

**EVALUATION OF SAFETY OF USE OF A GINGIVAL GEL BASED ON
HYALURONAN IN TWO FORMULATIONS WITH DIFFERENT FLAVOURS**

<i>MATERIAL TESTED</i>	<i>GENGIGEL BABY GENGIGEL JUNIOR</i>
<i>PLACE OF TESTING</i>	<i>OFFICES OF PROF. PIGATTO AND DR. GUZZI</i>
<i>START OF TRIAL</i>	<i>5th NOVEMBER 2002</i>
<i>END OF TRIAL</i>	<i>24th DECEMBER 2002</i>
<i>TRIAL DIRECTOR</i>	<i>Prof. Paolo Pigatto</i>
<i>SCIENTIFIC SUPERVISOR</i>	<i>Dr. Gianpaolo Guzzi</i>
<i>CLIENT</i>	<i>Riservice Srl Ricerche e Servizi Integrati alle Aziende Via Accademia, 33 20131 Milan</i>
<i>SPONSOR</i>	<i>Ricerfarma Srl Via Egadi, 7 20144 Milan</i>
<i>RISERVICE REFERENCE No.</i>	<i>S/02/0570</i>

Trial Director

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1. ABSTRACT

On request by *Riservice Srl*, a trial was conducted on a group of 40 male and female volunteers aged 5 to 14 years old, to establish the safety in daily use of a gingival gel based on hyaluronan (hyaluronic acid) called Gengigel, in baby and junior formulations which differ only in terms of flavouring.

The preparation was supplied to each volunteer at the time of inclusion in the trial, after obtaining parental consent. The volunteers were asked to apply the gel in the oral cavity twice a day or more, taking care to massage the gums gently. The clinical follow-up was performed after 1, 2 and 3 weeks' use, by evaluating three objective clinical safety parameters (xerosis, erythema and oedema) and three subjective parameters (stinging, pain and tolerability) as well as compliance.

RESULTS

The results obtained in the area treated with the gels did not indicate the onset of any objective disorder (xerosis, erythema or oedema).

In particular, the results of the study of the subjective parameters indicated total absence of stinging or pain. Pleasantness of flavour was judged excellent in the case of GENGIGEL JUNIOR, while 6 of the 20 volunteers expressed some dislike of the flavour of GENGIGEL BABY. However, this attitude did not lead to discontinuance of the treatment.

CONCLUSIONS

The results obtained during the trial demonstrate that the application of Gengigel in both formulations (Baby and Junior) to the intact oral mucosa of volunteers aged 5 to 14 years old does not lead to adverse events or noteworthy reactions.

When the treated areas were directly observed, it was found that application of the product tested helped to improve the minimum inflammatory gingival processes typical of childhood and adolescence, without the appearance of any adverse or unexpected symptoms.

In conclusion, in the light of the results obtained, it can be stated that the products tested, namely GENGIGEL BABY and GENGIGEL JUNIOR, demonstrated good local and systemic tolerability, and can therefore be effectively used to prevent alterations of the gingival area.

2. PRODUCT STUDIED

2.1 Identification

The following products were used for the trial:

01 Gengigel Baby

02 Gengigel Junior

The products tested were supplied by RICERFARMA Srl of Via Egadi 7, 20144 Milan.

2.2 Storage

The product to be tested was stored at ambient temperature, shaded from the light, and kept in a controlled-humidity environment.

Following the test, a countersample of the product will be stored for two years after the date of delivery of the final report.

2.3 Unused product

The quantity of product not used in the trial (except for the countersample) can be returned to the client if so agreed in advance.

3. TRIAL FORMAT

Volunteers

3.1 Selection

Only volunteers with intact oral mucosae were recruited to the trial.

The following selection criteria were employed:

Inclusion criteria:

- a) good state of general health
- b) no skin diseases
- c) no current topical and/or systemic pharmacological treatment
- d) no history of ACD (allergic contact dermatitis)
- e) no participation in similar tests in the three months prior to the trial.

Exclusion criteria:

- a) any condition other than those indicated in the inclusion criteria.

3.2 Origin

The volunteers who participated in the trial were chosen from among persons who had spontaneously manifested their willingness to participate in such activities.

3.3 Age and sex

The volunteers were males and females, aged between 5 and 14 years old. The demographic data of the population used are set out in Table 1.

Table 1: Demographic data of patients tested

Vol. no.	Initials	Age (years)	Sex	Test compound	Start of test	End of test

3.4 Number

The group of volunteers selected for the trial consisted of 40 subjects, 20 of whom took Gengigel Baby and 20 Gengigel Junior.

3.5 Registration

One form was filled in for each volunteer, containing their personal data and a sequential reference number to facilitate processing of the data obtained in accordance with section 10 of Data Protection Act no. 675 of 31 December 1996.

3.6 Consent

All volunteers were informed by the researchers of the purposes of the trial and the risks involved, and were given all information about the trial, the rules of conduct, and the persons to contact if adverse events occurred.

The volunteers' parents gave their consent to the trial.

