

Annex 30

to the Procedure of registration materials examination of medicinal products,
submitted for state registration (re-registration),
as well as expert review of material for changes to registration materials
during the validity of the registration certificate
(art. 4, section IV)

Clinical research report

- | | |
|---|---|
| 1. Name of medicinal product (if available – number of registration certificate): | <p>Septolete® total with lemon and ginger
flavor 3 mg/1 mg lozenges</p> <p>(benzylamine hydrochloride 3 mg /
cetylpyridinium chloride 1 mg)</p> |
| 2. The applicant | <p>KRKA tovarna zdravil d.d. Novo mesto,
Smarjeska cesta 6, 8501 Novo mesto,
Slovenia</p> |
| 3. Manufacturer | <p>KRKA tovarna zdravil d.d. Novo mesto,
Ulica Rada Pusenjaka 10, 9240 Ljutomer,
Slovenia</p> |
| 4. the undertaken study: | <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 30px; height: 30px; margin-right: 10px;"></div> <div> ☒ yes ☐ no if not explain </div> </div> |
| 1) the type of medicinal product for which the registration was made or planned | <p>Lozenge, locally active</p> |
| 5. Full name of clinical research, coded number of clinical research | <p>“A comparison of therapeutic equivalence
between the test and the reference
formulation of fixed combination of
cetylpyridinium chloride 1.0
mg/benzylamine hydrochloride 3 mg in
subjects with sore throat associated with
upper respiratory tract infections”</p> <p>Study code: KKL072012</p> |
| 6. Phase of clinical research | <p>III</p> |
| 7. Time frame of clinical research | <p>from 18.11.2013 until 27.2.2014</p> |
| 8. Countries where the clinical research was conducted | <p>RUSSIAN FEDERATION and SLOVENIA</p> |
| 9. The number of persons under investigation: | <p>Number of patients: Planned for screening:
340 Target sample size for the per protocol
analysis of primary endpoint: 273 Actually</p> |

randomised: 291 Altogether 116 of these subjects were randomized to receive RIMP, other 118 were randomized to receive TIMP and 57 to receive placebo. Analyzed (per protocol analysis): 288 Analysed (full set analysis): 291

10. Purpose and secondary objectives of the clinical research

- To demonstrate the therapeutic equivalence with respect to the primary efficacy endpoint between the Tested Investigational Medicinal Product (TIMP) and the Reference Investigational Medicinal Product (RIMP).

- to demonstrate the superiority of the treatment effect with respect to the primary efficacy endpoint of both RIMP and TIMP over the placebo treatment

- to assess the safety profile of TIMP in comparison with RIMP and placebo and to demonstrate similar safety profile in TIMP and RIMP

in subjects with sore throat associated with upper respiratory tract infections

11. Clinical research design

A randomised, partially blind, placebo-controlled parallel study. An initial dose of investigational medicinal products (IMP) was applied and clinical assessment made within 3 hours after the drug administration to obtain the data for the primary and secondary efficacy endpoints analysis. Thereafter, subjects were administered IMPs according to the prescribed schedule for additional 4 – 7 days, primarily to assess the safety profile of IMPs. In addition, efficacy was also assessed by tertiary efficacy endpoints after 4 and 7 days of treatment. Principal methodology was the sore throat pain intensity assessment by means of Visual analogue scale (VAS) and pain relief assessment with Sore throat pain relief (STPAR) scale.

