A comparison of therapeutic equivalence between test and reference formulations of the fixed combination of 3 milligrams benzydamine hydrochloride and 1 milligram cetylpyridinium chloride in the treatment of sore throat associated with upper respiratory tract infections

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Key words
Sore throat, cetylpyridinium chloride, benzydamine hydrochloride, analgesic, anti-inflammatory, antiseptic

Abstract

Cetylpyridinium chloride acts as a broad-spectrum antiseptic. Its antibacterial effect has been recognized for many years. Benzydamine hydrochloride is an indazole, a non-steroidal anti-inflammatory drug with analgesic, anti-inflammatory, local anaesthetic and antipyretic properties. It has been widely used across Europe for nearly four decades. The combination of antiseptic properties of cetylpyridinium chloride and anti-inflammatory and analgesic actions of benzydamine hydrochloride is therapeutically useful in the treatment of upper respiratory tract infections and inflammations. The aim of our study was to confirm efficacy and safety of the combination in the treatment of sore throat associated with upper respiratory tract infections.

The formulation, 3 mg benzydamine hydrochloride and 1 mg cetylpyridinium chloride (Septabene® lozenges, Krka, d. d., Novo mesto), was significantly superior to the placebo and comparable to the reference investigational medicinal product in all efficacy endpoints. The tested investigational medicinal product presented immediate onset of action. This was shown by the reduction of throat pain intensity and improvement in throat pain relief over the initial 15-minute period after the drug administration. Throat pain was statistically significantly reduced for at least three hours in comparison with the placebo. Similar improvement was observed in pain relief over three hours. After four days of the treatment, pain intensity was reduced by more than 85% from the baseline. At the end of the treatment, the disease was resolved in 89% of patients treated with the tested investigational medicinal product. Adverse reactions (dry mouth and heartburn) were reported in 2.54% subjects treated with the tested investigational medicinal product. The reactions were evaluated as mild and were abated within 24 hours. Both active treatments had a similar safety profile, which was clinically not significantly different from the placebo.*

This study demonstrated that the tested investigational medicinal product is effective and well tolerated and serves as an appropriate treatment option for patients with the sore throat associated with upper respiratory tract infections.

* In various markets the product is marketed under different names (Septolete total, Septolete omni, Septolete extra, Septolete duo, Septolete ultra).

Introduction

Upper respiratory tract infections (URTI) are among the most common acute infectious diseases and may cause an inflammation of the throat (pharyngitis). Pharyngitis is an inflammatory illness of the mucous membranes and the underlying structures of the throat. The acute sore throat, which typically describes self-limiting pharyngitis, tonsillitis, and laryngitis, is one of the most common complaints that patients present to their general practitioner or pharmacist. Most people with a sore throat, however, do not seek medical help.[1, 2]

Although bacterial causes are important causative agents, viral infections are responsible for the majority of sore throats. It has been estimated that 50–95% of sore throats in adults and 70% in children are caused by the infection with respiratory viruses, especially adenoviruses, the influenza virus and, particularly in the childhood, the herpes viruses. In less than 20% of cases of pharyngitis and tonsillitis, there is a primary or secondary involvement of bacteria.[3, 4]

As the majority of sore throats are not of bacterial origin, several international health authorities recommend that antibiotics should not be used as a primary treatment. Due to the predominantly viral cause of the sore throat, the resolution of symptoms is only marginally benefited by antibiotics and there is a risk of complications. Prescribing antibiotics for the sore throat treatment is therefore controversial. The clinical dilemma surrounding the treatment of the sore throat suggests the need for a non-antibiotic medication that would meet patients' expectations of providing rapid relief. [5–9]

