

FOI 13/02/002

25<sup>th</sup> April 2013



IRISH MEDICINES BOARD

**Re: Request for information pursuant to the Freedom of Information Act 1997 & 2003**

Dear Mr Bryce,

I refer to the request which you made under the Freedom of Information Acts 1997 and 2003 for records held by the Irish Medicines Board:

*I copy of all Periodic Update reports (PSURs) submitted to or held by the Irish Medicines Board since 1998 in relation to Lariam (mefloquine).*

From our records we identified the following PSUR's since 1998:

B-172211 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.1999 – 31.12.1999 A Periodic Update Report
1003979 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2000 – 31.12.2000 A Periodic Update Report
1007046 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2001 – 31.12.2001 A Periodic Update Report
1010603 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2002 – 31.12.2002 A Periodic Update Report
1013550 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2003 – 31.12.2003 A Periodic Update Report
1017241 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2004 – 31.12.2004 A Periodic Update Report
1019861 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2005 – 31.12.2005 A Periodic Update Report

Bord Leigheasra na hÉireann

Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2. Teil: +353-1-676 4971 Facs: +353-1-676 7836. www.imb.ie

Irish Medicines Board

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: +353-1-676 4971 Fax: +353-1-676 7836. www.imb.ie

1019861 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2005 – 31.12.2005 A Periodic Update Report
1025673 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2007 – 16.05.2007 A Periodic Update Report
1028512 Review on Adverse Events Associated with LARIAM (mefloquine) period 17.05.2007 – 16.05.2008 A Periodic Update Report
1032085 Review on Adverse Events Associated with LARIAM (mefloquine) period 17.05.2008 – 30.04.2009 A Periodic Update Report
1047641 Review on Adverse Events Associated with LARIAM (mefloquine) period April 2012 A Periodic Update Report

A Periodic Safety Update Report (PSUR) is a mechanism by which a company may summarise and evaluate safety data for a particular interval in time in a standardised manner for submission to certain regulatory authorities. Among the data that is summarised and evaluated are reports of adverse events that are communicated spontaneously to Roche by a variety of sources. The events may be reported by patients, family members, health care professionals, and others. The events may be due to a variety of factors, including the underlying disease for which the medication has been prescribed or another health condition, other medications or substances a patient is taking, environmental factors, events or exposures that are unknown or undisclosed, or the drug itself. Frequently, the available information pertaining to such factors is incomplete. A PSUR provides a listing of all adverse events, regardless of the cause of the event. The listing of or discussion about any adverse event in a PSUR, including any statement of 'relatedness of the event to the use of a drug', is not intended to suggest, imply or admit that a casual relationship exists between the adverse event and the use of the drug.

A final decision to part grant your request on 19<sup>th</sup> April 2013. If you have any queries regarding this correspondence you can contact me by telephone at 00 353 1 6764971.

In 2003, you requested PSUR information relation to Larium, the IMB consulted with Roche Products Ltd at that time in relation to the information from it that could be released. The IMB and Roche Products Ltd did not agree on what was considered could be released and the request was then appealed to the Information Commissioner and subsequently to the High Court. Roche Products Ltd and the Information Commissioner came to an agreement in advance of the court hearing in relation to the information which could be released.

Based on the previous request and decisions reached in relation to release of the information concerned, it is the IMB's opinion that the same information can be released in response to this request.

The purpose of this letter is to explain that decision. This explanation has the following parts:

1. a schedule of all of the records covered by your request;
2. concerning records to which access is granted, an explanation and a statement of the arrangements for this access
3. concerning records to which access is denied, an explanation of the relevant findings; and
4. a statement of how you can appeal this decision should you wish to do so.

This letter addresses each of these four parts in turn.

### **1. Schedule of records**

A schedule is attached at the end of this letter. It shows the documents that the Irish Medicines Board considers relevant to your request. It also gives you a summary and overview of the decision as a whole. The schedule describes each document, and indicates whether the document is released in full, released with deletions or not released. The schedule refers to the sections of the FOI Act which apply to prevent release. As to these documents, the schedule also provides brief reasons for the decision which are meant to supplement the fuller and more detailed explanation given under heading 3. below.

### **2. Access Arrangements**

You have sought access to the records by means of photocopies, and we consider this an appropriate form of access in this case. Accordingly, the records described as released in full or released with deletion are now enclosed.

### **3. Findings, particulars and reasons for decisions to deny access.**

The sections of the Act which can apply to deny access to documents are known as its exemption provisions.

I have outlined below the exemptions which have been applied to records which have been part granted and refused in full. These records are clearly outlined in the schedule of records.