12. Main inclusion criteria

Diagnosis and main criteria for inclusion:
Sore throat associated to upper respiratory tract infections (URTI)

	Main inclusion criteria: • Subjects with a sore throat associated with URTI • Onset of sore throat ≤ 6 days • Both sexes, age range 18-65 years • ≥ 4 points on the 10 point Tonsilopharyngitis assessment (TPA) score • Moderate to severe sore throat pain defined as a score ≥ 60 mm on the 100 mm VAS
13. Test medicinal product, method of administration, strength	Septolete® Total 3mg/1 mg lozenges, (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg) one lozenge 4 times daily each three hours during daytime at the same time; the lozenge is taken orally to be dissolved in the mouth
14. Reference substance, dose, method of administration, strength	GOLA ACTION 3mg/1mg orosoluble tablets, (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg) one orosoluble tablet 4 times daily each three hours during daytime at the same time; the orosoluble tablet is taken orally to be dissolved in the mouth
15. Concomitant therapy	/
16. Efficacy evaluation criteria	Primary endpoint: - Sore throat pain intensity difference at 1 hour after the initial single IMP administration (STPID1h) - The primary efficacy endpoint is defined as the mean difference between Sore throat pain intensity (STPI), assessed by VAS at 1 hour after the IMP administration and the baseline STPI, assessed before the IMP administration at Visit 1. Secondary endpoints: - Mean sore throat pain intensity difference at 2 hours after the IMP administration (STPID2h) - STPID2h is defined as the mean difference between STPI at 2 hours after the IMP administration and the baseline STPI, assessed before the IMP administration at Visit 1.

- Mean sore throat pain intensity difference at 3 hours after the IMP administration (STPID3h) - STPID3h is defined as the mean difference between STPI at 3 hours after the IMP administration and the baseline STPI, assessed before the IMP administration at Visit 1.

- Total pain relief over the time interval of 15 min to 3 hours after the IMP administration (TOTPAR) - TOTPAR is defined as mean area under the curve (AUC) of Sore throat pain relief (STPAR) scores, calculated according to the trapezoidal rule over the time interval between 15 minutes and 3 hours after the IMP administration at Visit 1.

- Percent of responders after the initial single IMP dose (% RESP) % RESP is defined as the share of subjects who respond to the therapy with respect to the total number of subjects taking the same IMP. The responder criterion is related to minimal clinically significant change in STPI at one, two and three hours after the IMP administration.

- Time to sore throat pain relief (TSTPAR) The TSTPAR is defined as the mean time in minutes to a detectable and sustained STPAR after the IMP administration at Visit 1.

Tertiary endpoints:

- Tonsilopharyngitis assessment score (TPAS) TPAS is defined as the mean TPAS score at day 5 (Visit 2) and/or day 8 (Visit 3) of the study

- Percent of subjects whose disease has been completely resolved (% RESOL) % RESOL is defined as the share of subjects whose disease has been completely resolved at day 5 (Visit 2) and/or day 8 (Visit 3) with respect to the total number of subjects having been taking the same IMP

- Percent of subjects who had to take a rescue medication at least once during the treatment (% SRM) % SRM is defined as the share of subjects who had to take a rescue medication at least once during the treatment

with respect to the total number of subjects having been taking the same IMP

17. Safety assessment criteria

Overall incidence of adverse reactions (drug-related adverse events) - Incidence of adverse reactions stratified by specific type of adverse reaction (e.g. system organ, frequency and severity) - A number/percent of subjects unable to finish the clinical assessment due to clinically significant adverse reaction, worsening of symptoms or lack of effect

18. Statistical methods

PRIMARY EFFICACY ENDPOINT The null hypothesis for the primary efficacy endpoint (STPID1h) is inequivalence between TIMP and RIMP, and the alternative hypothesis is equivalence defined by pre-specified equivalence margin (δ). Assessment of these hypotheses was planned to be based on a two-sided 95% confidence interval for the treatment difference. It was to be concluded that TIMP is equivalent to RIMP if the lower and upper bounds of the 95% confidence interval for the treatment difference lie entirely within $(-\delta, \delta)$ interval. The equivalence margin for the STPID1h was 13 mm of VAS score. In the setting of the active IMP comparison against placebo, the null hypothesis of no treatment difference is tested against the alternative hypothesis of superiority. If the null hypothesis can be rejected in favour of the alternative hypothesis, it is to be concluded that TIMP and RIMP are superior to Placebo. The primary efficacy analysis of the STPID1h was based on an analysis of covariance (ANCOVA) model with clinical site and treatment as factors, and baseline pain intensity score as covariate; pairwise treatment comparisons were estimated by differences in least square means with their corresponding 95% confidence intervals. Since the assumptions for normality of data were met, an ANCOVA on the ranks or Wilcoxon rank sum test were not needed to be performed.

