Propiconazole/Fenpropidin

Propiconazole/Fenpropidin EC (A9050B) – Acute Eye Irritation Study in Rabbits

Final Report

DATA REQUIREMENT(S): OECD Test Guideline 405 (2002)
EPA OPPTS 870.2400 (1998)
EC No 440/2008, B.5 (2008)

AUTHOR(S): Magdolna Török-Bathó, M.Sc.

STUDY COMPLETION DATE: 04 August 2011

PERFORMING LABORATORY: LAB Research Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

LABORATORY PROJECT ID: Report Number: 10/290-005N
Study Number: 10/290-005N
Task Number: TK0037097

SPONSOR(S): Syngenta Ltd.
Jealott's Hill International Research Centre,
Bracknell, Berkshire, RG42 6EY, UK

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the study plan, and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 9/2001. (III. 30.) EüM-FVM joint decree of the Minister of Health and the Minister of Agriculture and Regional Development which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: Bne Török Magdolna Date: 04 August 2011

Magdolna Török-Bathó, M.Sc.
Study Director

Performing Laboratory: LAB Research Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 10/290-005N

Study Title: Propiconazole/Fenpropidin EC (A9050B) – Acute Eye Irritation Study in Rabbits

Test Item: Propiconazole/Fenpropidin EC (A9050B)

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
09 March 2011	Study Plan	09 March 2011	09 March 2011
11 March 2011	Clinical Observation	11 March 2011	16 March 2011
24 May 2011	Draft Report	24 May 2011	24 May 2011
03 August 2011	Final Report	03 August 2011	03 August 2011

Signature: _____ Date: 04 August 2011

Szabolcs Gáty, M.Sc.
On Behalf of QA

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and LAB Research Ltd. (Test facility) the study titled "Propiconazole/Fenpropidin EC (A9050B) - Acute Eye Irritation Study in Rabbits" was performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 04 August 2011

Alyson Leyshon, M.Sc.
Senior Director of Toxicology Operations

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Judit Tavaszi, M.Sc.	Study Director – in life phase
Magdolna Török-Bathó, M.Sc.	Study Director – in reporting phase
István Buda, M.Sc.	Assistant Scientist
Szabolcs Gáty, M.Sc.	Quality Assurance Unit
Diána Czuczai, M.Sc.	Quality Assurance Unit
Ramóna Heiderné Grób, B.Sc.	Quality Assurance Unit
Eric Yau	Syngenta Study Manager

Study dates

Experimental Starting Date:	10 March 2011
Experimental Completion Date:	31 March 2011
Acclimatization:	02 – 09 March 2011
Treatment:	10 March 2011
Termination:	31 March 2011

Deviations from the study plan

The Draft Report was sent later than indicated in the Study Plan.

This deviation has no impact on the outcome of the study and interpretation of the results.

Deviations from the guidelines

The relative humidity (min. 24%) recorded during the study was outside of the guideline range (30-70%).

This deviation has no impact on the outcome of the study and interpretation of the results.

Retention of samples

See in other below.

Performing laboratory test substance reference number

100101

Other

The study documents:
- study plan and amendments,
- all raw data,
- sample of the test item,
- study report and any amendments,
- correspondence

will be archived according to the Hungarian GLP and applicable SOP's in the archives of LAB Research Ltd. 8200 Veszprém, Szabadságpuszta, Hungary.

After the retention time of 15 years has elapsed, all the archived materials listed above will be returned to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study Design

The primary eye irritation effect of the test item was evaluated according to OECD 405, OPPTS 870.2400 and EC No 440/2008, B.5. The test item was administered as an instillation of a single dose of 0.1 mL into the conjunctival sac of the left eye of each of 3 adult New Zealand White rabbits. The untreated right eyes served as the control. Scoring of irritation effects was performed approximately 1, 24, 48, 72 hours and 1, 2 and 3 weeks after test material instillation.

1.2 Results

Initial Pain Reaction (IPR) score 1, 2 or 3 was observed in all animals.

Conjunctival redness, chemosis and discharge were recorded in all treated animal from the 1-hour observation and persisted until the end of the observation period. Corneal opacity was noted in all treated animals and persisted up to and including the 3-week observation. The iris was inflamed in all the animals at 72 hours after the treatment and the inflammation persisted in two animals at the one week observation. Vascularisation was observed on the surface of cornea in all animals from the 1 week observation until the 3 weeks observation.

All animals showed a positive fluorescein stain during the study at all the observation points after the application.

The study was terminated after the 3 weeks observation.

