mucosa and the skin around the nostrils
  - Sneezing
  - Nasal discharge

- Nasal irritation

- Comparison of the treatment duration and occurrence of rebound nasal congestion between treatment with a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal®) and a nasal spray containing xylometazoline alone in two groups of patients.

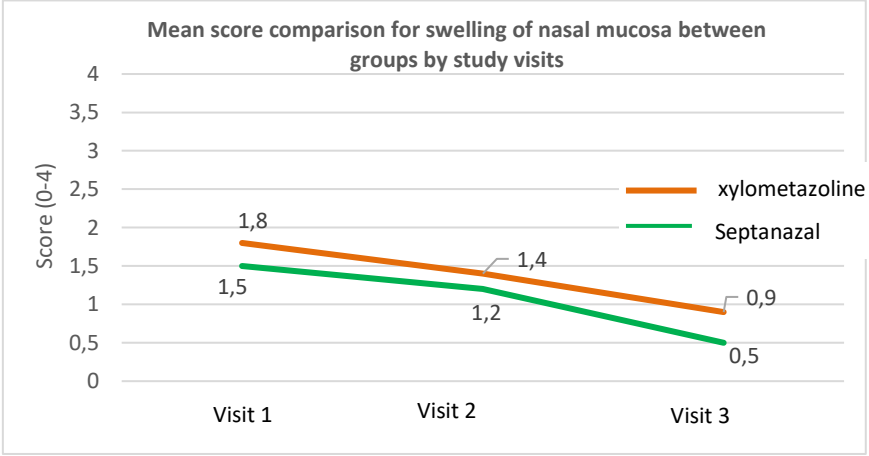
- Comparison of time to onset of action between treatment with a fixed-dose combination nasal spray containing xylometazoline and dexpanthenol (Septanazal®) and a nasal spray containing xylometazoline alone in two groups of patients.

Group 1: patients undergoing nasal or paranasal surgery

1. **Patient self-assessment of symptoms (IMP efficacy assessment form)**

Swelling of nasal mucosa:
Twenty-one (53%) patients assessed swelling of nasal mucosa on a 0–4 rating scale with a score of 2 or higher at Visit 1, 56% (13/23) of them from the group treated with xylometazoline and 48% (8/17) of them from the group treated with Septanazal. The mean score in this item was 1.8 in the xylometazoline group and 1.5 in the Septanazal group. It was assessed as being less severe at Visit 2 compared with Visit 1. It was assessed with a score of 2 or higher by 43% (10/23) of the patients in the xylometazoline group and by 30% (5/16) of the patients in the Septanazal group. The mean score in this item was statistically significantly lower in both groups if compared to Visit 1: 1.83 at Visit 1 and 1.43 at Visit 2 in the xylometazoline group (mean score reduction by 21%, p=0.023) and 1.53 at Visit 1 and 1.19 at Visit 2 in the Septanazal group (22% reduction, p=0.04). After the end of the treatment an even smaller number of patients in both groups assessed this item with a score of 2 or higher. The mean score in the xylometazoline group was 0.87 and that in the Septanazal group was 0.50. The mean score was significantly reduced in both groups if compared to Visit 2; by 39% (p=0.013) in the xylometazoline group and by 58% (p=0.004) in the Septanazal group. The difference between the groups was insignificant.
The results (Figure 11) showed that the above item improved during the treatment in both groups. There was a statistically significant improvement between Visit 1 and Visit 3 (52% reduction in the xylometazoline group, p=0.002, and 67% reduction in the Septanazal group, p=0.002), which additionally proves the efficacy of treatment with the IMP.
A comparison of the results for the item swelling of nasal mucosa demonstrated no significant differences between the mean scores for this item at study visits. Absolute differences were insignificant as well.

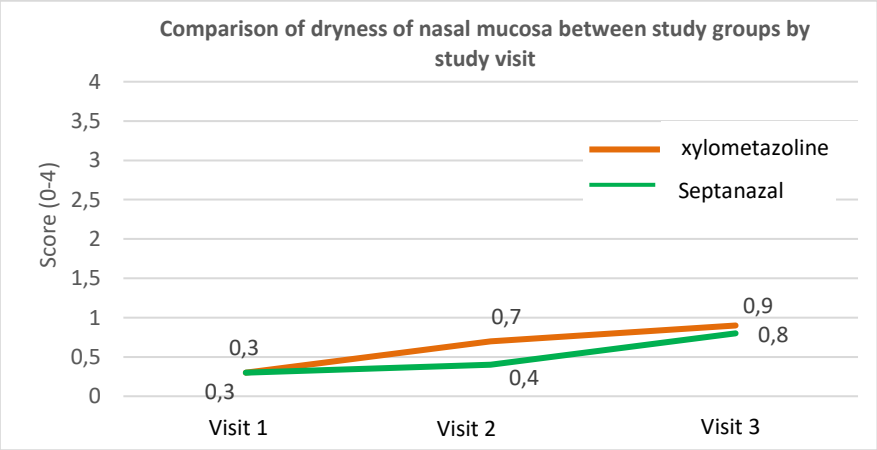
Figure 11: Comparison of mean scores for swelling of nasal mucosa between the study groups (Group 1)



Dryness of nasal mucosa:

The mean score for dryness of nasal mucosa increased slightly during the treatment in both groups. The results are shown in Figure 12. In the xylometazoline group, the mean score at Visit 1 was 0.3, then it increased statistically significantly to 0.7 (p=0.008) at Visit 2 and then statistically insignificantly to 0.9 at Visit 3. In the Septanazal group, a similar increase in dryness of nasal mucosa was observed at the study visits. The mean score in this item was 0.3 at Visit 1, then increased to 0.4 (statistically insignificantly) at Visit 2 and was 0.8 at Visit 3, which was a statistically significant increase (p=0.016). The difference in absolute values of this item between the groups was statistically insignificant in all periods between the study visits (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3).

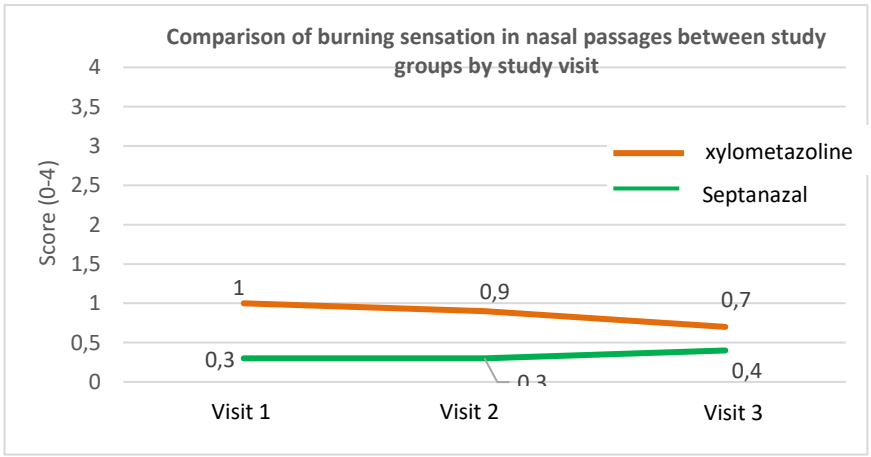
Figure 12: Comparison of mean scores for dryness of nasal mucosa between the study groups by study visit (Group 1)



Burning sensation in nasal passages:

The burning sensation in nasal passages mean score in the xylometazoline group at Visit 1 was 1.0 and in the Septanazal group it was 0.3 on a 0–4 scale. At Visit 2 it was 0.9 (statistically insignificant reduction by 13%) and at Visit 3 it was 0.7 (statistically insignificant reduction by 25% compared to Visit 2) in the xylometazoline group. In the Septanazal group a 15% reduction in the mean score, to 0.3, was observed at Visit 2 compared with baseline. At Visit 3 it was 0.4. The between-group differences in absolute values for this item were statistically insignificant between the study visits (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 13.