#### **Section 26 (Information obtained in confidence)**

In section 26, the Act states the following:

*'(1) Subject to the provisions of this section, a head shall refuse to grant a request under section 7 if*  
*(a) the record concerned contains information given to a public body in confidence and on the understanding that it would be treated by it as confidential (including such information as aforesaid that a person was required by law, or could have been required by the body pursuant to law, to give to the body) and, in the opinion of the head, its disclosure would be likely to prejudice the giving to the body of further similar information from the same person or other persons and it is of importance to the body that such further similar information as aforesaid should continue to be given to the body'.*

The IMB has a duty to protect confidential information submitted by companies. If companies do not have confidence in the IMB to protect such data, a loss of confidence may be experienced with the regulator which would have a detrimental impact on public health and thus the public interest would not be served.

**Section 27 (Commercially Sensitive Information)**

In section 27, the Act states the following:

*'(1) Subject to subsection (2), a head shall refuse to grant a request under section 7 if the record concerned contains*  
*(a) trade secrets of a person other than the requester concerned,*  
*(b) financial, commercial, scientific or technical or other information whose disclosure could reasonably be expected to result in a material financial loss or gain to the person to whom the information relates, or could prejudice the competitive position of that person in the conduct of his or her profession or business or otherwise in his or her occupation'.*

Parts of the information listed below are considered to be commercially sensitive.

The information contains specific data to the product which have all been provided to the IMB in confidence and the disclosure of such data would significantly compromise commercial data of the company.

In addition, I am of the view that the public interest is not served in releasing commercially sensitive data in this case.

**Section 28 (Personal Information)**

In section 28, the Act states the following:

*28.(1) Subject to the provisions of this section, a head shall refuse to grant a request under section 7 if, in the opinion of the head, access to the record concerned would involve the disclosure of personal information (including personal information relating to a deceased individual).*

*"personal information" is information about an identifiable individual that:*

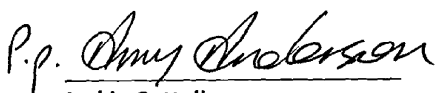
*(a) would, in the ordinary course of events, be known only to the individual or members of the family, or friends, of the individual, or (b) is held by a public body on the understanding that it would be treated by it as confidential*

This exemption is designed to protect the personal privacy of individuals. This provision puts in place controls to prevent the inappropriate release of personal information about individuals.

**4. Rights of appeal**

You may appeal this decision by writing to the Information Commissioner at 18 Lower Leeson Street, Dublin 2. There is a fee of €150 for such appeals, other than appeals against a decision to impose a fee. If you wish to appeal, you must usually do so not later than 6 months from the date of this notification. Should you write to the Information Commissioner making an appeal, please refer to this letter.

Yours sincerely,



**Jackie Cottell**  
**Information Officer**

FOI 13/02/002

Description of Records	Decision	Exemption Applied
B-172211 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.1999 – 31.12.1999 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1003979 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2000 – 31.12.2000 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1007046 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2001 – 31.12.2001 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1010603 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2002 – 31.12.2002 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1013550 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2003 – 31.12.2003 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1017241 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2004 –	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence

31.12.2004 A Periodic Update Report		Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1019861 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2005 – 31.12.2005 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1025673 Review on Adverse Events Associated with LARIAM (mefloquine) period 01.01.2007 – 16.05.2007 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1028512 Review on Adverse Events Associated with LARIAM (mefloquine) period 17.05.2007 – 16.05.2008 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1032085 Review on Adverse Events Associated with LARIAM (mefloquine) period 17.05.2008 – 30.04.2009 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information
1047641 Review on Adverse Events Associated with LARIAM (mefloquine) period April 2012 A Periodic Update Report	Part Released As per previous FOI request in 2003	Section 26 (1) (a) Information Obtained in Confidence Section 27 (1)(a)(b) Commercially Sensitive Information Section 28 (1) Personal Information

1047641

Review on Adverse  
Events Associated with  
LARIAM (mefloquine)  
period April 2012

## 2. INTRODUCTION

This PSUR for Lariam<sup>®</sup> (mefloquine) is written in line with Volume 9A of The Rules Governing Medicinal Products in the European Union. The methodology used to generate this PSUR is presented in Appendix 1 page 82. For a list of previous PSURs prepared for mefloquine please refer to Appendix 2 page 98.

Mefloquine is a 4-quinoline methanol derivative and is structurally related to quinine. Mefloquine acts on the asexual intraerythrocytic forms of the human malaria parasites: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Mefloquine is effective against malaria parasites resistant to other anti-malarials such as chloroquine, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations. Resistance of *P. falciparum* to mefloquine has been reported predominantly in areas of multi-drug resistance in South-East Asia. Cross-resistance between mefloquine and halofantrine and between mefloquine and quinine has been observed in some regions.

Lariam (mefloquine) is indicated for the prophylaxis, therapy and stand-by treatment of malaria.