Changing practices from over-prescribing antibiotics provides options for alternative treatments with medicated lozenges offering rapid reduction of pain and discomfort associated with the sore throat. The tested investigational medicinal product (TIMP), Septabene lozenges manufactured by Krka, d. d., Novo mesto, provides complete approach to the sore throat treatment, with the fixed combination of 3 mg benzydamine hydrochloride and 1 mg cetylpyridinium chloride. TIMP provides for the analgesic, anti-inflammatory and antiseptic treatment of the throat, mouth, and gums, irritations, and gingivitis, pharyngitis and laryngitis. Cetylpyridinium chloride is a quaternary ammonium antiseptic with demonstrated efficacy in the treatment of patients with infections and inflammations in the oral cavity and throat.[10–13] Benzydamine hydrochloride, a nonsteroidal anti-inflammatory drug, presents also a non-specific antibacterial activity. Benzydamine is extensively used in the clinical practice for the topical treatment of inflammatory conditions. It reduces locally induced inflammation, edema and granuloma formation in animals and demonstrates anti-exudative activities. Topical application increases the analgesic and anti-inflammatory activities of benzydamine much more than those of other anti-inflammatory drugs. [14, 15]

Methods

The study was conducted in Russia and Slovenia between November 2013 and February 2014. Male and female patients aged 18–65 years with a sore throat associated with URTI of ≤ 6 days' duration were eligible for inclusion in the study. Patients had to present the objective evidence of tonsilopharyngitis defined by the physician as a score of ≥ 4 points on the 10-point Tonsilopharyngitis Assessment (TPA) score. Furthermore, all participants were required to fulfil their perception of sore throat pain on the 100 mm Visual Analogue Scale (VAS) and only those with moderate to severe sore throat pain corresponding to the score ≥ 60 mm on the 100 mm VAS were eligible for study.

Patients were excluded from the study, if they presented any evidence of mouth breathing or coughing which could compromise respiratory function and worsen the sore throat; severe streptococcal tonsillitis assessed by rapid antigen detection test; severe changes of pharyngeal region with respect to TPA score; increased body temperature; chronic sore throat; other severe respiratory tract diseases, or oropharyngeal lesions. Patients were also excluded, if they had a pharmacological therapy with products which could influence study results, or a chronic disease requiring a long-term use of products which could influence study results. Patients with previously diagnosed hypersensitivity

to benzydamine, other NSAIDs, cetylpyridinium chloride, or any other component of study drugs were also excluded from the study. Pregnant or lactating women were excluded, as were any women of childbearing potential who were not taking adequate contraceptive precautions.

The study was randomised, comparative, placebo-controlled, parallel and partially blind. It was ensured that the study was blind with regard to the placebo and TIMP, while in relation to the reference investigational medicinal product (RIMP) the study was not blind due to technical difficulties. Even so, the labelling did not reveal the drug identity and the RIMP is not marketed in the countries involved, so the TIMP/RIMP appearance has not been familiar neither to the investigators, nor to the subjects. The subjects were assigned to three groups according to the randomisation schedule:

- Group A: Placebo lozenges
- Group B: RIMP (the fixed combination of benzydamine hydrochloride and cetylpyridinium chloride 3 mg/1 mg) lozenges
- Group C: TIMP – Septabene® (the fixed combination of benzydamine hydrochloride and cetylpyridinium chloride 3 mg/1 mg) 3 mg/1 mg lozenges

The key efficacy assessment was carried out at Visit 1 during the time interval of 15–180 minutes after the initial dose. At the same time, safety assessment has been carried out.

Assessment and procedures	Time of product application and clinical assessment points (min)												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Product application	x												
Subject symptoms assessment													
Sore Throat Pain Intensity (STPI) score	x	x	x	x	x	x	x	x	x	x	x	x	x
Sore Throat Pain Relief (STPAR) score		x	x	x	x	x	x	x	x	x	x	x	x
Adverse events assessment		x	x	x	x	x	x	x	x	x	x	x	x

Table 1. Study diagram

The therapy duration was 4 or 7 days, depending on whether the condition was completely resolved at the control visit after 4 days of the therapy. At days 5 and 8 the follow-up assessments were carried out principally to assess the safety profile for the entire treatment period. Some efficacy parameters have also been analysed at Visit 2 and Visit 3.