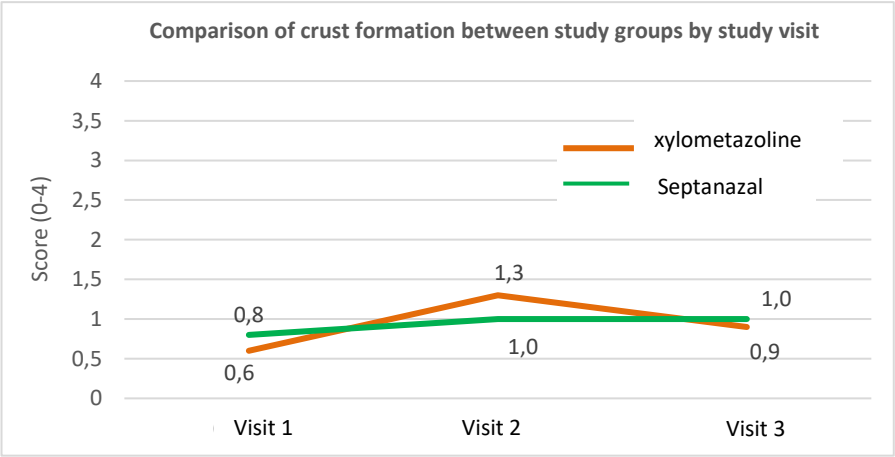
Figure 13: Comparison of mean scores for burning sensation in nasal passages between the study groups by study visit (Group 1)



Crust formation:

The baseline crust formation score was 0.6 at Visit 1 in the xylometazoline group. At visit 2 the score was 1.3. The difference was statistically significant with 0.70, p=0.0001. With 0.9 (p=0.021) at Visit 3, a statistically significant reduction in the mean score was observed if compared to Visit 2. In the Septanazal group no statistically significant differences were found in this item between the study visits, with 0.8 at Visit 1 and 1.0 at Visit 2 and Visit 3. The between-group differences in absolute values for this item by study visit were statistically insignificant (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 14.

Figure 14: Comparison of mean scores for crust formation between groups by study visit (Group 1).

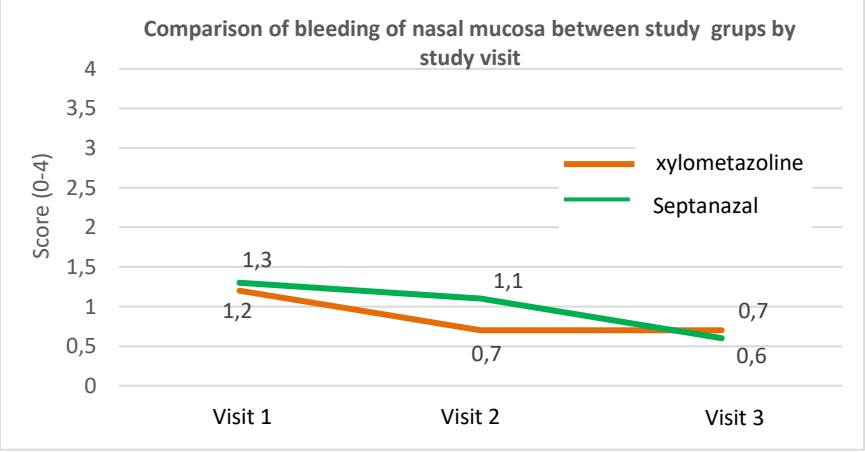


Bleeding of nasal mucosa:

The mean score for bleeding of nasal mucosa was reduced during treatment with xylometazoline (statistically insignificant reduction between the study visits). It was 1.2 at Visit 1, 0.7 at Visit 2 and 0.70 at Visit 3. There was a 41% reduction during the treatment, which, however, was not a statistically significant difference compared with baseline at Visit 1. In the Septanazal group, the mean score at Visit 1 was 1.3 and at Visit 2 it was 1.1 (statistically insignificant difference). A statistically significant difference was only observed at Visit 3, when the mean score was 0.6. Overall reduction of this item between Visit 1 and Visit 3 was 57%, which was statistically significant (p=0.0215). The results are shown in Figure 15.

The between-group difference in absolute values for this item by study visit was statistically insignificant (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3).

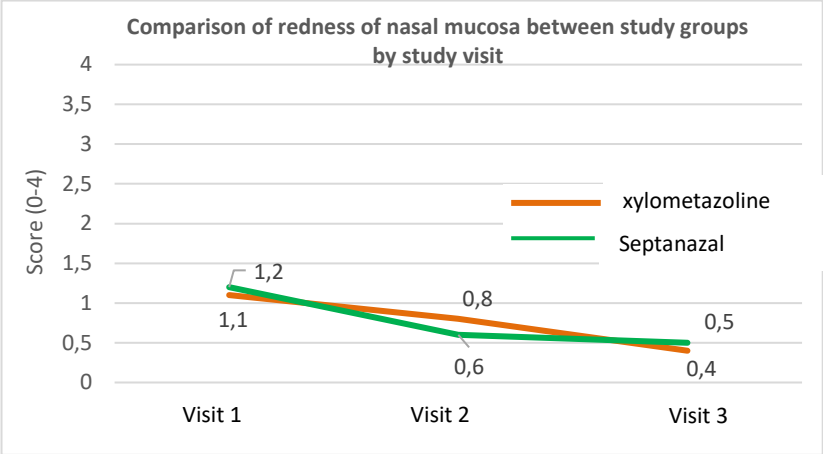
Figure 15: Comparison of mean scores for bleeding of nasal mucosa between study groups by study visit (Group 1)



Redness of nasal mucosa:

The mean score for this item in the xylometazoline group was 1.1 at Visit 1, 0.8 (28% reduction; p=0.023) at Visit 2, and 0.4 at Visit 3 (50% reduction from Visit 2, p=0.002). It was reduced by 64% during the treatment (p=0.007). The reductions observed at Visit 2 and Visit 3 were statistically significant compared with previous study visits. The difference between Visit 1 and Visit 3 was also statistically significant. Redness of nasal mucosa was reduced between the study visits in the Septanazal group. The mean score at Visit 1 was 1.2, at Visit 2 it was 0.6 (49% reduction but statistically insignificant) and at Visit 3 it was reduced to 0.5 (20% statistically insignificant reduction compared with Visit 2). There was a 60% reduction in this item during the treatment, between Visit 1 and Visit 3, which was statistically significant (p=0.04). No statistically significant differences were found in absolute values of this item between the groups by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 16.

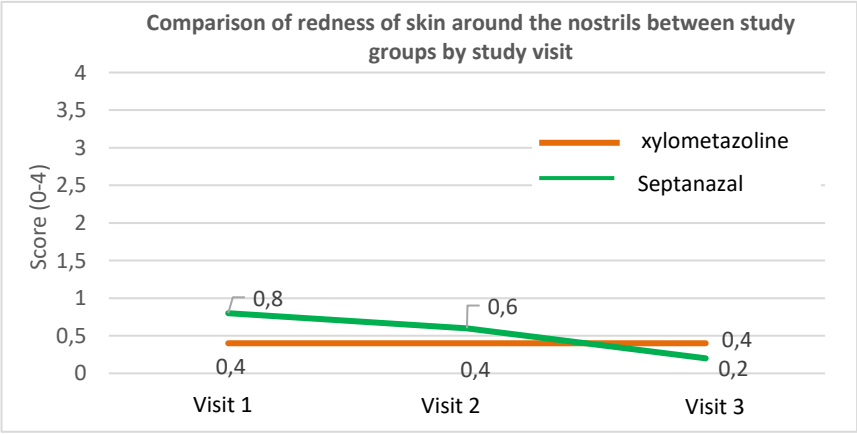
Figure 16: Comparison of mean scores for redness of nasal mucosa between groups by study visit (Group 1)



Redness of skin around the nostrils:

The mean score for redness of skin around the nostrils in the xylometazoline group was 0.43 at Visit 1, 0.4 at Visit 2 and 0.4 at Visit 3 and the reduction during treatment was thus statistically insignificant. In the group treated with Septanazal the baseline score of 0.8 was reduced to 0.6 (statistically insignificant difference). At Visit 3 the mean score was reduced to 0.2 and the reduction was statistically significant (67% reduction compared to Visit 2; p=0.016). This item was reduced by 77%, which was a statistically significant difference if compared wiht the baseline score at Visit 1. There were no statistically significant absolute differences in scores between the study groups by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 17.

