SYNOPSIS

Title of the study: A randomised, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of two doses of ketoprofen (as lysinate) lozenges (6.25 mg and 12.5 mg) in patients with sore throat

Investigator(s): [redacted]

Study center(s): International Study: in France (21 centers), Germany (10 centers), Mexico (6 centers), Russian Federation (10 centers), Spain (7 centers) and Egypt (3 centers)

Publications (reference): None

Study period:

Date first patient enrolled: 10 June 2009

Date last patient completed: 27 April 2010

Phase of development: phase III

Objectives:

Primary objective : To compare the single-dose efficacy of ketoprofen (as lysinate) lozenges (6.25 mg and 12.5 mg of ketoprofen base) with placebo, on total pain relief over 15 to 120 minutes ($TOTPAR_{15-120}$), which derived from the pain relief scale assessed every 15 minutes up to 2 hours after the first intake of investigational product (IP).

Main secondary objectives : To compare the single-dose efficacy of ketoprofen (as lysinate) lozenges (6.25 mg and 12.5 mg) with placebo after the first intake on:

- the total pain relief over 15 to 360 minutes ($TOTPAR_{15-360}$), which derived from the pain relief scale assessed every 15 minutes during the 2 hours following the first IP intake at study site, then every hour up to 6 hours as outpatient.
- the changes from baseline of global throat pain intensity assessed over 15 to 120 minutes and over 15 to 360 minutes
- the changes from baseline of throat soreness over 15 to 120 minutes and over 15 to 360 minutes
- the changes from baseline of swollen throat over 15 to 120 minutes and over 15 to 360 minutes

To compare pain relief, global throat pain intensity, throat soreness and swollen throat in the evening of Days 1, 2 and 3.

To evaluate the safety of ketoprofen (as lysinate) lozenges (6.25 mg and 12.5 mg) and placebo at follow-up visit on:

- Day 4: clinical and oral examination and adverse events (AE) reporting
- Day 7: adverse events reporting (followed by a clinical examination if needed)

Methodology: This was a phase III, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 2 doses of ketoprofen (as lysinate) lozenges (6.25 mg and 12.5 mg) in patients with sore throat. According to their randomized assignments, patients were to take the first lozenge of either ketoprofen (as lysinate) 6.25 mg, ketoprofen (as lysinate) 12.5 mg or matching placebo at inclusion. The second lozenge was to be taken 6 hours later, and then every 3 to 6 hours on an "as needed basis" up to a maximum of 5 lozenges within a 24-hour period. The treatment period was to last 3 days at the maximum. Follow-up evaluations were to be carried out on Day 4 and Day 7 of the study.

Number of patients : Planned: 835

Randomized:	placebo:	156;	ketoprofen 6.25 mg:	307;	ketoprofen 12.5 mg:	311;	total:	774	
Treated:	placebo:	156;	ketoprofen 6.25 mg:	307;	ketoprofen 12.5 mg:	311;	total:	774	

Evaluated:							
Efficacy (Intent-to-treat [ITT]):	placebo:	152;	ketoprofen 6.25 mg:	298;	ketoprofen 12.5 mg:	303;	total: 753
Efficacy (Per protocol [PP]):	placebo:	124;	ketoprofen 6.25 mg:	235;	ketoprofen 12.5 mg:	242;	total: 601
Safety:	placebo:	156;	ketoprofen 6.25 mg:	307;	ketoprofen 12.5 mg:	311;	total: 774

Pharmacokinetics: None.

Diagnosis and criteria for inclusion: Male or female patients aged 18 or over; patients with a sore throat associated or not with upper respiratory tract infection (URTI) ≥24 hours and ≤6-day duration, in the absence of A *Streptococcus*; evidence of tonsillo-pharyngitis (TPA score ≥5) at inclusion; with a score of throat soreness ≥6 (0-10 ordinal scale); with a perception of swollen throat ≥60 mm (visual analogue scale - VAS), with a global throat pain intensity such as pain at swallowing assessed by a VAS ≥60 mm; informed consent obtained in writing at the enrollment into the study; ability to understand and comply with study protocol.

Investigational product: ketoprofen (as lysinate) 6.25 mg and 12.5 mg

Dose regimen: According to their randomized assignments, patients took the first lozenge of either ketoprofen (as lysinate) 6.25 mg, ketoprofen (as lysinate) 12.5 mg or matching placebo at inclusion. The second lozenge could be taken 6 hours later, and then every 3 to 6 hours on an "as needed basis" up to a maximum of 5 lozenges within a 24-hour period.