Efficacy and safety measurements

Besides standard procedures to assess medical history, general physical examination, and vital signs assessment, special procedures were applied to assess the baseline status of the disease and changes after the therapeutic intervention. Two different scales were used to assess subjects' symptoms severity and relief:

- Sore throat severity was assessed according to the Sore Throat Pain Intensity (STPI) scale, i.e. 0–100 mm VAS.
- Sore throat pain relief was assessed by a categorical Sore Throat Pain Relief (STPAR) scale. This scale uses seven verbal phrases to identify the level of pain relief as displayed in the table 2.

Category	Points
Complete relief	6
Almost complete relief	5
Considerable relief	4
Moderate relief	3
Mild relief	2
Slight relief	1
No relief	0

Table 2. STPAR scale points

After the administration, pain relief and sore throat intensity were assessed according to the scales at each measuring point (every 15 min for up to 3 h).

The tonsillopharyngitis assessment was carried out to assess the intensity of URTI using the sum of ratings on a rating scale from 0 to +2 for each of the following five commonly observed clinical features of tonsillopharyngitis displayed in the table 3.

Parameter	Points		
	0	1	2
Body temperature (oral)	≤ 37ºC	37.1–38.2ºC	≥ 38.3ºC
Oropharyngeal colour	Pink	Red	Beefy red
Oropharyngeal enanthemas*	None	Some	Many
Cervical adenopathy**	None	Some	Marked
Cervical adenitis (tenderness)	None	Slight or moderate	Severe

* exudates, vesicles, petechie, ** increased size or number of lymph nodes

Table 3. TPA scoring

To assess the safety profile, an interview and physical inspection were used. At Visit 1, an interview was used to assess the safety profile. At each efficacy assessment point, subjects were asked about any sensations or other symptoms. Subjects were also encouraged to report spontaneously any symptoms they experienced or any signs they observed during the entire assessment period of 3 hours. At Visits 2 and 3, both interview and physical inspection were used for safety assessment. All captured adverse events were stratified according to drug relatedness, severity, seriousness, time to onset, frequency, a requirement for the treatment and expectedness.

Results

The study engaged 291 subjects. Out of 291 patients randomised, 57 were assigned to placebo, 116 to RIMP and 118 to TIMP. All 291 randomized subjects were included in all the efficacy endpoints and in safety analysis. The mean age was 39 years. The population was composed of 198 females and 93 males. No statistically significant differences were observed among treatment groups with regard to any of the demographic variables, physical status and disease related factors.

Efficacy

The basic measurement parameter for the assessment of efficacy endpoints was STPI. It was assessed by VAS ranging from 0 (*no sore*) to 100 (*very sore*) in mm. The assessment points (in minutes) at Visit 1 were: 0 (baseline), 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180. At each of the Visits 2 and 3, a single assessment was made. In the Figure 1, graphical presentation of STPI values by therapy are presented for all the measuring points.

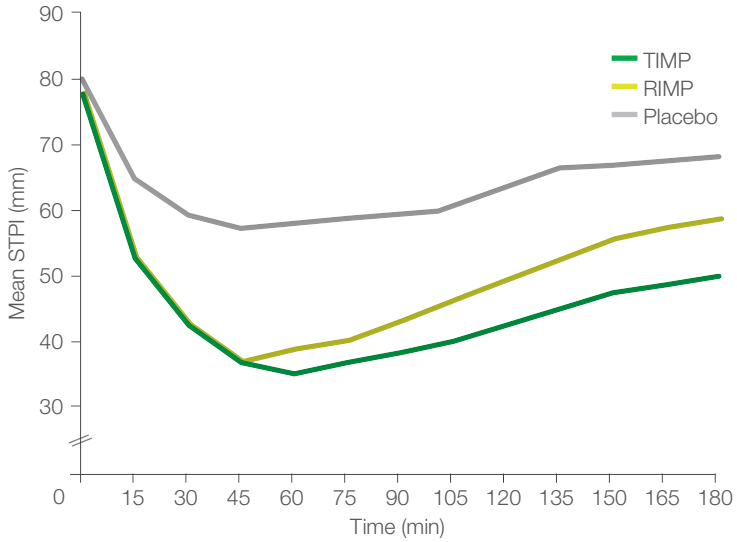

Figure 1. Dynamics of the STPI mean values over assessment times at Visit 1

Throat pain was significantly improved with TIMP in comparison to placebo. Effects were first noticed within 15 minutes following the administration and lasted for at least 3 hours.