No clinical signs of systemic toxicity or intercurrent deaths were observed in the animals during this study.

The body weights of all rabbits were considered to be within the normal range of variability.

1.3 Conclusion

Based upon the Kay and Calandra classification criteria, Propiconazole/Fenpropidin EC (A9050B) is considered to be “Very Severe Irritant” (Class 7) to the rabbit eye (Maximum Average Score = 67.33).

The effects had not fully reversed in any animal at the end of the observation period.

2.0 INTRODUCTION

2.1 Purpose

The study was performed to assess the irritancy potential of Propiconazole/Fenpropidin EC (A9050B), following a single application to the rabbit eye.

The albino rabbit has been shown to be a suitable model for this type of study and is recommended in the test method. The results of the study are believed to be of value in predicting the likely eye irritancy potential of the test material to man.

2.2 Guidelines

The study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

OECD Guidelines for the Testing of Chemicals, Section 4, number 405 "Acute Eye Irritation/Corrosion", adopted 24 April 2002.

United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.2400, Acute Eye Irritation EPA 712-C-98-195, August 1998.

Commission Regulation (EC) No 440/2008, B.5 (L 142, 30 May 2008)

3.0 MATERIALS AND METHODS

3.1 Test Substance

Name:	Propiconazole/Fenpropidin EC (A9050B)
Batch number:	SMO0G120
Purity:	Propicanozole – 129 g/L corresponding to 13.6 % w/w Fenpropidin – 278 g/L corresponding to 29.2 % w/w
Product code:	A9050B
Appearance:	Brown liquid
Density:	952 kg/m^3
Reanalysis date:	End of September 2015
Storage conditions:	<30 ^{o}C
Safety Precautions:	Routine safety precautions (lab coat, safety glasses gloves, face mask) for unknown materials were applied to assure personnel health and safety.

A Certificate of Analysis supplied by the Sponsor is given in Appendix 1.

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

For the purpose of the study, the test material was used as supplied.

3.2 Measurement of pH

The pH of the test material was 5.0.

According to Commission Regulation (EC) No 440/2008, B.5. and OECD Guidelines 405, a test item need not be tested if the pH-value is less than 2 or greater than 11.5, owing to its predictable corrosive properties.

3.3 Experimental Design

3.3.1 Animals

Species and strain:	New Zealand white rabbit
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Justification of strain:	The New Zealand White rabbit is one of the standard strains used for acute irritation toxicity studies.
Number of animals:	3 animals
Sex:	Male
Age of animals:	~11 weeks
Body weight range at dosing:	2827 - 3138 g
Body weight range at the end of in life phase:	3433 – 3844 g

3.3.2 Husbandry

Acclimation period:	8 days
Room:	619
Light:	12 hours of light/12 hours of dark
Temperature:	20 ± 3 °C
Relative humidity:	24 – 59%
Housing/Enrichment:	Rabbits were individually housed in AAALAC approved metal wire rabbit cages. Cages were of an open wire structure and cages were placed together to allow some social interaction with rabbit(s) in adjoining cages.

Ventilation: 15-20 air exchanges/hour.

The temperature and relative humidity was recorded twice every day during the acclimatisation and experimental phases.

3.3.3 Food and feeding

The animals received Purina Base – Lap gr. diet for rabbit produced by Agribrands Europe Hungary PLC, H-5300 Karcag, Madarasi út, Hungary, *ad libitum*. The numbers of lots used in the study were: 0500 019 and 0510 029. The detailed description of the contents of the lots used, are archived with the raw data at LAB Research Ltd.

3.3.4 Water supply and quality control

The animals received tap water, as for human consumption, *ad libitum*, from the automatic system supplied by the communal water network. The water was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

The quality control analysis is performed once every 3 months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u.36., Hungary). The quality control results are retained in the archive at LAB Research Ltd.

3.3.5 Test material administration

Approximately 24 hours before the start of the test, both eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect, including fluorescein staining. Only animals free of ocular damage were used.

Initially, a single rabbit was treated. A volume of 0.1 mL of the test material was placed into the conjunctival sac of the left eye, formed by gently pulling the lower lid away from the eyeball. The upper and lower eyelids were held together for about 1 second immediately after treatment, to prevent loss of the test material, and then released. The right eye remained untreated and was used for control purposes. Immediately after administration of the test material, an assessment of the initial pain reaction was made according to the 6 point scale shown in Appendix 2.

Following review of the ocular responses produced in the first treated animal, 2 additional animals were treated.

