Institute for Industrial Research & Toxicology
औद्योगिक अनुसंधान एवं विष विज्ञान संस्थान
Registration No. 1303/C/09/CPCSEA (Ministry of Environment & Forests, Government of India)
GLP Certified, NABL (ISO/IEC 17025) Accredited and FDA Approved (Drug & Cosmetics)
AN ISO 9001 : 2015, ISO 14001 : 2015, ISO 45001 : 2018 Certified Organization

INTRACUTANEOUS REACTIVITY OF GEL - ARTICLE NO - 10252203174" IN NEW ZEALAND WHITE RABBITS

(ISO Guideline: 10993-10)

SPONSORED BY

NUTRIN GMBH & GALAXA PHARMA APS

CRO

MITTAL GLOBAL CLINICAL TRIAL SERVICES (MGCTS)

DATA REQUIREMENTS

ISO GUIDELINE 10993 PART 10 BIOLOGICAL EVALUATION OF MEDICAL DEVICES- TEST FOR IRRITATION AND SKIN SENSITIZATION

TESTING LABORATORY

INSTITUTE FOR INDUSTRIAL RESEARCH & TOXICOLOGY
F-209, U.P.S.I.D.C., M.G. ROAD,
GHAZIABAD-201302

PROJECT NO	**:**	**202010-052**
REPORT NO	**:**	**IIRT/MD/202010/526/ICR**
ULR NO	**:**	**TC661219000000526P**
DATE	**:**	**24-08-2020**

TEST COMPOUND : GEL " ARTICLE NO - 10252203174"
SPONSORED BY : NUTRIN GMBH & GALAXA PHARMA APS
CRO : MITTAL GLOBAL CLINICAL TRIAL SERVICES (MGCTS)
STUDY : INTRACUTANEOUS REACTIVITY IN NEW ZEALAND WHITE RABBITS
PROJECT No. : 202010-052
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1. GLP STATEMENT OF COMPLIANCE

I, undersigned hereby declare that Project No **202010-052/Report No. IIRT/MD/202010/526/ICR** entitled **Intracutaneous Reactivity** of " **GEL - ARTICLE NO - 10252203174"** in New Zealand White Rabbits was performed in accordance with the standard operating procedures of Pharmacology/Toxicology Department, Institute for Industrial Research & Toxicology, Ghaziabad, UP, India, as well as the approved study plan.

I hereby attest the authenticity of the study and guarantee that this report represents a true and accurate record of results obtained and shall not be reproduced except in full, without the written approval of the Sponsor.

The study was conducted in compliance with International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10 following Good Laboratory Practice regulations (GLP), 21 CFR 58.

All original raw data including documentation, the draft report, a copy of the final report and the representative test item are archived in the archives at Pharmacology/Toxicology Department, Institute for Industrial Research & Toxicology, Ghaziabad, UP, India**.** There were no known circumstances that may have affected the quality or integrity of the study.

The sponsor is responsible for necessary evaluations of the test item concerning the chemicals purity, identity, stability and other required data.

Ms. Jyoti	Jyoti	**24-08-2020**
Study Director	**Signature**	**Date**

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
SPONSORED BY	**:**	**NUTRIN GMBH & GALAXA PHARMA APS**
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2. STATEMENT BY TEST FACILITY MANAGEMENT

Management of the test facility has made available all the resources to the Study Director which was necessary for conduct of the present study in compliance with the principles of GLP.

I, the undersigned, take overall responsibility for the reliability of the work described in the report with compliance of Good laboratory Practice.

_____ **24 -08- 2020**

Laboratory In-charge **Date**

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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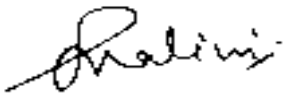
3. QUALITY ASSURANCE STATEMENT

This **Project No. 202010-052/Report No. IIRT/MD/202010/526/ICR** entitled **Intracutaneous Reactivity** of "**GEL- ARTICLE NO - 10252203174"** in New Zealand White Rabbits was carried out according to International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitisation following Good Laboratory Practice regulation, 21 CFR 58 was subjected to inspections by the Quality Assurance Unit.