Another measurement parameter relevant for the assessment of efficacy was STPAR at each of previously stated endpoints. Since STPAR denotes pain relief, there is no baseline measurement of this parameter. In the Figure 2, graphical presentation of STPAR values by therapy are presented for all the measuring points. Onset of pain relief with TIMP was observed 15 minutes after taking a lozenge and extended up to 3 hours.

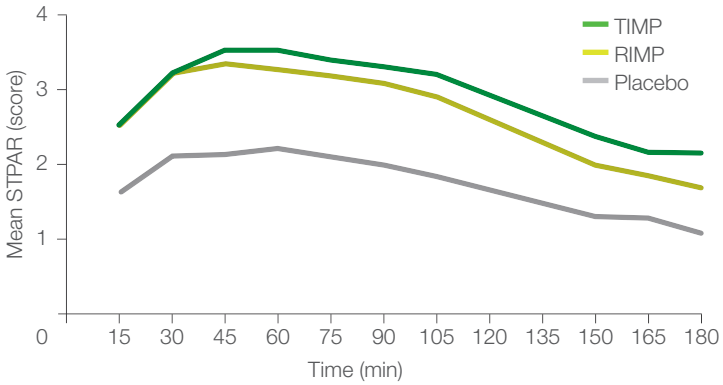

Figure 2. Dynamics of the STPAR mean values over assessment times at Visit 1

Primary efficacy endpoint

The primary efficacy endpoint was the difference in sore throat pain intensity at 1 hour (Sore Throat Pain Intensity Difference – $STPID_{1\,h}$) with respect to the baseline. Statistically significant greater $STPID_{1\,h}$ has been demonstrated for TIMP in comparison with placebo ($p < 0.0001$).

Secondary efficacy endpoints

As secondary efficacy endpoints, also $STPID_{2\,h}$ at predetermined time of two hours and $STPID_{3\,h}$ at predetermined time of three hours after the product application were used. Additionally total pain relief over the 15-minute to 3-hour interval ($TOTPAR_{15–180\,min}$) after the product administration and share of responders (% RESP) were assessed as secondary efficacy endpoints (Figure 3, Figure 4).

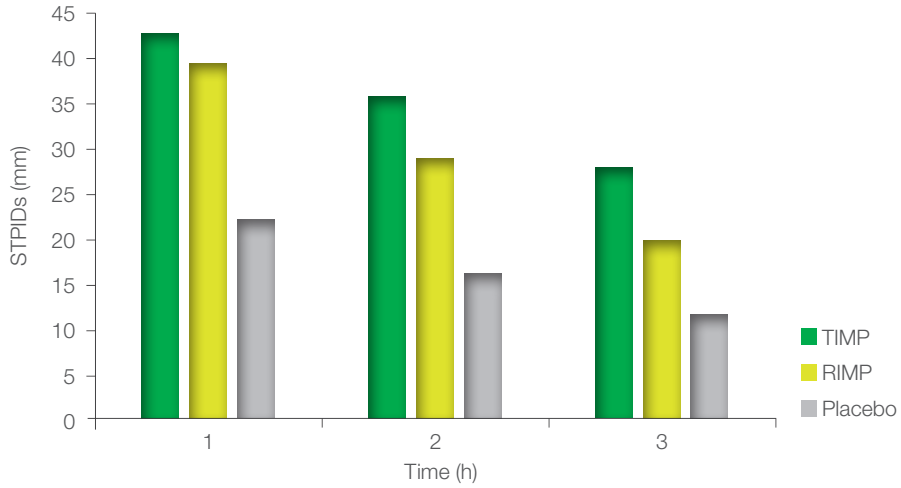

Figure 3. Dynamics of the STPIDs mean values over assessment times at Visit 1 by therapy group

$TOTPAR_{15–180\,min}$ was computed for each subject as the area under the curve of the pain relief scores according to the trapezoidal rule. The % RESP was defined as the share of subjects who responded to the therapy with respect to the total number of subjects who were taking the same product. A responder was considered every subject, whose STPI value was reduced by 13 mm or more at all three time points of 1 hour, 2 hours and 3 hours after the products single dose administration at Visit 1.