3.3.6 Observations

The eyes of the test animals were not washed out after application of test item.

Assessment of ocular damage/irritation was made approximately 1, 24, 48, 72 hours and 1, 2 and 3 weeks following treatment, according to the numerical evaluation given in Appendix 3, (from Draize J H (1977) "Dermal and Eye Toxicity Tests" In: Principles and Procedures for Evaluating the Toxicity of Household Substances, National Academy of Sciences, Washington DC p.48 to 49). Fluorescein staining was made 24, 48, 72 hours and 1, 2 and 3 weeks following treatment.

The treated eyes were further examined using 2% fluorescein solution at approximately 24 hours before treatment and then 24, 48, 72 hour, 1, 2 and 3 weeks after treatment. One drop of 2% sodium fluorescein was applied to the corneal surface for approximately 30 seconds, which is then rinsed with physiological saline solution. Examination was performed with the use of a hand slit-lamp and recorded as either the presence of staining or no staining.

The duration of the observation period was sufficient to identify reversibility of changes. Any clinical signs of toxicity or signs of ill-health during the study were recorded.

At the end of the observation period, each animal was euthanized by intramuscular injection of CP-Ketamin 10% and CP-Xylazine 2% followed by intravenous Euthasol® 40% anaesthesia. Death was verified by checking pupil and cornea reflex, absence of respiration and pulse.

Materials used for euthanasia

Name:	CP-Ketamin 10%
Batch No.:	10H12 4
Expiry Date:	07 2012
Produced by:	CP-Pharma, 31303 Burgdorf
Name:	CP-Xylazin 2%
Batch No.:	10G06 2
Expiry Date:	06 2013
Produced by:	CP-PHARMA, 31303 Burgdorf
Name:	Euthasol® 40%
Lot No.:	10C25 7
Expiry Date:	February 2013
Produced by:	AST Beheer B.V. Oudewater Netherlands

For treatment:

	Disposable Syringe Tuberculin 1 mL/CC
Lot No.:	12M01
Expiry Date:	October 2015
Supplier:	Penta Ferte

For fluorescein staining:

	Fluorescein 100 mg/mL solution
Batch number:	0273C41
Expiry Date:	06 2013
Produced by:	Novartis

For washing:

	NaCl (0.9%)
Batch number:	3390210
Expiry Date:	February 2013
Produced by:	Teva zRt.
	Disposable Syringe Omnifix (20 mL)
Lot No.:	9L09048
Expiry Date:	November 2014
Supplier:	Braun

3.4 Data Evaluation

The numerical values corresponding to each animal, tissue and observation time were recorded. The data relating to the conjunctivae were designated by the letters A (redness), B (chemosis) and C (discharge), those relating to the iris designated by the letter D and those relating to the cornea by the letters E (degree of opacity) and F (area of cornea involved). For each tissue the score was calculated as follows:

Score for conjunctivae	=	(A + B + C) x 2
Score for iris	=	D x 5
Score for cornea	=	(E x F) x 5

Using the numerical data obtained a modified version of the system described by Kay J H and Calandra J. C. (1962), J. Soc. Cosmet. Chem. 13, 281 289 (see Appendix 4) was used to classify the ocular irritancy potential of the test material. This was achieved by adding together the scores for the cornea, iris and conjunctivae for each time point for each rabbit. The group means of the total scores for each observation were calculated. The highest of these group means (the maximum group mean score) together with the persistence of the reactions enabled classification of the eye irritancy potential of the test material.

4.0 RESULTS AND DISCUSSION

4.1 Ocular Reactions

Initial Pain Reaction (IPR) score 1, 2 or 3 was observed in all animals.

Conjunctival redness, chemosis and discharge were recorded in all treated animal from the

1-hour observation and persisted until the end of the observation period. Corneal opacity was noted in all treated animals and persisted up to and including the 3-week observation. The iris was inflamed in all the animals at 72 hours after the treatment and the inflammation persisted in two animals at the one week observation. Vascularisation was observed on the surface of cornea in all animals from the 1 week observation until the 3 weeks observation.

All animals showed a positive fluorescein stain during the study at all the observation points after the application (Table 3).

The study was terminated after the 3 weeks observation.

4.2 Bodyweight

Individual bodyweights bodyweight changes are given in Table 4. All animals showed an expected gain in bodyweight by the end of the study.

4.3 Clinical Signs

No clinical signs of systemic toxicity were observed in the animals during this study.

4.4 Mortality

No intercurrent deaths occurred during this study.