This report has been audited by the Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed. In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

Standard Test Method Compliance Audit	:	20-07-2020
Test Material Preparation	:	21-07-2020
Date of Testing	:	24-07-2020
Draft Report Audit	:	18-08-2020
Final Report Date	:	24-08-2020



24-08-2020

Ms. Shalini Mishra	**----------**	**----------**
Quality Assurance Head	**Signature**	**Date**

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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STUDY INFORMATION

PROJECT NUMBER : 202010-052

REPORT NUMBER : IIRT/MD/202010/526/ICR

STUDY TITLE : Intracutaneous Reactivity of **"GEL-ARTICLE NO - 10252203174"** in New Zealand White Rabbits (ISO Guideline: 10993-10: 2010 (E).

SPONSOR : **NUTRIN GMBH & GALAXA PHARMA APS**

CRO : **MITTAL GLOBAL CLINICAL TRIAL SERVICES (MGCTS)**

TESTING LABORATORY : **INSTITUTE FOR INDUSTRIAL RESEARCH & TOXICOLOGY**
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Fax: +91 11 22235111

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4. STUDY PERSONNEL

Study Director	:	Ms. Jyoti, M.Sc. Toxicology
Study Personnel	:	Mr. Shahnawaz Ahmed, M.Sc. Toxicology
Histopathology & Veterinarian	:	Dr. Naresh Chandra, M. V. Sc. Pathology

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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5. SUMMARY

The potential of the test article, **GEL- ARTICLE NO - 10252203174"** to cause irritation following intradermal injection in rabbits was evaluated in accordance with the International Organization for Standardization 10993-10: Biological Evaluation of Medical Devices, Part 10: Tests for irritation and skin sensitization. The medical device extract was prepared according to International organization for standardization (ISO) 10993, Biological evaluation of Medical Devices Part-12, Sample Preparation and Reference Materials (2004). The test article was extracted in 0.9% sodium chloride USP solution (SC). A 0.2 ml dose of the appropriate test article extract was injected by the intradermal route into five separate sites on the right side of the back of each of two rabbits. Similarly, the control was injected on the left side of the back of each rabbit. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. In the present study, there was no erythema and no edema observed from the test extract injected intradermally into New Zealand White Rabbits. The test article extract met the requirements of the test since the difference between the test extract and control mean score **was less than 1.0 (<1.0).**

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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INTRODUCTION

a. Purpose

The test article identified below was evaluated for intracutaneous reactivity potential on single topical application using New Zealand White Rabbits.

b. Testing Guideline

The study was conducted based on the International Organization for Standardization 10993, Biological Evaluation of Medical Devices, Part 10- Test for Irritation and Skin Sensitization &

International organization for standardization (ISO) 10993, Biological evaluation of Medical Devices Part-12, Sample Preparation and Reference Materials (2004)

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6. MATERIALS AND METHOD

8.1 Sample Selection:

The test Article provided by the sponsor was identified and handled as follows for the testing of Intracutaneous Reactivity In New Zealand White Rabbits.

Test Article Name	:	**GEL " ARTICLE NO - 10252203174"**
Batch No.	:	rd20014
Storage Condition	:	Room Temperature
Control Article	:	0.9% Sodium Chloride Solution (USP)
Control Article Stability Testing	:	-

8.2 Control Article Strength, Purity and Composition

(Sodium Chloride) Strength: Not applicable, No active components in formulation, Purity: Meets the requirement of USP Sodium chloride for injection and is certified as USP Grade. 0.9% NaCl ± 5.0% of Label claim, balance is water, Composition: Sodium Chloride/Water.

8.3 Preparation:

Test article was extracted with 50ml of 0.9% w/v sodium chloride USP (mass/volume; 0.2 gm/ml). The gel in extracted solution was sealed as necessary to avoid loss of vehicle during extraction. The test article was extracted with agitation in sodium chloride at 50˚C for 72 hour. The vehicle (without test article) was similarly prepared to serve as the reagent control.

