Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam

Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C) – Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Final Report

DATA REQUIREMENT(S): OECD Test Guideline 425 (2008)
EPA OPPTS 870.1100 (2002)

AUTHOR(S): Judit Tavaszi, M.Sc.

STUDY COMPLETION DATE: 03 June 2010

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

LABORATORY PROJECT ID: Report Number: 09/264-001P
Study Number: 09/264-001P
Task Number: TK0008350

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

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with 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.).

This study was conducted in accordance with a written Study Plan, authorized by the Sponsor and LAB Research Ltd. management, and followed applicable Standard Operating Procedures.

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: _____ Date: 03 June 2010

Judit Tavaszi, 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: 09/264-001P

Study Title: Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C) – Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Test Item: Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C)

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 December 2009	Study Plan	09 December 2009	09 December 2009
10 December 2009	Treatment	10 December 2009	10 December 2009
03 March 2010	Draft Report	03 March 2010	03 March 2010
02 June 2010	Final Report	02 June 2010	02 June 2010

Signature: Kiss Istvánné Date: 03 June 2010

Istvánné Kiss, M.Sc.
QA Inspector

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and LAB Research Ltd. the study titled "Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 07 June 2010

Christopher Banks, DABT
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	**Function**
Judit Tavaszi, M.Sc.	Study Director
Viktória Zelenák, M.Sc.	Assistant scientist
István Pásztor, DVM	Veterinary control
Peter Maslej, DVM, PhD	Head of Pathology Unit
András Mátyás, M.Sc.	Technical Team Leader of Central Dispensary
Eric Yau	Syngenta Study Manager

Study dates

Experimental Starting Date	10 December 2009
Experimental Completion Date	31 December 2009
Reception of Animals	18 November 2009
Acclimatization	At least 22 days
Treatment	10 December 2009 (female no. 6549) 11 December 2009 (female no. 6545) 15 December 2009 (female no. 6551) 16 December 2009 (female no. 6544) 17 December 2009 (female no. 6546)
Observation	10-24 December 2009 (female no. 6549) 11-25 December 2009 (female no. 6545) 15-29 December 2009 (female no. 6551) 16-30 December 2009 (female no. 6544) 17-31 December 2009 (female no. 6546)

Deviations from the guidelines / Study Plan

Márta Tenk was not involved in the study.
Interpretation of the results according to the EU labelling regulations was not performed.
The Draft Report was sent on 03 March 2010 instead of 12 February 2010 as indicated in the Study Plan.

These deviations have no impact on the outcome of the study.

Performing laboratory test substance reference number
09/247K/1 091026

Other

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

will be archived according to the Hungarian GLP and to 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

A limit test was initially performed with 5 animals. A single oral (gavage) administration was administered followed by a 14 day observation period. The animals were fasted overnight prior to treatment. Animals were weighed before dosing and food was returned 3 hours after dosing.

Single animals were dosed sequentially at no less than 24 hour intervals. The time intervals between dosing were determined by the onset, duration and severity of toxic signs.

The first animal was treated at a dose level of 3000 mg/kg bw. As no mortality or significant clinical signs were observed, 4 additional animals were dosed with 3000 mg/kg bw sequentially such that a total of 5 animals were tested. No mortalities were observed, therefore the study was terminated.

Dosages

A limit dose of 3000 mg/kg was selected by the Sponsor. The test item was administered undiluted.

Rationale: Oral administration was considered to be an appropriate dose route as it is a possible route of human exposure.

Animal Number	Dosage [mg/kg body weight]
6549	3000
6545	3000
6551	3000
6544	3000
6546	3000

Animals were observed individually after dosing at 30 minutes, then 1, 2, 3, 4 and 6 hours post treatment and once each day for 14 days thereafter. Body weight was measured on Day -1, just before treatment and weekly after. All animals were examined macroscopically at the end of the study.

1.2 Results

No deaths occurred during the study.

All of the animals had red urine and red faeces for a maximum of 2 days following treatment. Decreased activity was observed in 3 animals (6545, 6551, 6546). Hunched back, lacrimation, piloerection, oedema on the head and on the whole body were described in 1 animal between 2 and 6 hours on the day of dosing only.

There were no treatment related changes in the body weights. The body weights of the animals were within the range commonly recorded for this strain and age.

Dilatation of the right/ left atria and/or right/left ventricles of the heart were observed in some animal at necropsy. However, this is a common finding in acute studies conducted at this lab and therefore is not considered treatment related. Uterus in estrus was recorded in 2 animals and a single cyst of the right kidney was also recorded in 1 animal.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose LD_{50} of the test item, Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C), was greater than 3000 mg/kg bw in female CRL:(WI) BR rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the oral toxicity of the test item Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C) when administered as a single oral gavage dose to rats at 1 defined dose level. The results of the study allowed the test item to be ranked according to most classification systems currently in use.