SECONDARY EFFICACY ENDPOINTS

The following secondary endpoints were tested in the same manner as the analysis of the primary efficacy endpoint: STPID2h,

STPID3h, and TOTPAR. Corresponding baseline scores were to be used as the covariates in the ANCOVA models. 95% confidence intervals for each treatment group and for the treatment differences were to be estimated. The secondary efficacy endpoint % RESP was analysed by Chi-square and pairwise Chi-square tests with their corresponding 95% confidence intervals. The secondary efficacy endpoint TSTPAR was to be analysed using survival analysis method. Log-rank test was used to determine the statistical significance of treatment group differences in the distribution of time to event.

TERTIARY EFFICACY ENDPOINTS The tertiary efficacy endpoints %RESOL and %SRM were analysed by Chi-square and pairwise Chi-square tests with their corresponding 95% confidence intervals. The tertiary efficacy endpoint TPAS was analysed by the non-parametric one way ANOVA. Summary statistics consists of sample size, frequencies and corresponding percentages for categorical endpoints. For continuous endpoints, descriptive statistics (number of available observations, mean, median, standard deviation, minimum and maximum are tabulated. Baseline characteristics are summarized by treatment group using appropriate descriptive statistics. Statistical analysis was performed on the locked data files using appropriate software (SPSS version 17.0).

19. Demographic indicators of the population study /
(gender, age, race, etc.)

20. Efficiency results

Presented in Synopses of Individual Studies in detail.

21. Safety results

Out of altogether 19 adverse events, 10 have been recognised as adverse reactions (drug related adverse events). The distribution of the adverse reactions (AR) among the study arms are displayed in Synopses of Individual Studies in detail.

The classification of AR by the study group according to system organ is displayed in Synopses of Individual Studies in detail.

Due to low number/frequency of the adverse event comparative statistical analysis has not been done. There were no patients withdrawn on account of safety. There were no serious adverse events in this trial. There were one case of accidental overdosing with TIMP (12 times recommended dose within three hours) but the patient had no adverse reaction.

22. Conclusion (evaluation)

The study clearly demonstrated equivalence between Septotele Total 3 mg/1 mg lozenges (TIMP) and the reference product GOLA ACTION 3 mg/1 mg orosoluble tablets (RIMP) in terms of primary efficacy endpoint. Out of secondary endpoints, TIMP was slightly but significantly better than RIMP in STPID after 2 and three hours, but the point estimate of the mean did not exceed the equivalence margin of 13 mm. There were no significant differences between the two active treatments in TOTPAR which is the indicator of pain relief over the entire 3 h dosing interval. Likewise no significant differences has been found between the TIMP and RIMP in percent of responders (% RESP). Time to onset of pain relief (TSTPAR) was significantly shorter in both active treatments compared to placebo, while the difference between the two active treatments was not statistically significant. The tertiary endpoint results supported the results with primary and secondary endpoints. Superiority of both TIMP and RIMP over the placebo treatment has been demonstrated in all the key efficacy endpoints of sore throat pain, sore throat pain relief and percent of responders to therapy. Altogether, 10 therapies related adverse events have been reported. There were all of mild intensity, none of them was serious and they were relatively evenly distributed between the treatment groups. Only descriptive statistics has been done due to low number of adverse reactions. In conclusion, therapeutic equivalence between TIMP and RIMP has been demonstrated with respect to primary efficacy endpoint. These

results have been corroborated with secondary and tertiary endpoints analysis. At the same time a superiority of both active treatments over placebo in all the key efficacy endpoints has been demonstrated. Both active treatments had similar safety profile clinically not significantly different from placebo.