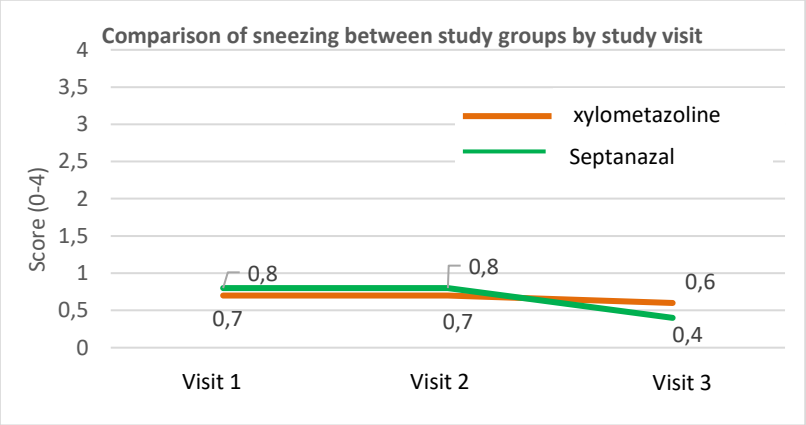
Figure 17: Comparison of mean scores for redness of skin around the nostrils between study groups by study visit (Group 1)



Sneezing:

The patients self-assessed the severity of the problem/symptom sneezing on a 0–4 scale at Visit 1, Visit 2 and Visit 3. The results are shown in Figure 18. The mean score in this item stayed unchanged in patients treated with xylometazoline. It was 0.7 at Visit 1, 0.7 at Visit 2 and 0.7 at Visit 3. In the Septanazal group there was a statistically insignificant reduction from the mean score of 0.8 at baseline to 0.8 at Visit 2. The mean score at Visit 3 was 0.4, which was a statistically significant reduction (p=0.016) compared with the previous study visit. This item was reduced by 47% during the treatment, which was a greater reduction compared with that in the xylometazoline group (statistically insignificant difference). No statistically significant absolute differences in scores were found between the groups by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3).

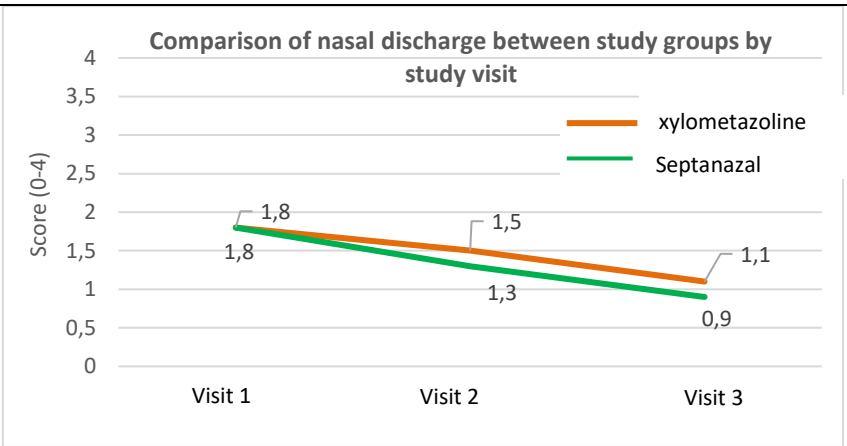
Figure 18: Comparison of mean scores for sneezing between study groups by study visit (Group 1)



Nasal discharge:

The patients self-assessed the severity of nasal discharge on a 0–4 scale during all three study visits (Figure 19). The mean score for nasal discharge was reduced between the study visits in both study groups. Statistically significant differences were observed between Visit 2 and Visit 3 and between Visit 1 and Visit 3. In patients treated with xylometazoline, the mean score was 1.8 at Visit 1, 1.5 at Visit 2 and 1.1 at Visit 3. There was a 15% reduction from Visit 1 to Visit 2 (statistically insignificant) and an additional 29% reduction from Visit 2 to Visit 3 (statistically significant, p=0.039). The overall reduction in the mean score for nasal discharge during treatment with xylometazoline was 39% (p=0.021). In patients treated with Septanazal, the mean score was 1.8 at Visit 1, 1.3 at Visit 2 and 0.9 at Visit 3. This was a 26% reduction between Visit 1 and Visit 2 (statistically insignificant). There was an additional 33% reduction between Visit 2 and Visit 3 (statistically significant; p=0.008). The overall reduction in nasal discharge during treatment with Septanazal was 50%. No statistically significant differences were found between the study groups by study visit in absolute differeces in the scores for this item (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3).

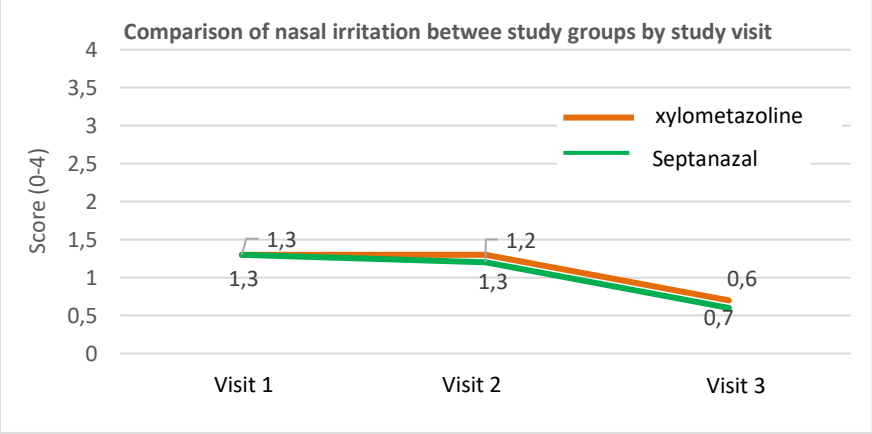
Figure 19: Comparison of mean scores for nasal discharge between study groups by study visit (Group 1)



Nasal irritation:

On a 0–4 scale, patients treated with xylometazoline had a mean score of nasal irritation of 1.3 at Visit 1, 1.3 at Visit 2 (3% statistically insignificant reduction) and 0.7 at Visit 3 (41% statistically significant reduction compared with Visit 2; p<0.0001). This item was reduced by 43% during the treatment, which was a statistically significant reduction compared with Visit 1 (p=0.013). The mean score in the group treated with Septanazal was 1.3 at Visit 1, 1.2 at Visit 2 (8% statistically insignificant reduction) and 0.6 at Visit 3 (47% statistically significant reduction compared with Visit 2; p=0.004). While this item was reduced by 52% during the treatment, the difference between its mean score at Visit 3 and at its mean score at Visit 1 was not statistically significant. Comparison of absolute differences between the study groups showed statistically insignificant differences by study visits (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 20.