*Prophylaxis:* Chemoprophylaxis with mefloquine is recommended for travellers to malarious areas, particularly those travelling to areas where there is a high risk of infection with strains of *P. falciparum* resistant to other antimalarials.

*Therapy:* Mefloquine is indicated for the oral treatment of malaria, particularly when caused by strains of *P. falciparum* resistant to other antimalarials. It may also be used for the treatment of *P. vivax* and mixed malaria.

*Stand-by treatment:* Mefloquine is also prescribed as a stand-by medication to be carried by the traveller and self-administered as an emergency measure for suspected malaria when prompt medical attention is unavailable within 24 hours.

Lariam (mefloquine) is available as a single formulation of tablet containing 250 mg mefloquine which is covered by this PSUR.

Further details on the mechanism of action, indications, pharmaceutical forms, instructions for use and undesirable effects are presented in the CDS in Appendix 4 page 121.

## 3. WORLDWIDE MARKETING AUTHORISATION STATUS

Lariam (mefloquine) was first approved in Switzerland on 20 February 1984, which marks its International Birth Date (IBD). The newly agreed Harmonised European Birth Date is 17 May 1985 in France. Lariam (mefloquine) was approved in the European Union through the national authorised procedures. Lariam (mefloquine) has been approved in about 50 countries worldwide and is sold in several countries on special license.

For the status of the worldwide marketing authorisation see Appendix 3 page 100, Worldwide Marketing Authorisation Status.

4. **UPDATE OF REGULATORY AUTHORITY OR  
MARKETING AUTHORISATION HOLDER ACTIONS  
TAKEN FOR SAFETY REASONS**

During the reporting period covered by this report *none* of the following actions were taken by the MAH or any Regulatory Authority for product safety reasons:

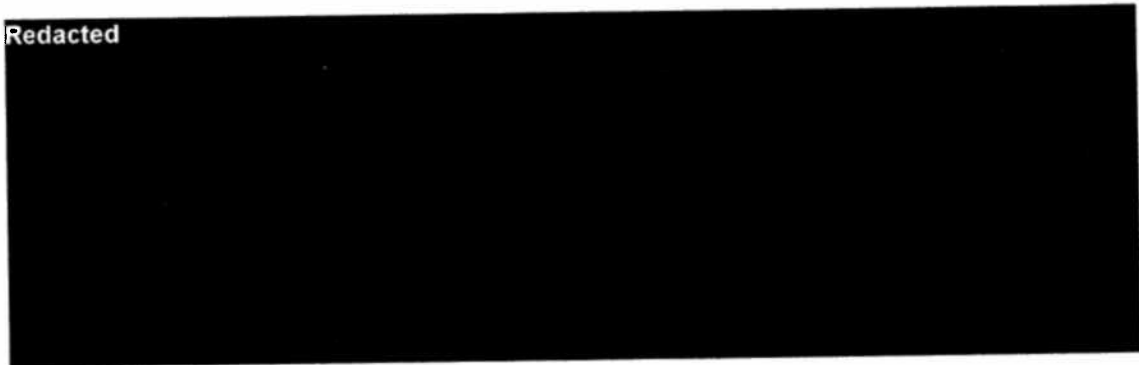
- Marketing authorisation withdrawal, revocation or suspension
- Failure to obtain a marketing authorisation renewal
- Restrictions on distribution
- Clinical trial suspension
- Dosage modification
- Changes in target population or indications
- Formulation changes
- Urgent Safety Restrictions
- Issuance of Dear Doctor Letter.

