Cyproconazole/Isopyrazam

Cyproconazole/Isopyrazam SC (A19022A) - Acute Eye Irritation Study in Rabbits

Final Report

DATA REQUIREMENT(S): OECD 405 (2002)
EPA OPPTS 870.2400 (1998)
EC No 440/2008, B.5 (2008)
Directive 2004/73/EC B.5 (L 152 2004)

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

STUDY COMPLETION DATE: 03 July 2012

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

LABORATORY PROJECT ID: Report Number: 12/055-005N
Study Number: 12/055-005N
Task Number: : TK0006572

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

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: Bud Török Magdolna Date: 03 July 2012

Magdolna Török-Bathó, M.Sc.
Study Director

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

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 12/055-005N

Study Title: Cyproconazole/Isopyrazam SC (A19022A) - Acute Eye Irritation Study in Rabbits

Test Item: Cyproconazole/Isopyrazam SC (A19022A)

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
29 March 2012	Study Plan	29 March 2012	29 March 2012
04 April 2012	Treatment	04 April 2012	04 April 2012
18 May 2012	Draft Report	18 May 2012	18 May 2012
03 July 2012	Final Report	03 July 2012	03 July 2012

Signature: _____ Date: 03 JUL 2012

Katalin Böröczki, M.Sc.
On Behalf of QA

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "Cyproconazole/Isopyrazam SC (A19022A) - Acute Eye Irritation Study in Rabbits" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 03 July 2012

Christopher Banks, DABT
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Magdolna Török-Bathó, M.Sc.	Study Director
Viktória Zelenák, M.Sc.	Assistant Scientist
Katalin Böröczki, M.Sc.	Quality Assurance Unit
Szabolcs Gáty, M.Sc.	Quality Assurance Unit
István Pásztor DVM	Veterinary Control
Claire Elliott, B.Sc.	Syngenta Study Manager

Study dates

Experimental Starting Date:	04 April 2012
Experimental Completion Date:	19 April 2012
Acclimatization:	28 March – 03 April 2012
Treatment:	04 and 05 April 2012
Termination:	19 April 2012

Deviations from the guidelines

In two occasions, the relative humidity was outside (min. 28%, Room 609) the guideline range (30-70%).

This deviation is considered to have 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

12003B

Other

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

will be archived according to the Hungarian GLP and applicable SOP's in the archives of CiToxLAB Hungary 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 test guideline no.: 405 (2002), EPA OPPTS 870.2400 (1998), Directive 2004/73/EC B.5 (L 152 2004) and EC No 440/2008, B.5 (2008). The test item was administered as an instillation of a single volume of 0.1 mL into the conjunctival sac of the left eye of 3 adult male 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 and 2 weeks after test material instillation. Observations with fluorescein staining were made at least 24 hours before treatment and then 24, 48, 72 hours and 1 and 2 weeks after treatment.

1.2 Results

An Initial Pain Reaction (IPR) score of 2 was observed in all animals.

Conjunctival redness was observed in all animals at 1, 24, 48, and 72 hours' observation, and in 2 animals at 1 week observation. Conjunctival discharge was seen in all animals at 1, 24 and 48 hours after treatment and in two animals at 72 hour observation. Conjunctival chemosis was observed in all animals at 1, 24 and 48 hours after treatment and in two animals at 72 hour and one animal at the 1 week observations. Corneal opacity was observed at 1, 24, 48 and 72 hour observation in one animal and in another animal at only the 24 hour observation

Positive fluorescein staining was observed on the cornea of the treated eye of all animals at 24 hours after treatment, in two animals at 48 hours and in one animal at 72 hour after treatment.

As all signs of eye irritation had fully reversed the study was terminated after a period of 2 weeks observation.

No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred.

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

1.3 Conclusion

Cyproconazole/isopyrazam SC (A19022A) was graded as a **moderate irritant (Class 5 on a 1 to 8 scale)** to the rabbit eye according to the modified Kay and Calandra classification system.

2.0 INTRODUCTION

2.1 Purpose

The study was performed to assess the irritancy potential of cyproconazole/isopyrazam SC (A19022A), 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.

Directive 2004/73/EC B.5 (L 152 2004 29th April)

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: Cyproconazole/isopyrazam SC (A19022A)

Batch number: J8657/147

Product code: A19022A

Purity:

Content of cyproconazole – 79.9 g/l corresponding to 7.45 % w/w

Content of isopyrazam (sum of epimers) – 129 g/l corresponding to 12.0 % w/w

Content of SYN534969 (syn-epimer of isopyrazam) – 112 g/l corresponding to 10.4 % w/w

Content of SYN534968 (anti-epimer of isopyrazam) – 17.0 g/l corresponding to 1.58 % w/w

Density: 1073 kg/m^3

Appearance: beige liquid

Recertification date: End of October 2013

Storage conditions:	Room temperature (<30 °C)
Safety Precautions:	Routine safety precautions (lab coat, gloves, goggles, 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.