5.0 CONCLUSIONS

Based upon the Kay and Calandra classification criteria, Propiconazole/Fenpropidin EC (A9050B) is considered to be “Very severe irritant” (Class 7) to the rabbit eye (Maximum Average Score = 67.33).

The effects had not fully reversed in any animal at the end of the observation period.

TABLES SECTION

TABLE 1 Individual and Individual Total Scores for Ocular Irritation

Rabbit number and sex	00784 Male IPR = 3							00795 Male IPR = 1							00798 Male IPR = 2						
Time after treatment	1 Hr	24 Hr	48 Hr	72 Hr	1 W *	2 W *	3 W *	1 Hr	24 Hr	48 Hr	72 Hr	1 W *	2 W *	3 W *	1 Hr	24 Hr	48 Hr	72 Hr	1 W *	2 W *	3 W *
CORNEA																					
E = Degree of Opacity	2	2	2	2	3	3	3	1	1	2	2	2	3	2	2	1	2	2	3	3	3
F = Area of Cornea involved	4	4	4	4	3	4	3	4	4	4	4	4	3	4	2	3	4	4	2	3	2
Score (E x F) x 5	40	40	40	40	45	60	45	20	20	40	40	40	45	40	20	15	40	40	30	45	30
IRIS																					
D	0	0	0	2	1	0	0	0	0	0	2	0	0	0	0	0	0	2	1	0	0
Score (D x 5)	0	0	0	10	5	0	0	0	0	0	10	0	0	0	0	0	0	10	5	0	0
CONJUNCTIVAE																					
A = Redness	1	2	2	2	3	1	1	1	3	3	3	3	1	1	1	3	3	3	3	2	1
B = Chemosis	3	3	3	3	2	1	1	3	3	3	3	2	2	2	3	3	3	3	3	1	1
C = Discharge	3	3	3	3	3	2	1	3	3	3	3	2	1	1	3	3	3	3	3	3	2
Score (A+B+C) x 2	14	16	16	16	16	8	6	14	18	18	18	14	8	8	14	18	18	18	18	12	8
Total Score	54	56	56	66	66	68	51	34	38	58	68	54	53	48	34	33	58	68	53	57	38

IPR: Initial pain reaction
Hr: Hour(s)
W: weeks
N: Negative
P: Positive
*: vascularisation on the surface of the cornea

TABLE 2 **Individual Total Scores and Group Mean Scores for Ocular Irritation**

Rabbit Number and Sex	Individual Total Scores At:						
	1 Hour	24 Hours	48 Hours	72 Hours	1 week	2 weeks	3 weeks
00784 Male	54	56	56	66	66	68	51
00795 Male	34	38	58	68	54	53	48
00798 Male	34	33	58	68	53	57	38
Group Total	122	127	172	202	173	178	137
Group Mean Score	40.67	42.33	57.33	67.33	57.66	59.33	45.67

TABLE 3 **Individual Fluorescein Staining**

Rabbit Number and Sex	Fluorescein Staining						
	24 Hours Prior to Instillation	24 Hours After Instillation	48 Hours After Instillation	72 Hours After Instillation	1 Week After Instillation	2 Weeks After Instillation	3 Weeks After Instillation
00784 Male	-	+	+	+	+	+	+
00795 Male	-	+	+	+	+	+	+
00798 Male	-	+	+	+	+	+	+

- : Absence of Fluorescein Stain
+ : Presence of Fluorescein Stain

TABLE 4 **Individual Bodyweights and Bodyweight Change**

Rabbit Number and Sex	Individual Bodyweight (g)		Bodyweight Change (g)
	Day 0	Day 21	
00784 Male	3000	3640	640
00795 Male	2827	3433	606
00798 Male	3138	3844	706

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

A9050B
propiconazole / fenpropidin EC (125/275)
SMO0G120

Batch Identification	**SMO0G120**
Product Code	**A9050B**
Other Product Code(s)	CGA64250/CGA114900 EC (125/275)

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredient(s)***	**confirmed**
– **Content of propiconazole ***	**13.6 % w/w corresponding to 129 g/l**
– **Content of fenpropidin ***	**29.2 % w/w corresponding to 278 g/l**

The Active Ingredient(s) content is within the FAO limits.

Methodology used for Characterization / Recertification	GC,

Physical Analysis

– **Appearance**	**brown, liquid**
– **Density ***	**952 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C**
– **Recertification Date**	**End of September 2015**

If stored under the conditions given above, this test substance can be considered stable until the recertification date is reached.