Administration: Oral lozenges were to be sucked slowly until completely melted and not chewed.

Batch number(s): [redacted]

Duration of treatment: maximum of 3 days.

Duration of observation: 7 days.

Reference therapy: placebo lozenges

Dose: placebo: 0 mg

Administration: Oral lozenges were to be sucked slowly until completely melted and not chewed.

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy:

Primary criterion:

$TOTPAR_{15\text{-}120}$, which is derived from the pain relief scale measured every 15 minutes during the 2 hours following the first intake of IP at study site calculated as the area under the score time curve ($AUC_{15\text{-}120}$) as determined with a 7-category pain relief scale from 0 (no relief) to 6 (complete relief)).

Main secondary criteria:

$TOTPAR_{15\text{-}360}$ which is derived from the pain relief scale measured every 15 minutes during the 2 hours following the first intake of study drug at study site, then every hour up to 6 hours as outpatient.

$SPID_{15\text{-}120}$ and $SPID_{15\text{-}360}$ which are the sum of the change from baseline in global throat pain intensity over 15 minutes to 120 minutes and over 15 minutes to 360 minutes following first intake, respectively as determined with a global throat pain visual analogue scale (VAS).

$STSD_{15\text{-}120}$ and $STSD_{15\text{-}360}$ which are the sum of the change from baseline in throat soreness over 15 minutes to 120 minutes and over 15 minutes to 360 minutes following first intake, respectively as determined with a throat soreness ordinal rating scale.

$STSwD_{15\text{-}120}$ and $STSwD_{15\text{-}360}$ which are the sum of the change from baseline in swollen throat over 15 minutes to 120 minutes and over 15 minutes to 360 minutes following first intake, respectively as determined with a swollen throat VAS.

Main secondary criteria (continued):

Total pain relief in the evening for Day 1 through Day 3

Global throat pain intensity change from baseline in evening for Day 1 through Day 3

Throat soreness change from baseline in evening for Day 1 through Day 3

Swollen throat change from baseline in evening for Day 1 through Day 3

Percent of maximum $TOTPAR_{15\text{-}120}$

Safety: Adverse events (AE) reported by the patient or reported by the Investigator; clinical examination for mouth and/or throat erythema, ulceration or petechial hemorrhages.

Pharmacokinetics: Not applicable.

Statistical methods:

Population:

The ITT population was to be the primary population used for the primary and secondary endpoints analysis.

The PP population was used for a sensitivity analysis.

Primary analysis:

The increase in $TOTPAR_{15\text{-}120}$ was analyzed using an analysis of variance (ANOVA) with a fixed categorical treatment effect (placebo, ketoprofen (as lysinate) 6.25 mg and 12.5 mg). In order to control the overall Type I error rate, the Bonferroni-Hommel multiple comparison procedure was used to determine the statistical significance of the primary efficacy comparison of each of the two ketoprofen (as lysinate) doses versus placebo: if p-values for both ketoprofen dose levels were <0.05, both ketoprofen dose levels were considered significantly different from placebo; if a p-value for one of the ketoprofen dose level was >0.05, the p-value had to be <0.025 for the other group dose level to be considered significantly different from placebo.

Secondary analysis:

The increase in $TOTPAR_{15\text{-}360}$ was analyzed using the same model as for $TOTPAR_{15\text{-}120}$.

$SPID_{15\text{-}120}$ and $SPID_{15\text{-}360}$, $STSD_{15\text{-}120}$ and $STSD_{15\text{-}360}$ and $STSwD_{15\text{-}120}$ and $STSwD_{15\text{-}360}$ were analyzed using the same model as for the primary variable to which centered baseline score and centered baseline score by treatment interaction were added.

Total pain relief (evening assessments) was analyzed using a repeated measure ANOVA. Changes from baseline in global throat pain, throat soreness and swollen throat for evening assessments were analyzed using a repeated measure analysis of covariance model.

No multiple comparison procedure was used for the statistical analysis of secondary variables. Only raw p-values were provided.

Safety:

The safety analyses were based on the reported AEs and other safety information. Treatment-emergent AEs (TEAE) were defined as AEs that occurred or worsened during the on-treatment period.