Figure 20: Comparison of mean scores for nasal irritation between study groups by study visit (Group 1)



2. Duration of treatment and onset of rebound nasal congestion during the use of xylometazoline and dexpanthenol fixed-dose combination and xylometazoline alone in patients undergoing nasal or paranasal sinus surgery

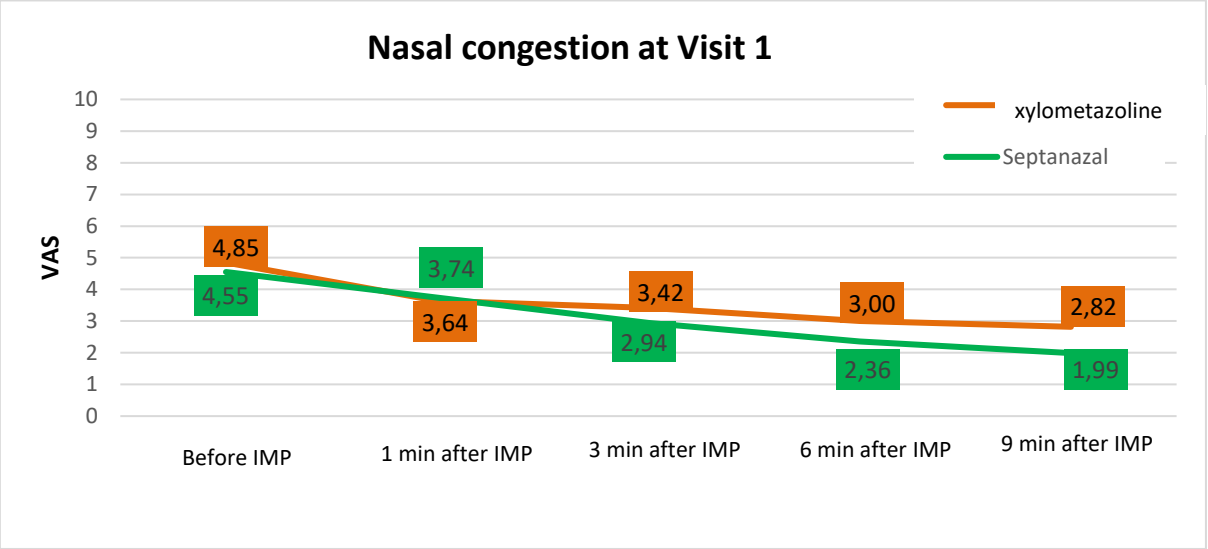
Possible occurrence of rebound nasal congestion during the study period was studied by assessing improvement in signs and symptoms (GAIB) at Visit 2 and Visit 3.

The results demonstrated that the treatment led to a significant improvement in the global sign and symptom score. In the group of patients treated with Septanazal, the mean score was reduced by 0.38 (absolute value), which means a 35% (p=0.008) reduction if the mean scores at Visit 2 and Visit 3 are compared. In the xylometazoline group, the mean score was reduced by 0.39 (absolute value), which is by 25% (p=0.002) if the mean scores at Visit 2 and Visit 3 are compared.

The investigators assessed response to treatment with the IMPs in both groups as good. However, a comparison of the mean global scores for improvement in the signs and symptoms during treatment did not show a statistically significant difference between the study groups (Figure 5).
No rebound nasal congestion was detected in either group, as demonstrated by improvement in the signs and symptoms after nasal and paranasal sinus surgery in both groups.

3. Comparison of the onset of action of xylometazoline and dexpanthenol fixed-dose combination and xylometazoline alone in patients undergoing nasal and paranasal sinus surgery
Both Septanazal and xylometazoline start to act within 1 minute after administration. A further increase in the reduction of nasal congestion is seen 3, 6 and 9 minutes after administration of either IMP (Figure 21).

Figure 21: Nasal congestion before and 1, 3, 6 and 9 minutes after administration of Septanazal or xylometazoline (Group 1)



The mean nasal congestion score on VAS before IMP administration was 4.55 in patients treated with Septanazal. One minute after administration it already fell to 3.64 (18% reduction). After 3 minutes it was 2.94 (35.4% reduction if compared with the score before IMP administration) and after 6 minutes it was only 2.36 (48.1% reduction if compared with the score before IMP administration). The final mean nasal congestion score, after 9 minutes, was 1.99 (56.3% reduction if compared with the score before IMP administration).
The mean nasal congestion score on VAS in patients treated with xylometazoline was 4.85 before IMP administration, 3.64 at 1 minute after IMP administration (25.0% reduction), 3.42 at 3 minutes after IMP administration (29.5% reduction compared with the score before IMP administration), and 3,00 at 6 minutes after IMP administration (38.1% reduction compared with the score before IMP administration).The final mean nasal congestion score, 9 minutes after IMP administration, was 2.82 (41.9% reduction compared with the score before IMP administration).

In patients treated with Septanazal, the nasal congestion score was reduced by 0.81 (18%) at 1 minute after IMP administration, by additional 0.8 (21%) at 3 minutes, by additional 0.58 (20%) at 6 minutes, and by additional 0.36 (15.0%) at 9 minutes after IMP administration.
In patients treated with xylometazoline, the nasal congestion score was reduced by 1.21 (25.0%) at 1 minute after IMP administration if compared with the score before it. The score was additionally reduced at 3 minutes, by 0.22 (6.0%), at 6 minutes, by 0.43 (12.0%), and at 9 minutes, by 0.17 (6.0%).
No statistically significant differences between the study groups were observed in the scores at 1, 3, 6 and 9 minutes after IMP administration.

Group 2: patients diagnosed with acute rhinitis

1. Patient self-assessment of symptoms

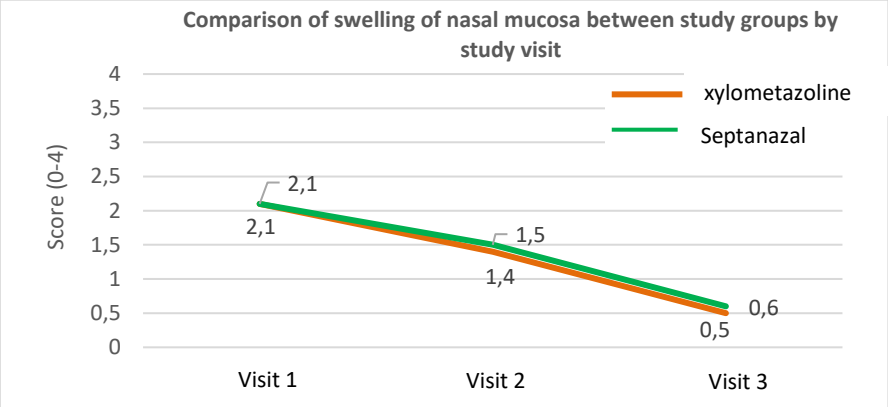
Swelling of nasal mucosa:

One hundred and thirteen (74%) patients assessed swelling of nasal mucosa on a 0–4 rating scale with a score of 2 or higher at Visit 1, 75% (59/80) of them from the group treated with xylometazoline and 73% (54/74) of them from the group treated with Septanazal. The mean score in this item was 2.1 in both groups. This item was scored 2 or higher at Visit 2 by only 43% (34/80) of the patients in the xylometazoline group. With 51% (38/74), the percentage was somewhat higher in the Septanazal group. The mean score in this item was in both groups statistically significantly lower if compared with Visit 1. It was 2.1 at Visit 1 and 1.4 at Visit 2 in the xylometazoline group (32% mean score reduction; p<0.0001) and 2.1 at Visit 1 and 1.5 at Visit 2 in the Septanazal group (29% mean score reduction; p<0.0001). At the end of the treatment the mean score was 0.5 in the xylometazoline group and 0.6 in the Septanazal group. There was a significant reduction in the mean score in both study groups if compared with Visit 2, with a 62% reduction (p<0.0001) in the xylometazoline group and a 60% reduction in the Septanazal group (p<0.0001).

The results demonstrated there was an improvement in this item in both study groups during the treatment. In the period between Visit 1 and Visit 3 it was statistically significantly reduced (by 74% in the xylometazoline group, p<0.0001, and by 72% in the Septanazal group, p<0.0001), which provides additional evidence supporting the efficacy of the IMP.

A comparison of the assessment scores for swelling of the nasal mucosa demonstrated that there were no statistically significant differences between the groups in the mean scores at individual study visits. Absolute differences between the scores were also statistically insignificant. The results are shown in Figure 22.