**For the European Union**

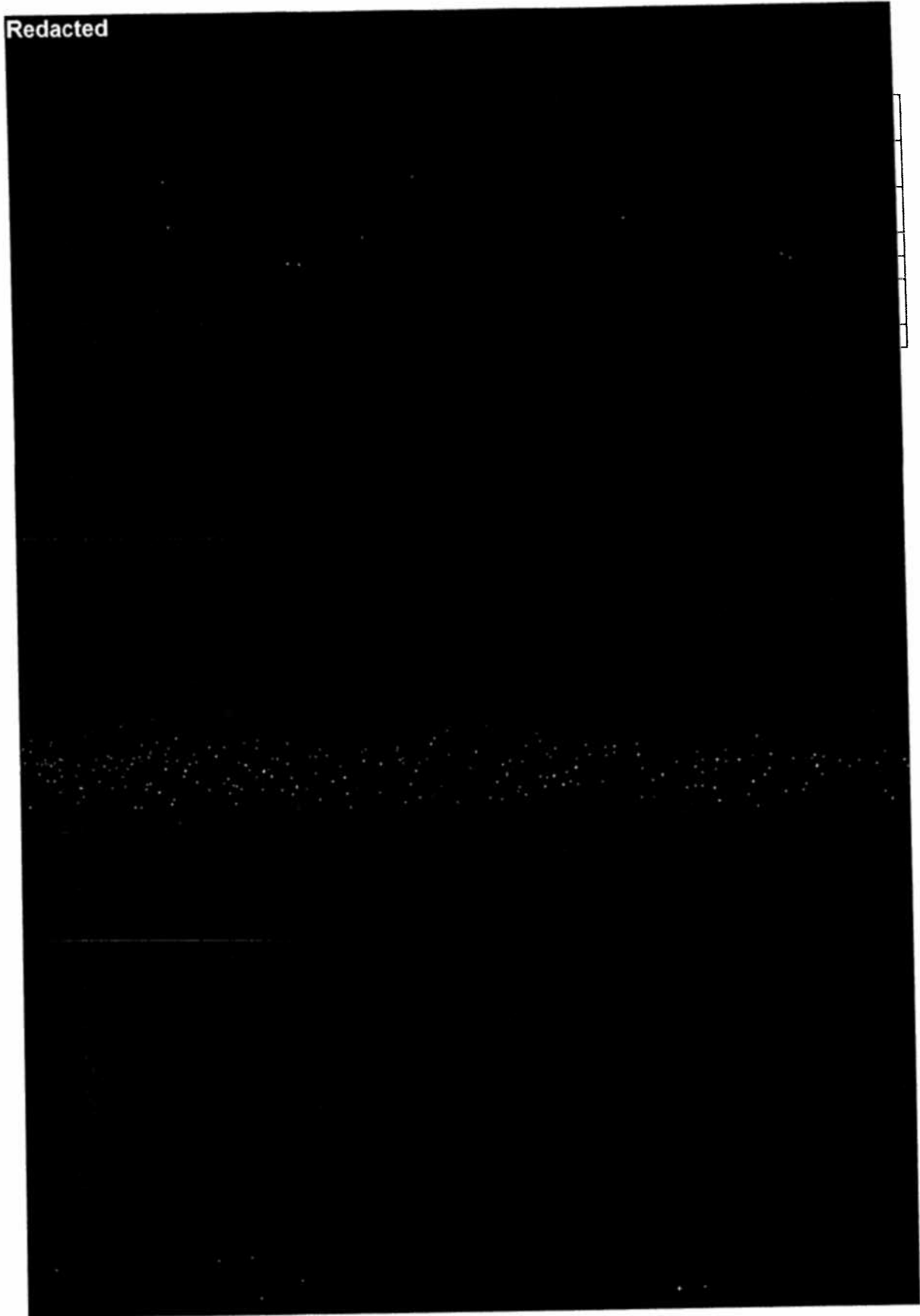
The assessment of the three yearly PSUR WS procedure DE/H/ PSUR/0022/001, covering the reporting period 01 January 2006 to 30 April 2009 with BfArM as P-RMS, is currently ongoing. Roche received the Request for Further Information (RFI) on 02 October 2009 and submitted their final responses in Q3 2010. The assessment of BfArM is awaited.

5. **CHANGES TO REFERENCE SAFETY INFORMATION**

The RSI that was in effect at the start of the reporting period for this PSUR is the CDS, version 3.0, that was last updated in August 2010. This is current version of the CDS for Lariam (mefloquine). A copy of the current CDS is provided in Appendix 4 page 121.



Redacted



## 7.2 OVERVIEW

### 7.2.1 SUMMARY TABULATION OF ADVERSE EVENTS BY SOC

Table 2 Summary Tabulation of Adverse Events by SOC

System Organ Class	No. Patients with at least 1 AE/SOC	Serious Adverse Events		Total Adverse Events	
		N	%	N	%
Infections and Infestations	4	2	1.7	4	2.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0.0	0	0.0
Blood and lymphatic system disorders	2	2	1.7	2	1.1
Immune system disorders	1	1	0.8	1	0.5
Endocrine disorders	1	0	0.0	1	0.5
Metabolism and nutrition disorders	1	0	0.0	1	0.5
Psychiatric disorders	33	56	46.3	67	35.8
Nervous system disorders	13	18	14.9	24	12.8
Eye disorders	2	0	0.0	2	1.1
Ear and labyrinth disorders	1	0	0.0	1	0.5
Cardiac disorders	5	4	3.3	6	3.2
Vascular disorders	1	1	0.8	1	0.5
Respiratory, thoracic and mediastinal disorders	4	2	1.7	4	2.1
Gastrointestinal disorders	17	14	11.6	23	12.3
Hepatobiliary disorders	0	0	0.0	0	0.0
Skin and subcutaneous tissue disorders	4	3	2.5	5	2.7
Musculoskeletal and connective tissue disorders	1	1	0.8	1	0.5
Renal and urinary disorders	0	0	0.0	0	0.0
Pregnancy, puerperium and perinatal conditions	5	2	1.7	5	2.7
Reproductive system and breast disorders	0	0	0.0	0	0.0
Congenital, familial and genetic disorders	1	1	0.8	1	0.5