Applicant (holder of
registration certificate)



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2521

to the Procedure of registration materials examination of medicinal products,
submitted for state registration (re-registration),
as well as expert review of material for changes to registration materials
during the validity of the registration certificate
(art. 4, section IV)

Clinical research report

- | | |
|---|--|
| 1. Name of medicinal product (if available – number of registration certificate): | <p>Septolete® total with lemon and ginger
flavor 3 mg/1 mg lozenges</p> <p>(benzylamine hydrochloride 3 mg /
cetylpyridinium chloride 1 mg)</p> |
| 2. The applicant | KRKA tovarna zdravil d.d. Novo mesto,
Smarjeska cesta 6, 8501 Novo mesto,
Slovenia |
| 3. Manufacturer | KRKA tovarna zdravil d.d. Novo mesto,
Ulica Rada Pusenjaka 10, 9240 Ljutomer,
Slovenia |
| 4. the undertaken study: | <div style="display: flex; align-items: center;"> ☒ yes ☐ no <div style="margin-left: 20px;">if not explain</div> </div> |
| 1) the type of medicinal product for which the registration was made or planned | Lozenge, locally active |
| 5. Full name of clinical research, coded number of clinical research | <p>“A comparative efficacy and safety of
cetylpyridinium chloride 1 mg/benzylamine
hydrochloride 3 mg fixed combination
lozenges in subjects with sore throat
associated with upper respiratory tract
infections”</p> <p>Study code: KKL022010</p> |
| 6. Phase of clinical research | III |
| 7. Time frame of clinical research | from 26.10.2011 until 15.6.2011 |
| 8. Countries where the clinical research was conducted | RUSSIAN FEDERATION |
| 9. The number of persons under investigation: | <p>Planned: 60 Analysed (per-protocol
analysis): 60 Altogether sixty subjects were
enrolled in the study: 20 of these subjects
were randomized to receive reference drug,</p> |

other 20 were randomized to receive test drug and 20 to receive placebo. All enrolled subjects successfully completed the study.

10. Purpose and secondary objectives of the clinical research

- To assess the parameters of the treatment effect of test investigational medicinal product (TIMP) in comparison with reference investigational medicinal product (RIMP) and placebo
- To assess the safety profile of TIMP in comparison with RIMP and placebo
- To evaluate the adequacy of efficacy and safety variables for the application in further studies with TIMP

11. Clinical research design

A randomised, partially blind, placebo-controlled parallel study. A single dose, single visit of investigational medicinal product was applied and clinical assessment made within 3 hours after the drug administration. The assessment followed the schedule of the assessment intervals 3 minutes at the beginning followed by 15 minutes till the assessment completion. Principal methodology was the sore throat assessment by means of Visual analogue scales (VAS) and pain relief assessment with Sore throat pain relief (STPAR) scale. Safety was followed by capturing adverse events during the 3 hour period after a single dose of a study drug.

12. Main inclusion criteria

Diagnosis and main criteria for inclusion: Sore throat associated to upper respiratory tract infections (URTI)

Inclusion criteria: • Subjects with a sore throat associated with URTI • Both sexes, age range 18-65 years • Written informed consent • Onset of sore throat ≤ 6 days • ≥ 3 points on the 10 point Tonsilopharyngitis assessment (TPA) score • Moderate to severe sore throat pain defined as a score ≥ 60 mm on the 100 mm Sore Throat Pain Intensity Scale (STPIS) • The ability to read and understand how to use Visual assessment scales