2.2 Guidelines

The study was performed according to the following guidelines:

OECD guideline reference 425 (2008): Acute Oral Toxicity - Up-and-Down Procedure.

United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190, December 2002.

3.0 MATERIALS AND METHODS

3.1 Test Substance

Data as supplied by the Sponsor.

Name:	Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C)
Batch number:	SMU9BP001
Product code:	A16503C
Appearance:	Liquid/ red
Density:	1143kg/m^3
Reanalysis date:	End of February 2012
Storage conditions:	< 30˚C, kept away from direct sunlight
Safety Precautions:	Routine safety precautions (lab coat, gloves, goggles, face mask) for unknown materials will be applied to assure personnel health and safety

The Certificate of Analysis as attached in Appendix 2.

3.1.1 Identification, Receipt

The test item of a suitable chemical purity together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made in the Central Dispensary Unit of LAB Research Ltd. on the basis of the information provided by Sponsor.

3.1.2 Formulation

The test item was administered undiluted.

3.2 Experimental Animals

Species and strain:	CRL:(WI)BR Wistar Rat
Source:	Toxi Coop, Cserkesz u. 90. 1103 Budapest, Hungary
Hygienic level at arrival:	SPF
Hygienic level during the study:	Standard housing conditions
Justification of strain:	Recognized by international guidelines as a recommended test system.
Number of animals:	5
Sex:	Female rats, nulliparous and non-pregnant.
Age when treated:	Young adult rats, 9-11 weeks old.
Body weight (at dosing):	Not more than 242 g
Randomization:	Selected by hand at time of delivery.
Acclimatization time:	At least 22 days

3.2.1 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the veterinarian.
Housing:	Individual caging
Cage type:	Type II. polypropylene/polycarbonate
Bedding:	Lignocel Bedding for Laboratory Animals was available to animals during the study.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	22 ± 3 °C
Relative humidity:	30 – 70%
Ventilation:	15-20 air exchanges/hour
Enrichment:	Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.

The temperature and relative humidity was recorded twice daily during the study and the acclimation period.

3.2.2 Food and water supply

Animals received ssniff® SM R/M-Z+H "Autoclavable complete feed for rats and rats – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest Germany *ad libitum*, and tap water from municipal supply, as for human consumption from 500 mL bottle *ad libitum*. The food was considered not to contain any contaminants that

could reasonably be expected to affect the purpose or integrity of the study. Details of the diet are archived with the raw data.

Water quality control analysis is performed once every three 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.

3.2.3 Identification

Animals were individually identified by numbers written on the tail with a permanent marker pen. The numbers were given on the basis of LAB Research Ltd.'s master file, for each animal allocated to the study. The boxes were identified by cards holding information on the study code, the sex of animals, the dose group, the cage number and the individual animal number.

3.3 Administration of the Test Item

3.3.1 Dosages

Justification of the doses:

A limit dose of 3000 mg/kg was selected by the Sponsor.

Rationale: Oral administration was considered to be an appropriate dose route as it is a possible route of human exposure.

3.3.2 Procedure

A single oral (gavage) administration was followed by a 14 day observation period. The day before treatment the animals were fasted. The food, but not water, was withheld overnight. Animals were weighed before dosing and the food was returned 3 hours after the treatment.

Single animals were dosed sequentially following an interval of at least 24 hours. The time intervals between dosing were determined by the onset, duration and severity of toxic signs. Treatment of an animal at the next dose was only performed when no significant clinical signs were noted in the previous animal.

3.4 Observations

3.4.1 Clinical observations

Animals were observed individually after dosing at 30 minutes, then 1, 2, 3, 4, and 6 hours after dosing and once each day for 14 days thereafter. Individual observations were

performed on the skin and fur, eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2 Body weight measurement

The body weights were recorded on Days -1, 0 (beginning of the experiment), 7 and 14.

3.5 Necropsy

All animals were subjected to macroscopic examination. All animals were exsanguinated under pentobarbital anaesthesia. After examination of the external appearance the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. All gross pathological changes were recorded for each animal on the post mortem record sheets.

3.6 Data Evaluation

Type, severity and duration of clinical observations are described.
Body weight and body weight changes are summarised in tabular form.
Necropsy findings are described and summarised in tabular form.

4.0 RESULTS AND DISCUSSION

4.1 Results

Individual clinical observations and mortality results are presented in Table 1. Individual body weights and necropsy results are presented in Tables 2 and 3, respectively.

4.2 Mortality

There were no mortalities observed.

4.3 Body Weights

The body weight and the body weight gain did not show any test item related effect.