System Organ Class	No. Patients with at least 1 AE/SOC	Serious Adverse Events		Total Adverse Events	
		N	%	N	%
General disorders and administration site conditions	18	9	7.4	22	11.8
Investigations	3	1	0.8	3	1.6
Injury, poisoning and procedural complications	10	3	2.5	11	5.9
Surgical and medical procedures	0	0	0.0	0	0.0
Special circumstances	2	1	0.8	2	1.1
<b>Total</b>	<b>N/A</b>	<b>121</b>	<b>100.0</b>	<b>187</b>	<b>100.0</b>

Please refer to section 1.3.1, titled Presentation of Summary Tabulations of Appendix 1 page 82 Methodology for events that have been excluded from this table.

A summary tabulation of AEs by SOC is presented in Table 2. During the reporting period for this PSUR, 79<sup>1</sup> medically confirmed cases containing 187 AEs were received from 77 patients. Fifty eight of the cases were serious with 121 of the events categorised as SAEs. A line listing of medically confirmed cases (excluding medically confirmed, spontaneous, non-serious listed cases) is presented in Appendix 5 page 138. There were 56 events categorised as non-serious listed AEs and are presented separately in Appendix 7 page 281.

The total of 79<sup>1</sup> medically confirmed cases also excludes blinded cases, however there were no blinded cases received during the reporting period of this PSUR (please note blinded cases are not appended to the PSUR).

The most frequently reported AEs were categorised in the Psychiatric Disorders SOC (35.8% of total AEs), the Nervous System Disorders SOC (12.8% of total AEs), the Gastrointestinal Disorders SOC (12.3% of total AEs) and the General Disorders and Administration Site Conditions SOC (11.8% of total AEs). All other SOC's individually contributed no more than 5.9% of the total number of AEs received during the reporting period.

The most frequently reported SAEs were categorised in the Psychiatric Disorders SOC (46.3% of total SAEs), the Nervous System Disorders SOC (14.9% of total SAEs), the Gastrointestinal Disorders SOC (11.6% of total SAEs) and the General Disorders and Administration Site Conditions SOC (7.4% of total SAEs). All other SOC's individually contributed no more than 3.3% of the total number of SAEs received during the reporting period.

## 7.2.2 CASE REPORTING EVENTS WITH A FATAL OUTCOME

There was one fatal case **Redacted** received by the MAH during the reporting period. The primary reported fatal event in this case was categorised in the Psychiatric Disorders SOC. The reported MedDRA preferred term with a fatal outcome was completed suicide. In this fatal case, there were risk factors for reported event with fatal outcome in the form of medical history and past drug administration. Please refer to 7.10.1 for details of this case.

A line listing of the fatal cases with a summary tabulation of AEs by SOC is presented in Appendix 8 page 312.

### 7.2.3 SOURCE OF CASES

The primary reporting sources of cases presented in this PSUR are summarised in Table 3. Of the 79 medically confirmed cases received during the current reporting period, the majority of cases were from spontaneous sources (64 cases, 164 AEs). A total of 15 cases (23 AEs) were of literature origins and no cases were originated from either study or other sources.

**Table 3 Cases by Primary Reporting Source**

Source	No. Cases	No. Serious Cases	Total Adverse Events
Spontaneous	64	44	164
Study	0	0	0
Literature	15	14	23
Other	0	0	0
<b>Total</b>	<b>79</b>	<b>58</b>	<b>187</b>

Please refer to section 1.3.1, titled Presentation of Summary Tabulations of Appendix 1 page 82, Methodology for events that have been excluded from this table.

Redacted



### 7.2.5 PATIENT DEMOGRAPHICS

Summary tables of patient age groups by gender and age class by gender are presented in Table 5.

The greater proportion of cases received during the current reporting period concerned female patients (40 cases) with 33 cases describing male patients and four cases describing patients of unknown gender. The gender of the patient was not specified in two patients. Regarding age groups, the majority of cases concerned adult patients (49 cases) followed by infants (three cases) and children (two cases). The age group in 25 cases was unknown.