This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted in compliance with GLP. Raw data, documentation, study plans, any amendments to study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility WMU at Syngenta Crop Protection Muenchwilen AG.

Study number of batch characterization: 121786
Study number(s) of batch recertification:

Authorisation: October 12, 2010

Dr. A.M. Dos Santos Alves
Analytical Development & Product Chemistry

APPENDIX 2 Initial Pain Reaction

When the material is instilled in the eye there may be an initial local pain reaction. The reaction will be graded as follows:

Class	Reaction by Animal	Descriptive Rating
0	No response	No initial pain
1	A few blinks only, normal within one or two minutes	Practically no initial pain
2	Rabbit blinks and tries to open eye, but reflex closes it	Slight initial pain
3	Rabbit holds eye shut and puts pressure on lids, may rub eye with paw	Moderate initial pain
4	Rabbit holds eye shut vigorously, may squeal	Severe initial pain
5	Rabbit holds eye shut vigorously, may squeal, claw at eye, jump and try to escape	Very severe initial pain

Often there is no correlation between the initial pain and the subsequent eye irritation.

APPENDIX 3 Draize Scale for Scoring Ocular Irritation

1. CONJUNCTIVAE

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs a considerable area around the eye	3

THE TOTAL SCORE = (A + B + C) x 2 **MAXIMUM TOTAL = 20**

2. IRIS

(D) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, haemorrhage, gross destruction (any or all of these)	2

THE TOTAL SCORE = D x 5 **MAXIMUM TOTAL = 10**

3. CORNEA

(E) Degree of Opacity (most dense area used)

No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris not discernible through the opacity	4

(F) Area of Cornea Involved

One quarter (or less) but not zero	1
Greater than one quarter but less than half	2
Greater than half but less than three quarters	3
Greater than three quarters, up to whole area	4

THE TOTAL SCORE = (E x F) x 5 **MAXIMUM TOTAL = 80**

MAXIMUM TOTAL SCORE POSSIBLE = 110

APPENDIX 4 Modified Kay and Calandra Interpretation of Eye Irritation Test

MAXIMUM MEAN SCORE		PERSISTENCE OF SCORE	DESCRIPTION RATING (AND CLASS)	
0.0 to 0.5	Group mean total score at 24 hours = 0		Non-irritant	(1)
	Group mean total score at 24 hours > 0		Practically non-irritant	(2)
0.5 to 2.5	Group mean total score at 24 hours = 0		Practically non-irritant	(2)
	Group mean total score at 24 hours > 0		Minimal irritant	(3)
2.5 to 15	Group mean total score at 48 hours = 0		Minimal irritant	(3)
	Group mean total score at 48 hours > 0		Mild irritant	(4)
15 to 25	Group mean total score at 72 hours = 0		Mild irritant	(4)
	Group mean total score at 72 hours > 0		Moderate irritant	(5)
25 to 50	Group mean total score at 7 days 20 or less	More than half of the individual total scores at 7 days 10 or less	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant	(6)
	Group mean total score at 7 days > 20		Severe irritant	(6)
50 to 80	Group mean total score at 7 days 40 or less	More than half of the individual total scores at 7 days 30 or less	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 but no individual total scores at 7 days > 60	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 and individual total score at 7 days > 60	Very severe irritant	(7)
	Group mean total score at 7 days > 40		Very severe irritant	(7)
80 to 100	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days 60 or less	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 and individual total score at 7 days > 100	Extremely severe irritant	(8)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)
100 to 110	Group mean total score at 7 days 80 or less		Very severe irritant	(7)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)

APPENDIX 5 GLP Certificate

ORSZÁGOS GYÓGYSZERÉSZETI INTÉZET
National Institute of Pharmacy

FŐIGAZGATÓ
1051 Budapest, Zrínyi u. 3.
tel: (1) 8869-320
fax: (1) 8869-480
e-mail: szepezdi.zsuzsanna@ogyi.hu

Ref. no: OGYI/8242-11/2010
Admin.: Urbin Magdolna Zita
Date: 16 December, 2010

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

LAB Research Kft.

(Base facility: H-8201 Veszprém, Szabadságpuszta, Hungary)

is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air;bio-accumulation , safety pharmacology testing, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **4-8 October, 2010.**

Zsuzsanna Szepezdi, Ph. D.
Director-General

Translation (from Hungarian to English):
Stamp Translation = Országos Gyógyszerészeti Intézet (OGYI) = National Institute of Pharmacy
Főigazgató = Director-General