13. Test medicinal product, method of administration, strength	SEPTOLETE TOTAL lozenges, 3mg/ 1 mg , (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg) a single dose of one orosoluble tablet (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg)
14. Reference substance, dose, method of administration, strength	GOLA ACTION orosoluble tablets, 3mg/1mg, (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg) a single dose of one orosoluble tablet (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg)
15. Concomitant therapy	/
16. Efficacy evaluation criteria	Primary endpoint: - Total pain relief (TOTPAR3-180min) assessed over the time period of 3 to 180 minutes after the IMP application. Secondary endpoints: - Percent of maximal Total pain relief (%max TOTPAR 3-180min), - Percent of responders (% RESP), - Sore throat Pain relief (STPAR), - Time to sore throat pain relief (TSTPAR), - Sore throat pain intensity differences (STPID3-180min) - Sore throat pain intensity (STPI) - Swollen throat differences (STD15- 180min) - Swollen throat (ST) - Difficulty in swallowing differences (DSD15-180min) - Difficulty in swallowing (DS)

17. Safety assessment criteria

- Overall incidence of adverse reactions (drug-related adverse events)
- Incidence of adverse reactions stratified by specific type of adverse reaction
- A number/percent of subjects unable to finish the clinical assessment due to clinically significant adverse reaction

18. Statistical methods

PRIMARY EFFICACY VARIABLE The superiority of TIMP AND RIMP over placebo and the extent of the TIMP efficacy with respect to RIMP were tested. TOTPAR3-180min score, which was calculated as Area under curve (AUC) is based on an analysis of covariance (ANCOVA) model with center and treatment as factors, and baseline pain intensity score as covariate; pairwise treatment comparisons were estimated by differences in least square means with their corresponding 95% confidence interval. The primary efficacy hypothesis test was performed using a 5% overall significance level.

SECONDARY EFFICACY VARIABLES For secondary efficacy variables, %maxTOTPAR3-180min, STPID3-180min, STD15-180min, and DSD15-180min, the similar ANOVA or ANCOVA models as for the primary variable was used. Secondary efficacy variables STPAR, STPI, ST and DS, were analysed using a Mixed Model Analysis for repeated measurements. Fixed factors in the model were treatment groups (TIMP, RIMP and placebo) and the assessments times. TSTPAR was analysed using survival analysis methods. % RESP was analysed by means of a Fisher's exact test. For the secondary endpoints, hypothesis tests were performed individually at the 5% significance level. Summary statistics consists of sample size, frequencies and corresponding percentages for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum and maximum are tabulated. Baseline characteristics are summarized by treatment group using appropriate descriptive statistics. Statistical

analysis was performed on the locked data files using appropriate software (SPSS version 17.0).

19. Demographic indicators of the population study (gender, age, race, etc.) /

20. Efficiency results

Presented in Synopses of Individual Studies in detail.

21. Safety results

All three therapies were equally well tolerated. There were no adverse events reported during the course of the treatment follow-up.

22. Conclusion (evaluation)

The study demonstrated superiority of both TIMP and RIMP over the placebo treatment in all the key endpoints of sore throat pain, sore throat pain relief and percent of responders to therapy. Time to affect onset was shorter in both active treatments compared to placebo, but the difference was not statistically significant. The time to onset of TIMP was around 5 minutes shorter compared to RIMP but it was not statistically significant. In some secondary endpoints which are related to other symptoms such as the feeling of swollen throat or difficulty of swallowing, there was a trend towards better effect of active treatments but it does not reach statistical significance, presumably due to high data variability and the fact that study has been statistically designed with respect to primary endpoint statistical features. As for the comparison between the TIMP and RIMP there was a consistent trend of a slightly greater effect of RIMP in almost all the endpoints, however we did not find any significant differences in any of endpoints between the two active therapies. There were no adverse events identified during the assessment follow-up period in this study. IN conclusion, superiority of both TIMP and RIMP over placebo in the key variables of sore throat pain and the absence of significant differences between the two active treatments indicate that RIMP and TIMP are effective in the treatment of sore

throat pain and that they have similar
therapeutic efficacy and safety profile.

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