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8.4 Test System:

Species	**:**	Rabbit (*Oryctolagus cuniculus*)
Source	**:**	Lala Lajpat Rai University
Strain	**:**	New Zealand White
Sex	**:**	Female
Body weight Range	**:**	1.80 kg ± 200 gm
Acclimatization	**:**	Minimum 5 days
No. of Animal	**:**	Three
Identification Method	**:**	Ear Tag

8.5 Justification of Test System

The intracutaneous injection test in New Zealand Rabbits is specified in the current ISO testing standards and has been used historically to evaluate extracted biomaterial from **GEL - ARTICLE NO - 10252203174"**.

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8.6 Animal Management:

Husbandry: The Conditions conformed to IIRT Standard Operating System that are based on the "***Guide for the Care and Use of Experimental Animals***"

Food: A commercially available rabbit feed from Pranav Agro Industries Ltd. was provided daily.

Water: Potable water was provided *ad libitum* through species appropriate water container or delivered through an automatic watering system.

Housing: Animals were individually housed in stainless steel suspended cages identified by a card indicating the lab number, animal number, test code, sex, and date dosed.

Environment: Air conditioned rooms with 10-15 air changes per hour, temperature between 22±3^{0}C, relative humidity 40-60% and illumination cycle set to 12 hours artificial fluorescent light and 12 hours dark.

Selection: Only healthy previously unused, animal free from irritation or other dermatological lesions that could not interfere with test were selected.

Personnel: Associates involved were appropriately qualified and well trained.

Veterinary Care: Standard veterinary medical care was provided in this study.

8.7 IAEC Approval:

This procedure has been approved by IIRT Institutional Animal Ethical Committee and is reviewed at least annually by the same committee.

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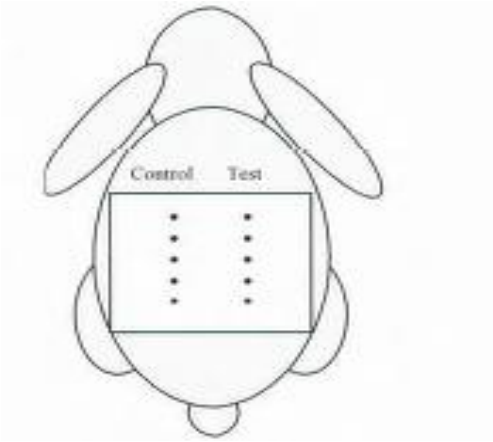
6.8 Method

Within a 4 to 18 hour period before treatment, each rabbit was clipped free of fur from the back and both sides of the spinal column which is sufficient area for injection. A 0.2 mL dose of the test article extract was injected by the intracutaneous route into five separate sites on the right side of the back of each rabbit. Similarly, the control was injected on the left side of the back of each rabbit. Injections were spaced approximately 2 cm apart.

The appearance of each injection site was noted immediately after injection. The animals were returned to their respective cages following the procedure.



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9. LABORATORY OBSERVATIONS

9.1 Observation and scoring

Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. Reactions were scored on a 0 to 4 basis as mentioned in Reference Table 1.

Table 1: Intracutaneous Reactivity Category in Rabbits

Response Category	Comparative mean score (PII)
Negligible	>0 to 0.4
Slight	0.5 to 1.9
Moderate	2 to 4.9
Severe	5 to 8

The animals were observed daily for abnormal clinical signs.

Detailed dermal observations were recorded at 24 ± 2, 48 ± 2 and 72 ± 2 hours as mentioned in Reference Table 2.

Any reaction at the injection sites was also noted.

The reactions were evaluated according to the following subjective rating scale is presented in Reference Table 2.

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Table 2: The tissue reactions were rated for gross evidence of erythema and oedema.