Summary:

Efficacy results:

Primary efficacy criterion: TOTPAR $_{15\text{-}120}$ (ITT population).

Statistical analysis is summarized in the following table showing statistically significant differences from placebo in pain relief over the first 2 hours following first intake for both ketoprofen dosages:

	Placebo (N = 152)	**Ketoprofen 6.25 mg (N = 298)**	**Ketoprofen 12.5 mg (N = 303)**
LSMean (SE)	3.6 (0.2)	4.3 (0.2)	4.7 (0.2)
LSMeans difference from placebo (95% CI)		0.7 (0.2; 1.3)	1.1 (0.5; 1.7)
p-value		0.0103	<0.001

LS: least square; SE: standard error; CI: confidence interval

Secondary criteria:

Statistical analysis of the TOTPAR$_{15\text{-}360}$ (ITT population) is summarized in the following table showing statistically significant differences from placebo in pain relief over the first 6 hours following first intake for both ketoprofen doses:

	Placebo (N = 152)	**Ketoprofen 6.25 mg (N = 298)**	**Ketoprofen 12.5 mg (N = 303)**
LSMean (SE)	13.0 (0.7)	15.2 (0.5)	16.1 (0.5)
LSMeans difference from placebo (95% CI)		2.1 (0.4; 3.9)	3.1 (1.3; 4.9)
p-value		0.0191	<0.001

LS: least square; SE: standard error; CI = confidence interval

Results of statistical analyses for the other main secondary criteria (ITT population) are summarized in the following table:

Statistically significant differences from placebo were more consistently observed in the ketoprofen 12.5 mg group than in the ketoprofen 6.25 mg group.

	Ketoprofen 6.25 mg	Ketoprofen 12.5 mg
	p-value	**p-value**
$SPID_{15-120}$	**0.0273**	**<0.001**
$SPID_{15-360}$	0.0917	**<0.001**
$STSD_{15-120}$	**0.005**	**<0.001**
$STSD_{15-360}$	0.0753	**0.0036**
$STSWD_{15-120}$	0.086	**<0.001**
$STSWD_{15-360}$	0.2105	**0.0023**
Total pain relief (evening)	0.4491	0.0602
Global throat pain intensity change* (evening)	0.9545	0.0596
Throat soreness change* (evening)	0.8448	0.2296
Swollen throat change* (evening)	0.3722	**0.0207**
Percent maximum $TOTPAR_{15-120}$	**0.0075**	**<0.001**

SPID: sum of global throat pain intensity difference; STSD: sum of sore throat score difference; STSWD: sum of swollen throat score difference
* Change from baseline (repeated ANCOVA)
In bold: statistically significant statistical significance

Safety results :

The percentage of patients with any TEAE was slightly higher in the ketoprofen groups (8.5% in the ketoprofen 6.25 mg group and 10.6% in the ketoprofen 12.5 mg group) compared to the placebo group (7.7%).

The clinical safety profile of the ketoprofen lozenges compared to the placebo was mostly represented by the following TEAEs:

- Cough: 10 patients overall, including 7 in the ketoprofen groups.
- Rhinitis: 8 patients overall, including 6 in the ketoprofen groups.
- Headache: 6 patients overall, all in ketoprofen groups.
- Sinusitis: 5 patients overall, including 4 in the ketoprofen groups.
- Throat irritation: 5 patients overall, including 4 in the ketoprofen groups.
- Pharyngitis: 4 patients overall, including 3 in the ketoprofen groups.

Two SAEs, both in the infections and infestations system organ class, occurred in the ketoprofen groups:

- In the ketoprofen 6.25 mg group: severe peritonsillar abscess considered to be treatment related.
- In the ketoprofen 12.5 mg group: severe gastroenteritis considered to be treatment unrelated.

Discontinuations due to a TEAE occurred in 1 patient of the placebo group and in 3 patients in each of the ketoprofen groups:

- In the placebo group: 1 patient discontinued treatment due to severe oropharyngeal pain.
- In the ketoprofen 6.25 mg group: 3 patients discontinued treatment: 1 patient due to severe peritonsillar abscess, 1 patient due to mild vomiting and 1 patient due to mild vomiting and abdominal pain.
- In the ketoprofen 12.5 mg group: 3 patients discontinued treatment due to diarrhea, dyspepsia and bacterial pharyngitis, respectively.

Conclusions: [redacted]
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