3.7 Investigation method

The tolerability and pleasantness of the two products were evaluated by means of clinical (objective) observation of the following parameters relating to the oral cavity mucosa:

1. Xerosis (1)
2. Erythema (1)
3. Oedema (1)

The volunteers' subjective opinions were also evaluated by analysing the following subjective parameters:

1. Stinging (2)
2. Pain (2)
3. Tolerability (3)
4. Compliance (3)

(1) In accordance with the following evaluation criteria: 0: None; 1: Mild; 2: Clearly visible; 3: Moderate; 4: Serious

(2) In accordance with the following evaluation criteria: 0: None; 1: Mild; 2: Clearly perceptible; 3: Moderate; 4: Serious

(3) In accordance with the following evaluation criteria: 1: Poor; 2: Good; 3: Very good; 4: Excellent

3.8 Statistical analysis

The results relating to the evaluation of tolerability/pleasantness obtained at the end of the trial relating to the use of Gengigel Baby and Gengigel Junior were subjected to statistical analysis with the Kruskal-Wallis non-parametric test, using Manugistic Statgraphics software for PC.

4. RESULTS AND CONCLUSIONS

The data obtained are reported in the Tables of results. Tables 1-6 relate to the product Gengigel Baby, and Tables 7-12 to the results obtained with the product Gengigel Junior.

CONCLUSIONS

The results obtained during the trial demonstrate that the application of Gengigel in both formulations (Baby and Junior) to the intact oral mucosa of volunteers aged 5 to 14 years old does not lead to adverse events or noteworthy reactions.

When the treated areas were directly observed, it was found that application of the product tested helped to improve the minimum inflammatory gingival processes typical of childhood and adolescence, without the appearance of any adverse or unexpected symptoms.

In conclusion, in the light of the results obtained, it can be stated that the products tested, namely GENGIGEL BABY and GENGIGEL JUNIOR, demonstrated good local and systemic tolerability, and can therefore be effectively used to prevent alterations of the gingival area.

The statistical analysis demonstrates that the product *Gengigel Baby* was significantly less well tolerated/liked than the product *Gengigel Junior*, as specified in the annexed table (Table 13).

5. FILING

All information relating to the product studied is stored in the archives by the client company for the period of 10 years.

N.B.: All experimental studies conducted by *Gengigel Baby* and *Junior* are performed in accordance with the Helsinki Declaration (1986), as amended.

TABLES OF RESULTS**1. GENGIGEL BABY****OBJECTIVE SYMPTOMS**

Table 1: OBJECTIVE EVALUATION OF XEROSIS

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly visible

3: Moderate

4: Serious

1. GENGIGEL BABY

Table 1: OBJECTIVE EVALUATION OF ERYTHEMA

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly visible

3: Moderate

4: Serious

1. GENGIGEL BABY

Table 3: OBJECTIVE EVALUATION OF OEDEMA

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly visible

3: Moderate

4: Serious

1. GENGIGEL BABY**SUBJECTIVE SYMPTOMS**

Table 4: SUBJECTIVE EVALUATION OF STINGING

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly perceptible

3: Moderate

4: Serious

1. GENGIGEL BABY

Table 5: OBJECTIVE EVALUATION OF PAIN

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly perceptible

3: Moderate

4: Serious

1. GENGIGEL BABY

Table 6: SUBJECTIVE EVALUATION OF TOLERABILITY AND COMPLIANCE

<i>Vol.</i>	<i>Tolerability</i>	<i>Compliance</i>
<i>mean</i>		

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

1: Poor

2: Good

3: Very good

4: Excellent

2. GENGIGEL JUNIOR

Table 7: OBJECTIVE EVALUATION OF XEROSIS

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly visible

3: Moderate

4: Serious

2. GENGIGEL JUNIOR

Table 8: OBJECTIVE EVALUATION OF ERYTHEMA

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly visible

3: Moderate

4: Serious

2. GENGIGEL JUNIOR

Table 9: OBJECTIVE EVALUATION OF OEDEMA

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly visible

3: Moderate

4: Serious

2. GENGIGEL JUNIOR

SUBJECTIVE SYMPTOMS

Table 10: OBJECTIVE EVALUATION OF BURNING

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly perceptible

3: Moderate

4: Serious

2. GENGIGEL JUNIOR

Table 11: OBJECTIVE EVALUATION OF PAIN

Vol.				
<i>mean</i>				

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

0: None

1: Mild

2: Clearly perceptible

3: Moderate

4: Serious

2. GENGIGEL JUNIOR

Table 12: SUBJECTIVE EVALUATION OF TOLERABILITY AND COMPLIANCE

<i>Vol.</i>	<i>Tolerability</i>	<i>Compliance</i>
<i>mean</i>		

Key:

Vol. = volunteer

t0: inclusion in trial; t1: examination after 1 week; t2: examination after 2 weeks; t3: examination after 3 weeks (end of trial)

1: Poor

2: Good

3: Very good

4: Excellent

STATISTICAL ANALYSIS

It proved unnecessary to perform a statistical evaluation of the parameters studied, as no variations were recorded at any of the test times. The sole exception was represented by the subjective parameter “compliance”, for which different opinions were recorded in the two groups. To establish the level of statistical significance, the data were analysed with the Kruskal-Wallis non-parametric test. The data were processed with dedicated software (Manugistic for PC).

As demonstrated by the results reported in Table 13, the level of compliance with the product Gengigel Junior was superior to compliance with the product Gengigel Baby to a moderately significant extent ($p < 001$).

Table 13: COMPARISON BETWEEN THE TWO GROUPS IN RELATION TO SUBJECTIVE EVALUATION OF COMPLIANCE