**Table 5 Patient Demographics**

Age Group	Female	Male	Not specified	Unknown	Total Cases
Neonate	0	0	0	0	0
Infant	1	2	0	0	3
Child	1	1	0	0	2
Adolescent	0	0	0	0	0
Adult	25	24	0	0	49
Elderly	0	0	0	0	0
Unknown	13	6	4	2	25
<b>Total</b>	<b>40</b>	<b>33</b>	<b>4</b>	<b>2</b>	<b>79</b>

Neonate (Birth-<1 month) Infant ( $\geq 1$  month-<2 yrs) Child ( $\geq 2$ -<12 yrs) Adolescent ( $\geq 12$ -<18 yrs)  
Adult ( $\geq 18$ -<65 yrs) Elderly ( $\geq 65$  yrs)

### 7.3 EVALUATION OF SELECTED ADVERSE EVENTS

Unless otherwise stated, AE data received in the reporting period of this PSUR are discussed in Section 7.4 according to the System Organ Class (SOC) of the primary reported event.

#### 7.3.1 CASE NARRATIVES

Individual Case Safety Report (ICSR) narratives are provided for cases which present **new and relevant safety information** in Appendix 9 page 317 (please see Appendix 1 for the methodology used to determine the narratives presented in this listing).

### **7.3.2 ADVERSE EVENTS UNDER CLOSE SURVEILLANCE**

Routine pharmacovigilance and signal detection is continuously carried out by the MAH in order to detect and evaluate potential signals to assess risk. The established routine pharmacovigilance activities using the cases entered onto the Company Global Safety Database performed by the MAH is summarised in Section 10.1.

In addition to the robust process of routine pharmacovigilance and signal detection, the following AEs have been closely monitored during the reporting period (cross references to the section of the PSUR where the events are discussed are presented in parenthesis):

Suicide (Refer to Section 7.10.3)

**Homicide (Refer to Section 7.10.3)**

Physical assault (Refer to Section 7.10.3)

Psychiatric events persisting more than 90 days after discontinuation of mefloquine (Refer to Section 7.10.3)

Neurological events (vestibular disorders) persisting more than 90 days after discontinuation of mefloquine (Refer to Section 7.11.2)

Severe pulmonary disorders (Refer to Section 7.16.1)

Pancreatitis (Refer to Section 7.17.2)

Renal toxicity (including acute renal failure and renal failure) [Refer to Section 7.21)

Hepatotoxicity (Refer to Section 7.18)

Rhabdomyolysis (Refer to Section 7.20.1)

Maculopathy (Refer to Section 7.12.1)

Cases with long term treatment with mefloquine (Refer to Section 10.8)

In addition, the MAH also monitored the paediatric population of less than 20 kg body weight (Refer to Section 10.8).

### **7.4 INFECTIONS AND INFESTATIONS SOC**

During the current reporting period, four AEs were reported in four patients. Of these, two AEs (malaria and encephalitis Japanese B) were serious and unlisted and two were non-serious. The most frequently reported AE was malaria (two AEs).

No fatal case, where the primary fatal event was categorised in this SOC, was received in this SOC during the current reporting period.

**Table 6 Serious unlisted related events (N=10 AEs)**

Redacted	Adverse Events (MedDRA Terms)	Event outcome	Redacted
	Completed suicide	Fatal	
	Derealisation	Unknown	
	Thinking abnormal	Unknown	
	Fear of disease	Not recovered/not resolved	
	Hostility	Not recovered/not resolved	
	Psychotic disorder	Not recovered/not resolved	
	Suicidal ideation	Not recovered/not resolved	
	Mania	Recovered/resolved	
	Suicide attempt	Recovered/resolved	
	Tearfulness	Recovering/resolving	

This is a non-validated output.

**7.10.3 ADVERSE EVENTS UNDER CLOSE SURVEILLANCE IN THE PSYCHIATRIC DISORDERS SOC**

The events related to suicide, **homicide** and physical assault and psychiatric events persisting more than 90 days after discontinuation of mefloquine have

been closely monitored during the review period. Four case reports with the monitored events were received during the current reporting period and are discussed below.

**Completed Suicide** [Redacted]: Refer to Section 7.10.1 for the comment.

**Suicide attempt** [Redacted]: Refer to Section 7.10.2 for the comment.

**Homicide** [Redacted]: Refer to Section 7.29.1 for the comment.

**Suicidal ideation** [Redacted]: This spontaneous case reports was received via [Redacted] and concerns a 32-year-old male patient who started on mefloquine 120 mg/week for malaria prevention. Two days later, he experienced excitement, restlessness, anxiety, depression, mood swings, panic disorder, confusion, hallucination, hostility, psychosis, fear of insanity and suicidal ideation. The events were persisting at the time of report and there was insufficient information concerning therapy ongoing status of mefloquine. [Redacted]

[Redacted]

During the current reporting period, no case reports were received where the psychiatric event persisted for more than 90 days after the discontinuation of mefloquine. However, 21 case reports were received in this SOC where the information regarding outcome of psychiatric event was either insufficient or the events were persisting at the time of reporting.

[Redacted]

## 7.11 NERVOUS SYSTEM DISORDERS SOC

During the current reporting period, 24 AEs were reported in 13 patients. Of these, 18 AEs were serious and six were non-serious. The most frequently reported AE was dizziness (eight AEs), which was also the most frequently reported SAE (five SAEs).