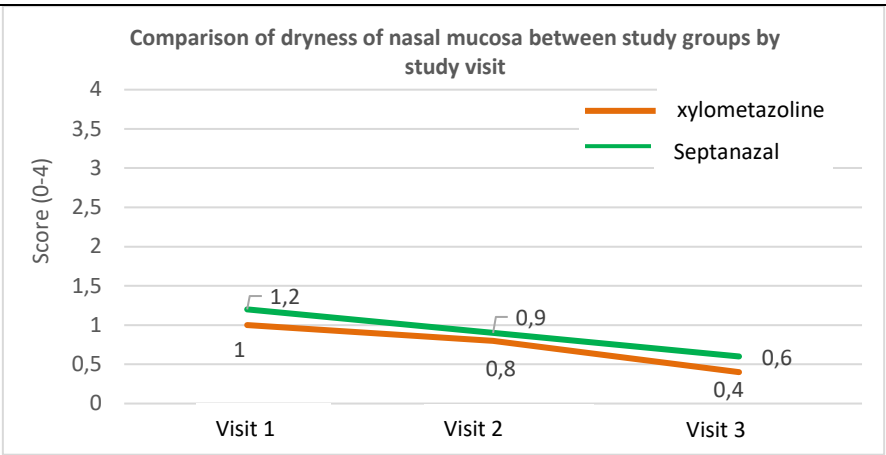
Figure 22: Comparison of mean scores for swelling of nasal mucosa between the study groups by study visit (Group 2)



Dryness of nasal mucosa:

The mean score for dryness of nasal mucosa was statistically significantly improving. In patients treated with xylometazoline the mean score at Visit 1 was 1.0, at Visit 2 it was 0.8 (a 15% reduction, p=0.04) and at Visit 3 it was 0.4 (a 56% reduction compared with Visit 2, p<0.0001) on a 0–4 scale. There was a 62% reduction in this item during the treatment. Dryness of nasal mucosa also improved statistically significantly between the study visits in the Septanazal group. The mean score for this item was 1.2 at Visit 1, 0.9 (a 22% reduction, p=0.041) at Visit 2 and 0.6 at visit 3 (a 36% reduction compared with Visit 2, p=0.0009). The mean score was reduced by 50% during the treatment and was 0.6 at the end of it. A comparison of differences in the mean scores between the study groups showed a statistically significant difference at Visit 3 (p<0.02).

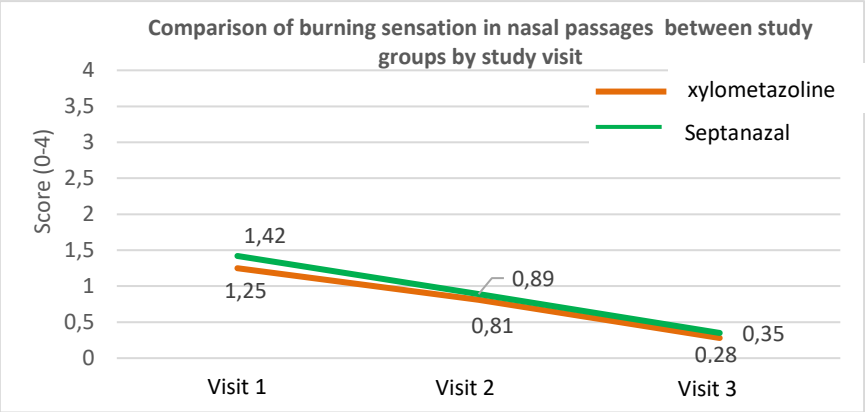
Figure 23: Comparison of mean scores for dryness of nasal mucosa between study groups by study visit (Group 2)



Burning sensation in nasal passages:

The mean score for this item at Visit 1 was 1.25 in the xylometazoline group and 1.42 in the Septanazal group, on a 0–4 scale. It was statistically significantly reduced in both groups at Visit 2 and Visit 3. The mean score in the xylometazoline group was 0.8 at Visit 2 (a 35% reduction, p<0.0001) and 0.28 at Visit 3 (a 66% reduction compared with Visit 2, p<0.0001). There was a 78% (p<0.0001) reduction in this item during the treatment and the mean score for it at end of the study was 0.28. Similar results were observed in the Septanazal group, as there were no statistically significant differences between the study groups in the mean scores at the study visits. With 0.89 the mean score at Visit 2 was improved by 37% (p<0.0001) compared with the baseline mean score. A further 61% improvement was observed at the final study visit, when the mean score was 0.35. The overall reductionin this item was 76% during the treatment (p<0,0001). The absolute differences in scores for this item between the study groups were statistically insignificant by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 24.

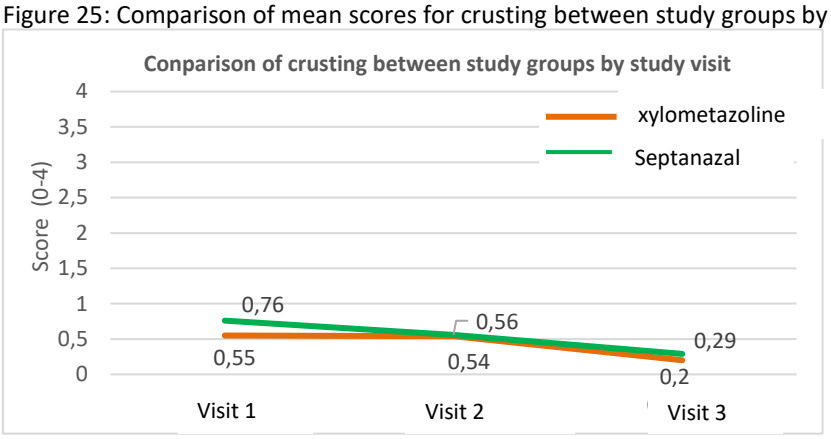
Figure 24: Comparison of mean scores for burning sensation in nasal passages between study groups by study visit (Group 2)



Crust formation:

In this item the mean score on a 0–4 scale was 0.55 in the xylometazoline group and 0.76 in the Septanazal group. The difference in the mean scores between Study visit 1 and Study visit 2 was statistically insignificant. However, a statistically significant improvement in the mean score was observed in both study groups at Visit 3. The mean score in the xylometazoline group was 0.20 and was reduced by 63% (p=0,0029)during the 7-day treatment. The mean score in the Septanazal group was 0.29 (p=0,0033). There was a 63% overall reduction during the 7-day period. The mean score in the Septanazal group was 0.29, and an overall reduction of it by 61% (p=0,0003)was observed during the same period. The differences in absolute values between the study groups for this item by study visit were statistically insignificant as well (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 25.

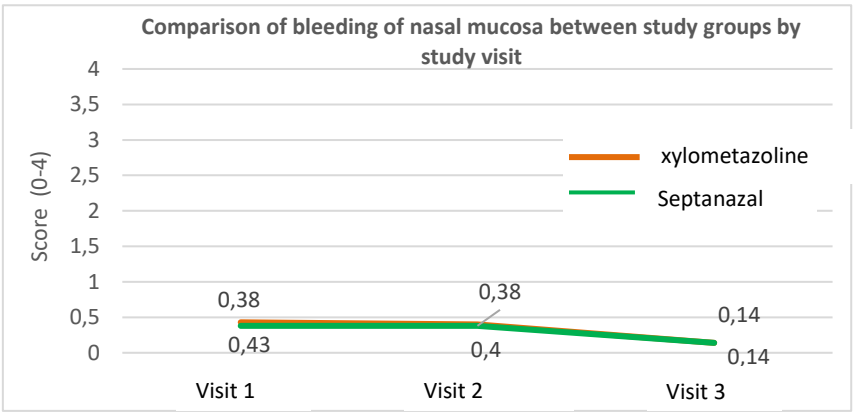
Figure 25: Comparison of mean scores for crusting between study groups by study visit (Group 2)



Bleeding of nasal mucosa:

The mean score for this item was 0.4 on a scale from 0 to 4 in both study groups. No statistically significant difference was found in this item between the study groups at Visit 2 compared with Visit 1, as its mean score was still 0.4. A statistically significant difference in this score was observed at Visit 3 in both study groups. In both the xylometazoline and Septanazal group the mean score for this item was 0.14. It was reduced during the 7-day treatment by 67% (p=0.0005) in the xylometazoline group and by 63% (p=0.0023) in the Septanazal group. A statistically insignificant difference between the study groups was shown in a comparison of differences in absolute values by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 26.