4.4 Clinical Signs

All of the animals had red urine and red faeces for a maximum of 2 days following dosing. Decreased activity was observed in 3 animals (6545, 6551, 6546). Hunched back, lacrimation, piloerection, oedema on the head and on the whole body were described in 1 animal between 2 and 6 hours on the day of dosing only.

4.5 Macroscopic Findings

Dilatation of the right/ left atria and/or right/left ventricles of the heart were observed in some animal at necropsy. However, this is a common finding in acute studies conducted at this lab and therefore is not considered treatment related. Uterus in estrus was recorded in 2 animals and a single cyst of the right kidney was also recorded in 1 animal. These changes were considered to be incidentally.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose LD_{50} of the test item, Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (A16503C), was greater than 3000 mg/kg bw in female CRL:(WI) BR rats.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

Cage	Sex	Dose Level (mg/kg)	Animal Number	Observations	Observation days																			
					0						1	2	3	4	5	6	7	8	9	10	11	12	13	14
					30'	1h	2h	3h	4h	6h														
1	Female	3000	6549	Symptom Free	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+
				Red faeces	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-
				Red urine	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-
2			6545	Symptom Free	+	+	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+
				Activity decreased	-	-	+1	+2	+3	+3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Hunched back	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Red faeces	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
				Red urine	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
				Lacrimation	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Piloerection	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Oedema head	-	-	-	+2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Oedema whole body	-	-	-	-	+2	+2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3			6551	Symptom Free	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+
				Activity decreased	+1	+1	+2	+2	+2	+1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Red faeces	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
				Red urine	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
4			6544	Symptom Free	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
				Red faeces	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
				Red urine	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
5			6546	Symptom Free	+	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+
				Activity decreased	-	+1	+1	+2	+1	+1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
				Red faeces	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
				Red urine	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-

Remarks:
Severities: 1=Slight/Small/Few; 2=Moderate/Medium; 3=Marked/Large/Many +: increased, or present; -: decreased, or absent
Treatment day = Day 0

TABLE 2 Body Weight and Body Weight Gain

Group	Dose Level (mg/kg)	Sex	Animal No.	Body weight (g) Days				Body Weight Gain (g)			
				-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
1	3000	Female	6549	247	242	259	273	-5	17	14	26
2	3000	Female	6545	254	235	260	273	-19	25	13	19
3	3000	Female	6551	245	232	259	276	-13	27	17	31
4	3000	Female	6544	246	229	261	274	-17	32	13	28
5	3000	Female	6546	243	225	243	259	-18	18	16	16

TABLE 3 Macroscopic Findings

Group	Dose (mg/kg)	Animal ID	Sex	Necropsy Date	External Observations	Internal Observations	Location
1	3000	6549	Female	24 December 2009	No external observations recorded	Cyst, single, right	Kidneys
						In estrus	Uterus
						Dilatation, right and left atria	Heart
						Dilatation, right and left ventricle	
2		6545		25 December 2009	No external observations recorded	Dilatation, right and left atria	Heart
						Dilatation, right and left ventricle	
3		6551		29 December 2009	No external observations recorded	No internal observations recorded	Not applicable
4		6544		30 December 2009	No external observations recorded	In estrus	Uterus
5		6546		31 December 2009	No external observations recorded	Dilatation, right and left ventricle	Heart

Remarks:

* = Found Dead

**= Moribund

APPENDICES SECTION

APPENDIX 1 Pathology report

LAB Study code. 09/264-001P

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute oral toxicity of Sedaxane/Difenoconazole/Fludioxonil/Tiamethoxam FS (A16503C) when administered in a single dose to rats at one or more defined dose levels. The results of the study allow the calculation of the estimated oral LD_{50} of the test item and permits test item to be ranked according to most classification systems currently in use.

RESULTS AND DISCUSSION

All animals were euthanized upon completion of the treatment period on Day 14. Rats were anesthetized with pentobarbital, followed by exsanguination. Gross pathology consisted of an external examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination. Histopathological examination was not performed.

All rats survived until the scheduled termination of the study.

TERMINAL (DAY 14)

Macroscopic Findings

Dilatation of the right/ left atria and/or right/left ventricles of the heart were observed in 3/5 animal at necropsy. This is a common finding seen acute studies and therefore is not considered treatment related.

Uterus in estrus (6544 and 6549) and single cyst of the right kidney (6549) were regarded as incidental observations.

CONCLUSION

A single oral gavage of Sedaxane/Difenoconazole/Fludioxonil/Tiamethoxam FS (A16503C) to the CRL: (WI) BR rat at a dose level of 3000 mg/kg bw was not associated with any test item-related gross findings. Dilatation of the right/ left atria and/or right/left ventricles of the heart were macroscopically observed in 3/5 rats.