Erythema (ER)	Value	Edema (ED)
No erythema	**0**	No oedema
Very slight erythema (barely perceptible)	**1**	Very slight oedema (barely perceptible)
Well-defined erythema	**2**	Well-defined oedema (edges of area well-defined by definite raising)
Moderate erythema	**3**	Moderate oedema (raised approximately 1 mm)
Severe erythema (beet-redness) to eschar formation preventing grading of erythema	**4**	Severe oedema (raised more than 1 mm and extending beyond exposure area)

9.2 Evaluation Criteria

- The mean erythema and edema scores for the test and control extract for each animal at 24, 48, and 72 hours after injection were calculated. All mean erythema and edema scores for the test and control extracts were totalled and divided by 12 (2 animals x 3 grading periods x 2 grading categories) to determine the overall mean score for the test extract and control.
- The difference between the overall mean score of the test and control extracts was calculated by subtracting the overall mean score for the control from the overall mean score for the test extract.
- The requirements of the test were met if the difference between the test extract mean score and control mean score was 1.0 or less.

9.3 Termination

The rabbits were sacrificed by lethal injection with a sodium pentobarbital based solution (Euthasol) after the final observation period.

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10. RESULTS

All animals appeared normal throughout the study. Results of scores for individual rabbits are presented in Table 3. All injection sites appeared normal immediately following injection. The overall mean difference for the extract is summarized as mentioned below:

Extract	**Overall Test Group Mean**	**Overall Control Group Mean**	**Overall Mean Difference (Test – Control)**
SC	0.0	0.0	0.0

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Table 3: Intracutaneous Reactivity Score

Rabbit#	24 hour				48 hour				72 hour				Total Score
	Test		Control		Test		Control		Test		Control		
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	
1	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean Score	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean Score	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Note: ER= Erythema, ED= Edema

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11. CONCLUSION

Under the conditions of this study, it has been concluded that there was **no erythema and no edema** from the SC test extract injected intracutaneously into New Zealand White Rabbits. The SC test article extract met the requirements of the test since the difference between the test extract and control mean score was **less than 1.0 (<1.0).** , the test article is considered a negligible irritant. Results and conclusions apply only to the test article tested.

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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11. ARCHIVE

On completion of the study, the raw data and other material, sample of the test substance and the study report are being retained for nine years at Institute for Industrial Research and Toxicology, Ghaziabad, U.P India.

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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12. CERTIFICATE

This is to certify that the Intracutaneous Reactivity of the Sodium Chloride extract of **GEL " ARTICLE NO - 10252203174"** supplied by **NUTRIN GMBH & GALAXA PHARMA APS** with CRO **MITTAL GLOBAL CLINICAL TRIAL SERVICES (MGCTS)** was perfomed according to the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitisation met the requirements of the test since the difference between the test extract and control mean score was **less than 1.0 (<1.0)** in New Zealand White Rabbits.

The report of the Intracutaneous Reactivity test conducted has been submitted through **Study no. 202010-052** which can be concluded that the test material **GEL- ARTICLE NO - 10252203174"** is **safe** for use.

Note: Results and conclusions apply only to the test article tested.

Any extrapolation of these data to other samples is the sponsor's responsibility.

Jyoti

Study Director

TEST COMPOUND	**:**	**GEL " ARTICLE NO - 10252203174"**
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STUDY	**:**	**INTRACUTANEOUS REACTIVITY IN NEW ZEALAND WHITE RABBITS**
PROJECT No.	**:**	**202010-052**
REPORT No.	**:**	**IIRT/MD/202010/526/ICR**
ULR No.	**:**	**TC661219000000526P**

13. Annexure I: References

International Organization for Standardization (ISO) 10993, Biological Evaluation of Medical Devices Part-2, Animal Welfare Requirements (2006)

International organization for standardization (ISO) 10993, Biological evaluation of Medical Devices Part-12, Sample Preparation and Reference Materials (2004)

International organization for standardization (ISO) 10993, Biological evaluation of Medical Devices Part-10, Test for Irritation and Skin Sensitization (2010)