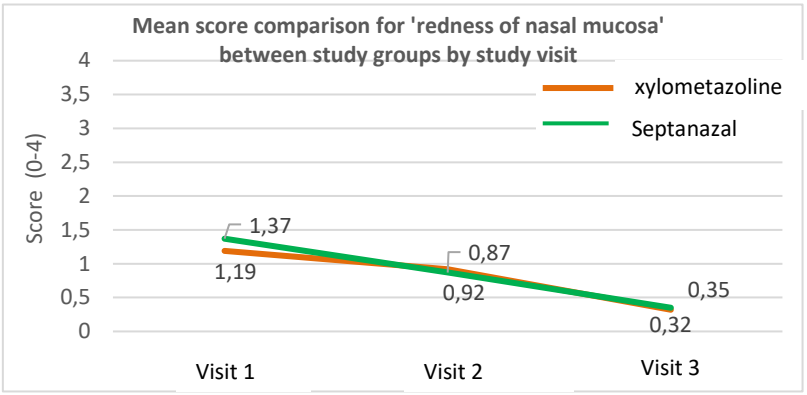
Figure 26: Comparison of mean scores for 'bleeding of nasal mucosa' between the study groups by study visit (Group 2)



Redness of nasal mucosa:

The mean score for this item improved statistically significantly during the treatment in all included patients. The mean score for this item in the xylometazoline group was 1.19 at Visit 1, 0.92 at Visit 2 (a 23% reduction, p<0.0001) and 0.32 at Visit 3 (a 66% reduction compared with Visit 2, p<0.0001) on a scale from 0 to 4. This item was reduced by 74% (p<0,0001) during the treatment. Statistically significant reductions in redness of nasal mucosa between the study visits were also observed in the Septanazal group. The mean score for this item was 1.37 at Visit 1, 0.87 at Visit 2 (36% reduction, p<0.0001) and 0.35 at Visit 3 (60% reduction compared with Visit 2, p<0.0001). This item was reduced by 75% during the treatment and its mean score the end of the treatment was 0.35. A comparison between the study groups in the absolute difference in was 0.35 at the end of the treatment. Absolute differences in scores between the study groups by study visit were statistically insignificant (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 27.

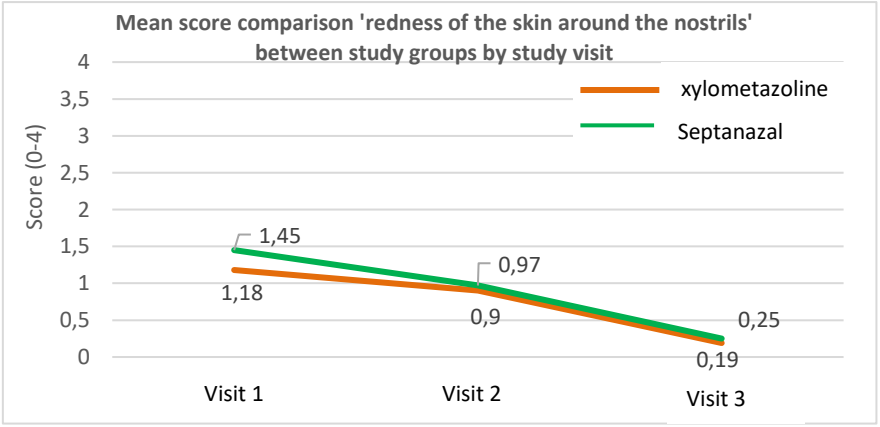
Figure 27: Comparison of mean scores for redness of nasal mucosa between study groups by study visit (Group 2)



Redness of the skin around the nostrils:

The mean score for this item was statistically significantly reduced during the treatment, in the xylometazoline group from 1.18 at Visit 1 to 0.9 at Visit 2 (a 23% reduction, p=0.008) and 0.19 at Visit 3 (a 79% reduction compared with Visit 2, p<0.0001), on a 0–4 scale. There was an 84% reduction in this item at the end of the treatment (p<0,0001). The results in the Septanazal group were similar, with statistically significant reductions in this item between the study visits. The mean scores were 1,45 at Visit 1, 0.97 at Visit 2 (33% reduction, p<0.0001) and 0.25 at Visit 3 (a 74% reduction compared with Visit 2, p<0.0001). The overall reduction in this item at the end of the treatment was 83% (p<0,0001). A comparison of absolute differences in the score for this item between the groups and between study visits showed no statistically significant differences (Visit 1 vs Visit, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 28.

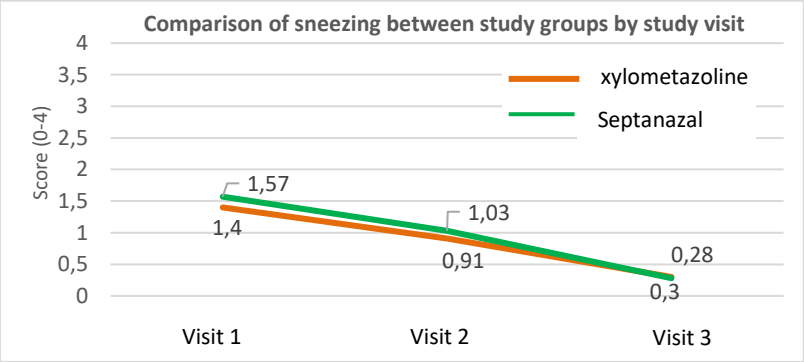
Figure 28: Comparison of mean scores for redness of the skin around the nostrils between study groups by study visit



Sneezing:

The mean score for this item was statistically significantly improving during the treatment. In patients treated with xylometazoline it was 1.4 at Visit 1, 0.9 at Visit 2 (a 35% reduction, p<0.0001) and 0.30 at Visit 3 (a 67% reduction compared with Visit 2, p<0.0001), on a 0–4 scale. There was an overall reduction of 78% in sneezing (p<0,0001). Sneezing was also reduced between the study visits in the Septanazal group. The mean score for sneezing was 1.57 at Visit 1, 1.03 at Visit 2 (a 34% reduction, p<0.0001) and 0.28 at Visit 3 (a 73% reduction compared with Visit 2, p<0.0001). The reduction in this item over the treatment period was 82%, which is more than in patients treated with xylometazoline (p<0,0001). The calculated difference between the groups was statistically insignificant. A comparison of the absolute differences in the scores for this item between the study groups showed that there were no statistically significant differences in scores by study visits (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3). The results are shown in Figure 29.

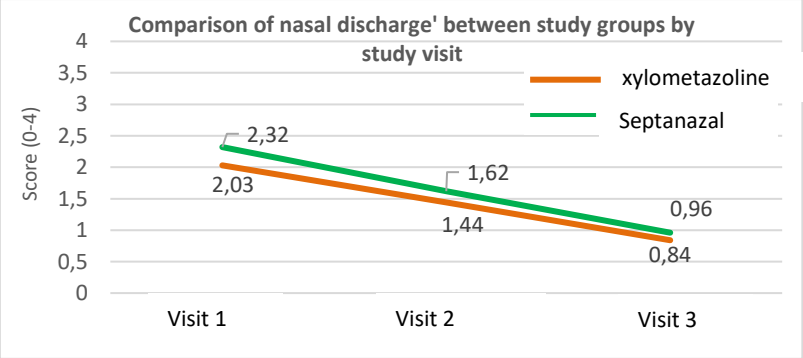
Figure 29: Comparison of mean scores for 'sneezing' between study groups by study visit (Group 2)



Nasal discharge:

The mean score for nasal discharge was statistically significantly reduced in both study groups (Figure 39). In the xylometazoline group it was 2.03 at Visit 1, 1.44 at Visit 2 and 0.84 at Visit 3 on a 0–4 scale. Nasal discharge was reduced by 29% between Visit 1 and Visit 2 ($p<0.0001$) and by further 42% ($p<0.0001$) between Visit 2 and Visit 3. A total reduction of 59% ($p<0,0001$) in the mean score was observed after treatment with xylometazoline. In the Septanazal group the mean score for this item was 2.32 at Visit 1, 1.62 at Visit 2 and 0.96 at Visit 3. The mean score was reduced by 30% between Visit 1 and Visit 2 and by further 41% ($p<0.0001$) between Visit 2 and Visit 3. The difference between study visits was of statistical significance. The total reduction in sneezing during treatment with Septanazal was equal to that in the xylometazoline group (59%, $p<0,0001$). A comparison of absolute differences in the scores for this item between the study groups showed no statistically significant differences by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 vs Visit 3).