There were four AEs reported that were both serious and unlisted.

Redacted

## 7.28 SURGICAL AND MEDICAL PROCEDURES SOC

No AEs were reported in this SOC during the current reporting period.

## 7.29 SOCIAL CIRCUMSTANCES SOC

During the current reporting period, two AEs were reported in two patients. Of these, one AE (homicide) was serious and one (pregnancy of partner) was non-serious.

There was one AE (homicide) reported that were both serious and unlisted.

No fatal case, where the primary fatal event was categorised in this SOC, was received in this SOC during the current reporting period.

A line listing and summary table of medically confirmed cases received in the reporting period is presented in Appendix 5 page 138. A table of cumulative events (listed and unlisted) is presented in Appendix 10 page 329.

### 7.29.1 OVERVIEW OF SERIOUS UNLISTED REACTIONS IN THE SOCIAL CIRCUMSTANCES SOC

Of the two events categorised in this SOC, one (homicide) was serious and unlisted and assessed as related to mefloquine.

**Homicide** Redacted A patient of unknown demographics started on mefloquine (therapy details unspecified) for an unknown indication. After an unspecified duration, the patient who was a soldier experienced homicidal behaviour which led to homicidal killing (MedDRA PT: Homicide) of 17 Redacted. It was reported that the patient was suffering from traumatic brain injury (TBI) and was administered mefloquine against military rule (mefloquine is directly contraindicated in patients with TBI as per Redacted rule). The outcome of homicide was not reported and there was insufficient information regarding therapy ongoing status of mefloquine. Homicide is a monitored event. The lack of information concerning patient's medical history and concomitant medications precludes adequate assessment of the case.

Redacted

Redacted

## 8. STUDIES

Redacted

### 8.3 PUBLISHED SAFETY STUDIES

The MAH continually monitors recognised medical and scientific literature for safety information on mefloquine.<sup>5</sup> A thorough search of the medical literature, from 01 May 2011 to 30 April 2012, utilising the Medline and Embase Databases, identified 364 new relevant medical articles, three of which contained important safety findings and are discussed below.

#### **Mefloquine For Uncomplicated Plasmodium Falciparum Malaria In Children.<sup>6</sup>**

**Background:** Children with uncomplicated *Plasmodium falciparum* imported malaria are treated with various antimalarial regimens including mefloquine depending on national guidelines. Little is known regarding mefloquine treatment efficacy in this setting.

**Methods:** In this prospective study, children three months to 16 years of age admitted in a tertiary hospital emergency ward in France with uncomplicated *P. falciparum* malaria were treated with oral mefloquine. Each dose was given with an antiemetic.

**Results:** Between 2004 and 2009, 95 children were evaluated. In all, 94% had travelled in the Indian Ocean region (Comoros and Madagascar); 79% used a malaria chemoprophylaxis, but none was fully compliant with World Health Organization recommended regimens. Main clinical features at admission were fever (91%), vomiting (44%), and headaches (44%). Haemoglobin <80 g/L and

<sup>5</sup> Please note: This section is not intended to include literature articles reporting a single adverse event report published within the literature, these are identified via separate processes and are included in the safety database as single case reports.

<sup>6</sup> Minodier P, Noel G, Tall M, Retornaz K, Piarroux R, Parzy D et al. The Paediatric Infectious Disease Journal 2011; 30(10): 883-886.

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Appendix 5  
Line Listing and Summary Table of  
Medically Confirmed Cases

Ro 21 (mefloquine)

Roche PSUR 1047640 1st May 2012 2th Apr. 2012 145

Date: 01MAY2012  
 Mefloquine: 01MAY2011 to 30APR2012

Summary Table for the Line Listing of **Medically Confirmed Cases**: Serious Adverse Events

		No. of Serious AEs Received During the Reporting Period											
		Spontaneous		Study		Literature		Other					
SOC (Abbr)	AE MedDRA Preferred Term	Total No. AEs	Serious Unlisted	Serious Listed	Serious Unlisted	Serious Listed	Serious Unlisted	Serious Listed	Serious Unlisted	Serious Listed	Total No. Serious Unlisted AEs	Cumulative No. of Serious Unlisted AEs	
Sub-total		3	2	1	0	0	0	0	0	0	2	2	
SeeCi	Homicide	1	1	0	0	0	0	0	0	0	1	2	
Sub-total		1	1	0	0	0	0	0	0	0	1	2	
Total		121	30	75	0	0	1	15	0	0	31	1015	

Ro 21 (mefloquine)