3.2 Measurement of pH

The pH of the test material was 4.5. According to the test guidelines this study was performed to a test item does not need to 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:	2884 – 2925 g
Body weight range at the end of the observation period:	3232 – 3425 g

3.3.2 Husbandry

Animal health:	Only healthy animals were used for the study, as certified by the veterinarian.
Acclimation period:	7 days
Room:	609
Light:	12 hours of light/12 hours of dark
Temperature:	20 ± 3 °C
Relative humidity:	28 – 67 %
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 were recorded twice every day during the acclimatisation and experimental phases.

3.3.3 Food and feeding

The animals received UNI diet for rabbit produced by Agribrands Europe Hungary PLC, H-5300 Karcag, Madarasi út, Hungary, *ad libitum*. The numbers of the lots used in the study were: 0030 03 12 and 0060 04 12. A detailed description of the contents of the lots used are archived with the raw data at CiToxLAB Hungary 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 CiToxLAB Hungary Ltd.

3.3.5 Test material administration

Before the start of the test, both eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect using a hand-held slit-lamp. Only animals free of ocular damage were used. The eyes were not anaesthetised.

Initially, a single rabbit was treated. A single 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 a few seconds 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 the 1- and 24-hour examinations review of the ocular responses produced in the first treated animal, 2 additional animals were treated.

3.3.6 Observations

Assessment of ocular damage/irritation was made approximately 1, 24, 48, 72 hours and 1 and 2 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).

The eyes were further examined using 2% fluorescein solution at least 24 hours before treatment and then 24, 48, 72 hours and 1 and 2 weeks after treatment. One drop of 2% fluorescein solution was applied to the corneal surface for approximately 30 seconds, then rinsed with physiological saline solution. Examination was performed with the use of a hand-held 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-Xylazin 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.:	11A2 22
Expiry Date:	December 2012
Produced by:	CP-Pharma
Name:	CP-Xylazin 2%
Batch No.:	11C10 1
Expiry Date:	February 2014
Produced by:	CP-Pharma
Name:	Euthasol® 40%
Lot No.:	11H15 8
Expiry Date:	July 2014
Produced by:	Produlab Pharma

For treatment:

Name:	Disposable Syringe Tuberculin 1 mL
Lot No.:	13P02
Expiry Date:	December 2016
Supplier:	Penta Ferte

For fluorescein staining:

Name:	Disposable Syringe Omnifix, 20 mL
Lot No.:	9L09048

Expiry Date:	November 2014
Supplier:	Braun
Name:	Physiological Saline (NaCl (0,9%))
Batch number:	6880610 / 5441011
Expiry Date:	June 2013 / October 2013
Produced by:	Teva Co.
Name:	Fluorescein 100 mg/mL
Batch number:	0273C41
Expiry Date:	June 2013
Produced by:	Novartis

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

An Initial Pain Reaction (IPR) score of 2 was observed in all animals.

Conjunctival redness was observed in all animals at 1, 24, 48, and 72 hours' observation, and in 2 animals at 1 week observation. Conjunctival discharge was seen in all animals at 1, 24 and 48 hours after treatment and in two animals at 72 hour observation, respectively. Conjunctival chemosis was observed in all animals at 1, 24 and 48 hours after treatment and in two animals at 72 hour and one animal at the 1 week observations. Corneal opacity

was observed at 1, 24, 48 and 72 hour observation in one animal and in another animal at only the 24 hour observation

Positive fluorescein staining was observed on the cornea of the treated eye of all animals at 24 hours after treatment, in two animals at 48 hours and in one animal at 72 hour after treatment.

As all signs of eye irritation had fully reversed the study was terminated after a period of 2 weeks observation.

4.2 Bodyweight

Individual bodyweights and bodyweight changes are given in Table 4. The bodyweights of all rabbits were considered to be within the normal range of variability.

4.3 Clinical Signs

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

4.4 Mortality

No mortality occurred in this study.

5.0 CONCLUSIONS

Cyproconazole/Isopyrazam SC (A19022A) was graded as a **moderate irritant (Class 5 on a 1 to 8 scale)** to the rabbit eye according to the modified Kay and Calandra classification system.