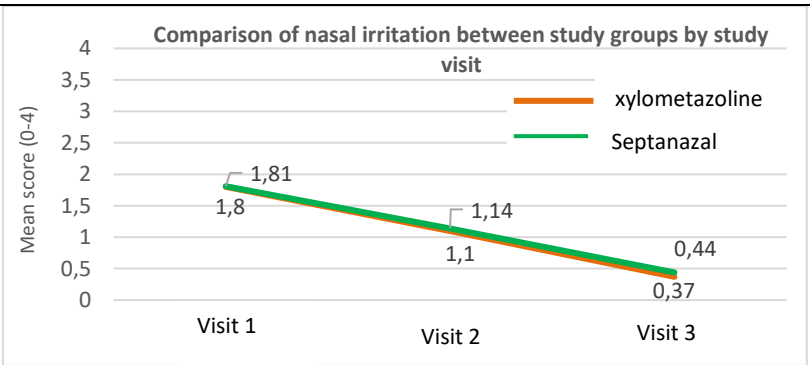
Figure 30: Comparison of mean scores for nasal discharge between study groups by study visit (Group 2)



Nasal irritation:

The mean score for nasal irritation was improving during the treatment in both study groups. The patients treated with xylometazoline had a mean score of 1.80 at Visit 1, 1.10 at Visit 2 (39% reduction, $p<0.0001$) and 0.37 at Visit 3 (a 67% reduction compared with Visit 2, $p<0.0001$), on a 0–4 scale. The total reduction in this item at the end of the treatment was 80% ($p<0,0001$). Nasal irritation was also statistically significantly reduced between the study visits in the Septanazal group. The mean score for this item was 1.81 at Visit 1, 1.14 at Visit 2 (37% reduction, $p<0.0001$) and 0.44 at Visit 3 (a 61% reduction compared with Visit 2, $p<0.0001$). This item was reduced by 75% ($p<0,0001$) during the treatment. A comparison of absolute differences in the scores for this item between study groups showed no statistical significance by study visit (Visit 1 vs Visit 2, Visit 1 vs Visit 3, Visit 2 versus Visit 3). The results are shown in Figure 31.

Figure 31: Comparison of mean scores for nasal irritation between study groups by study visit (Group 2)



2. Duration of treatment and onset of rebound nasal congestion during the use of xylometazoline and dexpanthenol fixed-dose combination and xylometazoline alone in patients with acute rhinitis

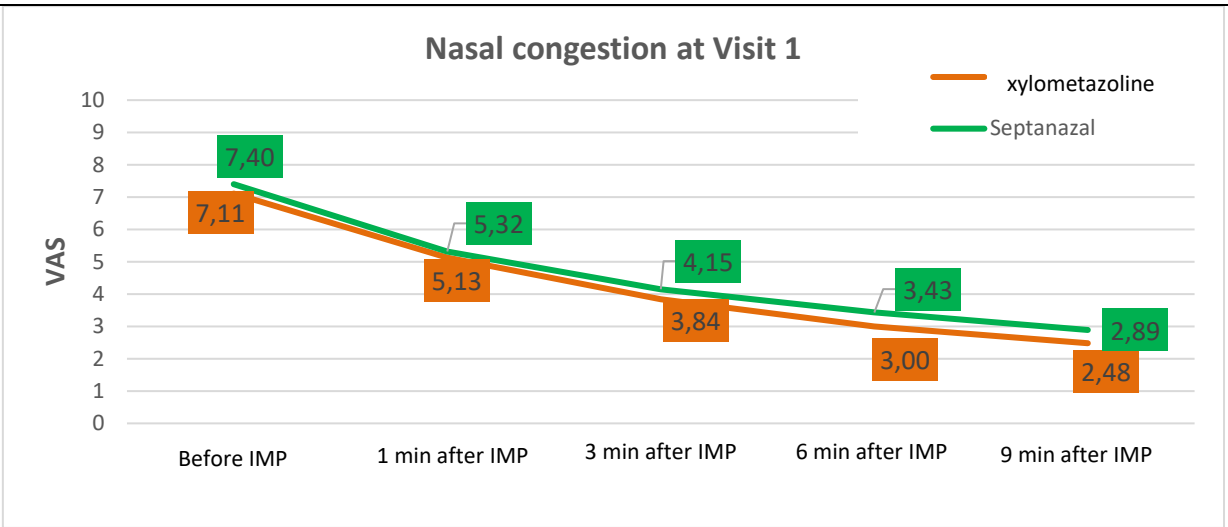
Possible occurrence of rebound nasal congestion during the study period was studied by assessing improvement in the signs and symptoms (GAIB) at Visit 2 and Visit 3.

The results demonstrated that the treatment led to a significant improvement in the global sign and symptom improvement score. In the group of patients treated with xylometazoline, the mean score was reduced by 0.72 (absolute value), which is by 47% if comparing the mean scores at Visit 2 and Visit 3 ($p<0.0001$). The patients in the Septanazal group had a reduction in the mean global sign and symptom score of 0.96 (absolute value), which is a 52% reduction if the mean scores at Visit 2 and Visit 3 are compared ($p<0.0001$). A comparison of the mean global sigh and symptom improvement scores between the study groups shows a statistically significant difference at Visit 2, with a higher score in the Septanazal group ($p<0.027$). The difference between the study groups at Visit 3 was statistically insignificant. It can thus be seen that despite the score in the Septanazal group was higher at Visit 2, it was reduced at Visit 3 to the same level as observed in the xylometazoline group. A comparison of the reduction in the mean scores between Visit 2 and Visit 3 also shows that there was a greater reduction in the Septanazal group (between-group difference = 0.24, $p<0.028$). There were no cases of rebound nasal congestion in either study group, as demonstrated by an improvement in the signs and symptoms of acute rhinitis in both groups.

3. Comparison of the onset of action of the xylometazoline and dexpanthenol fixed-dose combination and xylometazoline alone in patients with acute rhinitis

Both Septanazal and xylometazoline start to act within 1 minute after administration. An increase in the reduction of nasal congestion is seen at 3, 6, and 9 minutes after the administration of either IMP (Figure 32).

Figure 32: Nasal congestion before and 1, 3, 6 and 9 minutes after administration of Septanazal or xylometazoline (Group 2)



The mean VAS score for nasal congestion in patients treated with Septanazal was 7.40 before IMP administration. It was reduced to a mean score of 5.32 (28.2% reduction) at 1 minute, 4.15 at 3 minutes (43.3% reduction compared with that before IMP administration) and 3.43 at 6 minutes (53.1% reduction compared with that before IMP administration). The final mean score for nasal congestion at 9 minutes was 2.89 (60.8% reduction in nasal congestion compared to that before IMP administration).
In the xylometazoline group, the mean score for nasal congestion was 7.11 before IMP administration, 5.13 at 1 minute after IMP administration (27.5% reduction), 3.84 at 3 minutes after IMP administration (a 45.6% reduction compared with that before IMP administration) and 3.00 at 6 minutes after IMP administration (57.4% reduction compared with that before IMP administration). The final mean score for nasal congestion at 9 minutes was 2.48 (65.6% reduction compared to that before IMP administration).
In patients treated with Septanazal the mean score for nasal congestion was reduced by 2.08 (28.2%) compared to baseline at 1 minute after IMP administration, by further 1.17 (22%) at 3 minutes, by further 0.72 (17.4%) at 6 minutes and by further 0.54 (15.8%) at 9 minutes.
In the xylometazoline group, the reduction in the mean score for nasal congestion was 1.99 (27.5%) at 1 minute after IMP administration compared with baseline. It was reduced by further 1.29 (25.2%) after 3 minutes, 0.84 (21.9%) after 6 minutes and 0.53 (17.3%) after 9 minutes.
Differences between the study groups in the scores before IMP administration and at 1, 3, 6 and 9 minutes after IMP administration were statistically insignificant.