28 May 2010

Peter Maslej, D.V.M., Ph.D. Date
Head, Pathology Department

APPENDIX 2 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

A16503C
Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (050/025/025/175)
SMU9BP001

Batch Identification	**SMU9BP001**
Product Code	**A16503C**
Other Product Code(s)	Sedaxane/Difenoconazole/Fludioxonil/Thiamethoxam FS (050/025/025/175)

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredients***	**confirmed**
– **Content of Sedaxane ***	**50.4 g/l**
– **Content of Difenoconazole ***	**25.3 g/l**
– **Content of Fludioxonil***	**24.9 g/l**
– **Content of Thiamethoxam ***	**176 g/l**
Methodology used for Characterization / Reanalysis	HPLC

The Active Ingredients content is within the FAO limits.

Physical Analysis

– **Appearance**	**red liquid**
– **Density ***	**1143 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C, keep away from direct sunlight**
– **Reanalysis date**	**End of February 2012**

The stability of this test substance will be controlled by reanalysis of material held in the inventory at Syngenta Crop Protection Muenchwilen AG at the appropriate time.

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.

Characterization: 119696 Reanalysis: 15/04/2009

Authorization:

Jérôme Giovannoni
Analytical Development & Product Chemistry

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APPENDIX 3 Test Report of the Diet

AGROLAB Laborgruppe
www.agrolab.de

LUFA-ITL GmbH

Dr.-Hell-Str. 6, 24107 Kiel, Germany
Tel.: +49(0431)1228-0, Fax: +49(0431)1228-498
eMail: zentrale@lufa-itl.de

LUFA - ITL Dr.-Hell-Str. 6, 24107 Kiel

SSNIFF SPEZIALDIÄTEN GMBH
FERDINAND-GABRIEL-WEG 16
59494 SOEST

EINGEGANGEN

RS

Date 15.10.2009
Customer no. 1000187

TEST REPORT
Order no. 648085

ssniff Spezialdiäten GmbH Freigabe / Release Nach SV Seite FS

Sample No.	**851768**
Order No.	**71101SO-091240**
Project	**145 ssniff**
Sample Arrival	**07.10.2009**
Sample code	**ssniff R/M-Z+H, 15 mm, autoclavable Ch.-No.: 767 3000 - MHD: 03/2010**
Sample packing	**plastic bag**

	Unit	Result	Declaration		Substance	Method
Nutrition values						
Water	%	**11,1**			OM	VDLUFA III 3.1
Crude ash	%	**6,1**	6,50		OM	VDLUFA III 8.1
Crude proteine (Nx6,25)	%	**19,3**	19,00		OM	VDLUFA III 4.1.1
Total fat	%	**3,8**	3,50		OM	VDLUFA III 5.1.1 B
Crude fibre	%	**4,5**	3,60		OM	VDLUFA III 6.1.1
Calculated values (nutrition/ingredients)						
N-free substances	%	**55,2**			OM	calculated

Explanation: "<", n.d.: not detected, below limit of detection .
The actual limit of detection can be different to the standard value for a particular analysis due to matrix effects or insufficient sample volume.
Remark: OM=original matter, DM=dry matter

LUFA - ITL Dr. E. Hansen, Tel. 0431/1228-130
feeding stuffs

This electronically transmitted report was checked and released. It's in accordance with the requirements of DIN EN ISO/IEC 17025:2005 for simplified reports and valid without signature.

Copies
SSNIFF SPEZIALDIÄTEN GMBH

The analytical results are valid for the delivered sample material only. The testing period is the time between the receipt of the sample and the reporting date. Validation of results is not possible for samples of unknown origin .

APPENDIX 4 GLP-Certificate

ORSZÁGOS GYÓGYSZERÉSZETI INTÉZET
National Institute of Pharmacy

H-1051 Budapest, Zrinyi u. 3.
Mail: 1372 P.O. Box 450.
Phone: +36 1 8869-300
Fax: +36 1 8869-460
E-mail: ogyi@ogyi.hu

Budapest, 20th December 2008
No: 38625/48/2007
Our ref.: Szilvia Karsai
Subject: GLP Certificate

GOOD LABORATORY PRACTICE (GLP)
CERTIFICATE

Based on the Inspection report and the discussion of follow up activities it is hereby certified that the test facility

LAB Research Ltd.
H-8201 Veszprém, Szabadságpuszta, Hungary

is able to carry out **Physical-chemical testing, Toxicity studies, Mutagenicity studies, Environmental toxicity studies on aquatic and terrestrial organisms, Studies on behaviour in water, soil and air; bioaccumulation, Bioanalytical, Analytical and clinical chemistry testing** compliance with the Principles of GLP (Good Laboratory Practice).

Date of the inspection: **13-22 October 2008.**

This GLP Certificate is valid for 2 years.

Zsuzsanna Szepezdi, Ph. D.
Director-General