TABLES SECTION

TABLE 1 **Individual Draize Scores and Individual Total Scores* for Ocular Irritation**

Rabbit number and sex	**00591 Male** IPR = 2						**00530 Male** IPR = 2						**00527 Male** IPR = 2					
Time after treatment	1 Hr	24 Hr	48 Hr	72 Hr	1 w	2 w	1 Hr	24 Hr	48 Hr	72 Hr	1 w	2 w	1 Hr	24 Hr	48 Hr	72 Hr	1 w	2 w
CORNEA																		
E = Degree of Opacity	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0
F = Area of Cornea involved	0	3	0	0	0	0	0	0	0	0	0	0	4	4	4	4	0	0
* Score (E x F) x 5	0	15	0	0	0	0	0	0	0	0	0	0	20	20	20	20	0	0
IRIS																		
D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
* Score (D x 5)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CONJUNCTIVAE																		
A = Redness	1	2	2	1	0	0	2	2	1	1	1	0	2	2	2	2	1	0
B = Chemosis	1	2	1	1	0	0	2	1	1	0	0	0	2	2	1	1	1	0
C = Discharge	1	3	3	1	0	0	3	3	1	0	0	0	3	3	3	2	0	0
* Score (A+B+C) x 2	6	14	12	6	0	0	14	12	6	2	2	0	14	14	12	10	4	0
* Total Score	6	29	12	6	0	0	14	12	6	2	2	0	34	34	32	30	4	0

IPR: Initial pain reaction
Hr: Hour(s)
w: Week
** Kay J H and Calandra J C (1962)*

TABLE 2 Individual Total Scores and Group Mean Scores for Ocular Irritation Calculated from Draize Scores

Rabbit Number and Sex	* Individual Total Scores At:					
	1 Hour	24 Hours	48 Hours	72 Hours	1 week	2 weeks
00591 Male	6	29	12	6	0	0
00530 Male	14	12	6	2	2	0
00527 Male	34	34	32	30	4	0
* Group Total	54	75	50	38	6	0
* Group Mean Score	18	25	16.67	12.67	2.00	0.00

*: Kay J H and Calandra J C (1962)

TABLE 3 Individual Fluorescein Staining

Rabbit Number and Sex	Fluorescein Staining (treated eye)					
	24 / 48 Hours Prior to Instillation	24 Hours After Instillation	48 Hours After Instillation	72 Hours After Instillation	1 week After Instillation	2 weeks After Instillation
00591 Male	-	+	+	-	-	-
00530 Male	-	+	-	-	-	-
00527 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 14	
00591 Male	2884	3302	418
00530 Male	2925	3232	307
00527 Male	2904	3425	521

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry

Syngenta Crop Protection Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

A19022A
cyproconazole/isopyrazam SC (080/125)
J8657/147

Batch Identification	**J8657/147**
Product Code	**A19022A**
Other Product Code(s)	SAN619/SYN520453 SC (080/125)

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredients***	**confirmed**
– **Content of Cyproconazole***	**79.9 g/l corresponding to 7.45 % w/w**
– **Content of Isopyrazam (sum of epimers)***	**129 g/l corresponding to 12.0 % w/w**
– **Content of SYN534969 (syn-epimer of isopyrazam)***	**112 g/l corresponding to 10.4 % w/w**
– **Content of SYN534968 (anti-epimer of isopyrazam)***	**17.0 g/l corresponding to 1.58 % w/w**

The Active Ingredients content is within the FAO limits.

Methodology used for Characterization: HPLC

Physical Analysis

– **Appearance**	**beige liquid**
– **Density***	**1073 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C**
– **Recertification Date**	**End of October 2013**

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: 123779

Study number(s) of batch recertification: ---

Authorisation:

14 November 2011

Dr. R. Kettner
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**

*: Total scores according to Kay and Calandra system (1962)

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 Group mean total score at 24 hours > 0		Non-irritant Practically non-irritant	(1) (2)
0.5 to 2.5	Group mean total score at 24 hours = 0 Group mean total score at 24 hours > 0		Practically non-irritant Minimal irritant	(2) (3)
2.5 to 15	Group mean total score at 48 hours = 0 Group mean total score at 48 hours > 0		Minimal irritant Mild irritant	(3) (4)
15 to 25	Group mean total score at 72 hours = 0 Group mean total score at 72 hours > 0		Mild irritant Moderate irritant	(4) (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

Until 1st September 2011 the facility name was LAB Research Ltd. From thisdate, the registered name has been changed to CiToxLAB Hungary Ltd.,this information has been passed on to the GLP competent authority. The above GLP certificate is valid for this facility (now known as CiToxLAB Hungary Ltd.) until the certificate expires (16 December 2012).