SAFETY RESULTS:

- Overall incidence of adverse reactions (treatment-related adverse events)
- Frequency of adverse reactions by outcome
- Number or percentage of patients withdrawing from the study due to clinically relevant adverse reactions

Group 1: Patients who underwent nasal or paranasal sinus surgery

1. Overall incidence of adverse reactions (treatment-related adverse events)

Ninety per cent (36/40) of the patients did not experience any adverse reactions (Table 3). Data on adverse reactions were missing in one patient. Three patients (7.5%) each experienced an adverse reaction that was (2 patients) or was not (1 patient) related to the IMP. One out of 40 patients (2.5%) experienced adverse events during the first period (recorded at Visit 2) and 2 patients during the second period (recorded at Visit 3).

Twenty patients (87%) in the xylometazoline group did not have any adverse reactions. Three patients (13%) had adverse reactions that were or were not related to the IMP. None of the patients in the Septanazal group had either an IMP-non-related or an IMP-related adverse reaction.

Table 3: Patients with or without adverse reactions (all Group 1 patients)

	First period		Second period		Both periods	
	N	%	N	%	N	%
Patients with adverse reactions:	1	2.5%	2	5.0%	3	7.5%
- patients with adverse reactions	1	2.5%	1	2.5%	2	5.0%
- patients with adverse reactions not related to the IMP	0	0.0%	1	2.5%	1	2.5%
Patients without adverse reactions	38	95.0%	37	92.5%	36	90.0%
Patients without available data (/)	1	2.5%	1	2.5%	1	2.5%
	40	100%	40	100%	40	100%*

* Due to rounding, percentages may not add up to 100%.

Adverse reactions experienced solely in the xylometazoline group included: hypertension (1/23, 4.3%), fatigue (1/23, 4.3%) and head tension (1/23, 4.3%).
None of the patients had an adverse reaction classified as severe or moderate (no data on intensity of adverse reaction were available for 1 patient). All recorded adverse reactions were mild and only occurred in the group treated with xylometazoline.

2. Frequency of adverse reactions by outcome

In two patients (8.7%) in the xylometazoline group the recorded frequency of adverse reactions was uncommon. None of the patients had persistent adverse reactions.
One out of 23 patients (4.3%) treated with xylometazoline had persistent adverse reactions and 1 out of 23 patients (4.3%) had adverse reactions that resolved. One patient (4.3%) experienced adverse events that were unrelated to the IMP.

3. Number or percentage of patients withdrawing from the study due to clinically relevant adverse reactions

None of the patients in any of the study groups discontinued the treatment and withdrew from the study. Two patients with adverse reactions out of 23 in the xylometazoline group continued active treatment without any actions taken. One patient treated with xylometazoline experienced an adverse event that was not related to the IMP.

Group 2: Patients diagnosed with acute rhinitis

1. Overall incidence of adverse reactions (treatment-related adverse events)

A percentage of 92.2% (142 out of 154) of the patients included in the study did not experience any adverse reactions (Table 4). An adverse event related to the IMP was reported by 7.1% (11) of the patients. Nine out of 154 patients (5.8%) experienced adverse reactions during the first period (data collected at Visit 2) and 6 during the second period (data collected at Visit 3).
No adverse reactions were experienced by 76 (95%) patients treated with xylometazoline. Four patients (5%) experienced an adverse reaction related to the IMP. In the group treated with Septanazal 89.2% (66 out of 74) patients did not have adverse reactions and 9.5% (7) had adverse reactions related to the IMP. No data on study visits were available for one patient in the Septanazal group.

Table 4: Patients with or without adverse events (all Group 2 patients)

	First period		Second period		Both periods	
	N	%	N	%	N	%
Patients with adverse events:	9	5.8%	6	3.9%	11	7.1%
- patients with adverse reactions	9	5.8%	6	3.9%	11	7.1%
- patients with adverse events not related to the IMP	0	0.0%	0	0.0%	0	0.0%
Patients without adverse reactions	144	93.5%	145	94.2%	142	92.2%
Patients without available data (/)	1	0.6%	3	1.9%	1	0.6%
	154	100%	154	100%	154	100%*

Adverse reactions observed during the clinical study in both study groups included:

- bleeding from the nose (7 patients, 4.5%) – 2 in the xylometazoline group, 5 in the Septanazal group
- burning sensation in the nose (6 patients, 3.9%) – 2 in the xylometazoline group, 4 in the Septanazal group
- bad taste in the mouth (2 patients, 1.3%) – 2 in the xylometazoline group
- tachycardia (2 patients, 1.3%) – 2 in the Septanazal group
- palpitations (1 patient, 0.6%) – 1 in the Septanazal group

None of the patients had a severe adverse reaction (the severity of the adverse reaction was unknown in 1 patient). Adverse reactions were moderate or mild.
While only mild adverse reactions were observed in patients treated with xylometazoline (4 patients, 5%), most of the adverse reactions experienced by patients treated with Septanazal were also of mild nature (6 patients, 8.1%), except for 1 which was of moderate severity (1.4%).

2. Frequency of adverse reactions by outcome

Five patients (3.2%) had a single occurrence of an adverse reaction, 2 in the xylometazoline group and 3 in the Septanazal group. Five patients (3.2%) had adverse reactions classified as uncommon. Out of these 5 patients 2 were in the xylometazoline group and 3 in the Septanazal group. None of the patients included in the study had any persistent adverse reactions.

In patients experiencing adverse reactions during treatment with the IMP, most adverse reactions were resolved (9 patients, 5.8%). Three (3.8%) of these patients were in the xylometazoline group and 6 (8.1%) in the Septanazal group.

3. Number or percentage of patients withdrawing from the study due to clinically relevant adverse reactions

One patient treated with Septanazal discontinued treatment during the study period and did not appear at Visit 2. The remaining 10 (6.5%) patients continued treatment with the IMP without any actions taken for adverse event.

CONCLUSIONS:

The study results provide evidence that the xylometazoline/dexpanthenol fixed-dose combination in Septanazal is an effective and safe medicine for treating nasal congestion both in patients undergoing nasal or paranasal sinus surgery and in patients with acute rhinitis. Septanazal starts acting in 1 minute after administration. The study also demonstrated that, in addition to improving nasal congestion, the fixed-dose combination of a decongestant and dexpanthenol significantly improves other signs and symptoms affecting patients undergoing nasal or paranasal sinus surgery (such as nasal bleeding, sneezing, nasal discharge, nasal irritation and redness of nasal mucosa or around the nostrils) and patients with acute rhinitis (such as nasal discharge, dryness of nasal mucosa, burning sensation in nasal passages, nasal irritation, sneezing and redness of the skin around the nostrils). None of the patients in any of the study groups had rebound nasal congestion. The addition of dexpanthenol to xylometazoline in the nasal spray is thus an important improvement in the treatment of acute rhinitis and postoperative states after nasal or paranasal sinus surgery. With its effect on epithelial healing and a favourable effect on mucosal function it mainly enhances the restoration of nasal patency and reduces other disturbing symptoms caused by the disease itself and by mucosal injury caused by surgery. The symptoms become mild and stop hindering the patients in daily activities, thereby improving their quality of life.