Roche PSUR 1047640 1st May 2011 10th Apr. 2012 230

Date: 01MAY2012  
 Mefloquine: 01MAY2011 to 30APR2012

Medically Confirmed Cases

AER No.	Indication Medical History	Route Cumulative Dosage Regimen Treatment: Start/ Stop or Duration	Medication (# - Suspect Drug) (\$ - Interacting Drug)	AE Onset Date or Latency (first dose)	AE Reported Term AE Preferred Term (\$ = Serious AE)	Event Outcome

SOCIAL CIRCUMSTANCES

<b>Reda</b>	Product used for unknown indication	# Mefloquine Hydrochloride	Homicide s Homicide	Not Reported
Unknown				
Not specified				
Spca				
Not Reported				

Comments:

Other AER NOs for this patient:  
 None

Appendix 9  
Appendix of Case Narratives for Selected  
Cases

### Case Narratives for Selected Cases

<b>Injury, poisoning and procedural complications</b>
<b>Redacted</b> Maternal exposure during pregnancy
Initial Information for this spontaneous Spontaneous case, <b>Redacted</b> was received on 16 November 2011 from a physician and concerns a Male patient who was treated with MEFLOQUINE HYDROCHLORIDE (Lariam) for an unknown indication. No medical history was reported. No concurrent illnesses were reported. No concomitant medications were reported. On an unspecified date, the patient started MEFLOQUINE HYDROCHLORIDE (Dosing amounts not available, Frequency not reported). On an unspecified date, his wife became pregnant. On an unspecified date, mother had early miscarriage. There was insufficient information regarding therapy ongoing status of MEFLOQUINE HYDROCHLORIDE. The reporter did not provide causal relationship between MISCARRAIGE and MEFLOQUINE HYDROCHLORIDE. The company assessed the event MISCARRAIGE as medically significant. No further information was provided.
<b>Redacted</b> Overdose
INITIAL INFORMATION FOR THIS SPONTANEOUS CASE WAS RECEIVED ON 27 MAY 2011, FROM A <b>Redacted</b> AND CONCERNS A 40 YEAR OLD MALE PATIENT WHO EXPERIENCED DRUG OVERDOSE WHILE TREATED WITH MEFLOQUINE (LARIAM) FOR AN UNKNOWN INDICATION. NO CONCURRENT CONDITIONS AND MEDICAL HISTORY WERE REPORTED. NO CONCOMITANT OR PAST DRUGS WERE REPORTED. ON 24 MAY 2011, THE PATIENT STARTED THERAPY WITH MEFLOQUINE TABLETS AT ONE DOSE FORM DAILY. THE PATIENT TOOK ONE TABLET OF MEFLOQUINE PER DAY DURING FOUR FOLLOWING DAYS. ON 24 MAY 2011, THE PATIENT EXPERIENCED DRUG OVERDOSE. ON 27 MAY 2011, THE TREATMENT WITH MEFLOQUINE WAS STOPPED. ON THE SAME DAY, THE EVENT OF DRUG OVERDOSE RESOLVED. THE REPORTER ASSESSED THE NON-SERIOUS EVENT OF OVERDOSE AS RELATED TO MEFLOQUINE. FURTHER INFORMATION WAS REQUESTED. ADDITIONAL INFORMATION WAS RECEIVED ON 27 MAY 2011. THE EVENT TERM WAS AMENDED TO OVERDOSE (PREVIOUSLY REPORTED AS DRUG OVERDOSE). THE REPORTER ASSESSED THE NON-SERIOUS EVENT OF OVERDOSE AS RELATED TO MEFLOQUINE. NO FURTHER INFORMATION WAS PROVIDED.

<b>Social circumstances</b>
<b>Redacted</b> Homicide
Initial Information for this Spontaneous case, <b>Redacted</b> was received on 29/Mar/2012 from a <b>Redacted</b> and concerns a patient of unknown demographics who was treated with Mefloquine Hydrochloride (Lariam) for an unknown indication. Medical history included TBI (Traumatic brain injury). No concurrent illnesses were reported. No concomitant medications or past drugs were reported. On an unknown date, the patient started Mefloquine Hydrochloride (dose, form and frequency not reported). On an unknown date the patient who was a soldier in <b>Redacted</b> Army developed homicidal behavior and led to Homicide killing 17 <b>Redacted</b> . It was reported that this patient was administered Mefloquine in direct contradiction to <b>Redacted</b> military rules that Mefloquine should not be given to soldiers who had suffered TBI (Traumatic brain injury) due to its propensity to cross blood brain barriers inciting psychotic, homicidal or suicidal behavior. The outcome of Homicide was not Reported. There was insufficient information regarding the therapy ongoing status of Mefloquine Hydrochloride. The reporter did not provide the seriousness criteria of the event of Homicide and its causal relationship with Mefloquine Hydrochloride. <b>Redacted</b>
<b>Redacted</b>