The significant superiority of TIMP over the placebo treatment was clearly demonstrated at all assessment points specified with primary as well as secondary efficacy endpoints.

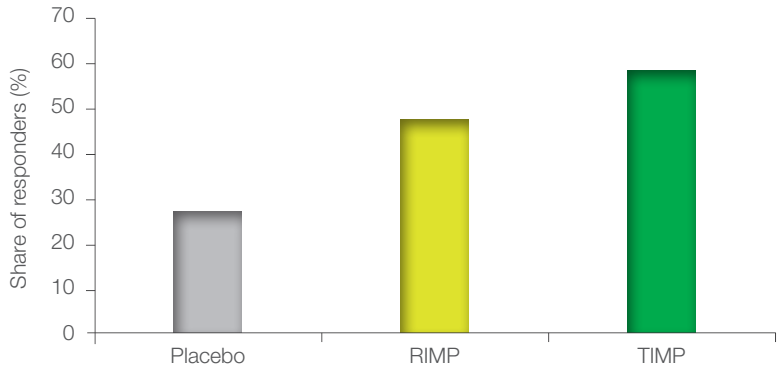

Figure 4. % RESP according to the therapy groups

Tertiary efficacy endpoints

The principal aim of the extended follow-up was safety assessment, hence tertiary efficacy endpoints only served as supportive data to the assessment of the efficacy by primary and secondary efficacy endpoints.

The share of subjects whose disease has been completely resolved (% RESOL) was assessed at Visit 2 and Visit 3. In the assessment of Visit 3, those subjects who successfully completed the treatment at Visit 2 were counted as having the disease resolved. At the end of the treatment, the

disease was resolved in 89% of patients treated with TIMP. A significant difference between TIMP and placebo was demonstrated also at Visit 2 ($p = 0.007$) and Visit 3 ($p < 0.001$).

The TPA was carried out to assess the intensity of URTI. It was assessed at Visit 2 and Visit 3. Subjects who already finished the treatment at Visit 2 were included into Visit 3 analysis with TPA score values from Visit 2 assessment. The significant difference between TIMP and placebo has been demonstrated at both follow up control points (Figure 5).

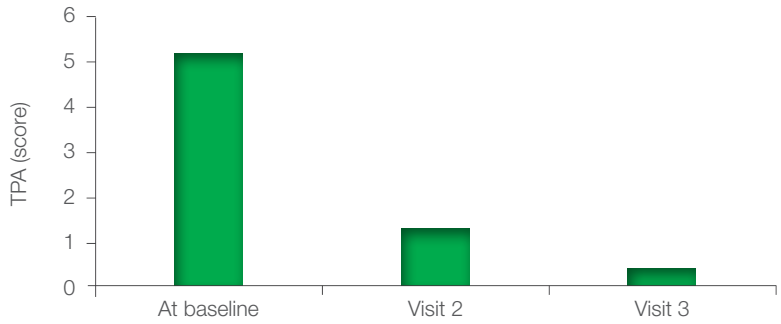

Figure 5. Reduction of TPA score with TIMP

Safety

The safety population comprised all 291 enrolled subjects. The total number of adverse events was 19, out of these 10 have been recognized as adverse reactions (ARs), drug related adverse events. There were altogether 10 ARs in all three groups with relatively balanced distribution between the groups. Dry mouth and heartburn were reported in 2.54% subjects treated with TIMP. They were evaluated as mild and were abated within 24 hours. There were no significant ARs that would demand subjects' withdrawal from the study. Both active treatments had similar safety profile clinically not significantly different from placebo.[16]

Conclusions

Due to the combination of active ingredients, the novel formulation Septabene® offers a comprehensive analgesic, anti-inflammatory and antiseptic approach to the treatment of sore throat. This study demonstrated that the novel formulation is an effective and well-tolerated treatment for sore throat. The efficacy of Septabene® was significantly superior to the placebo and comparable to RIMP.

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