# Therapeutic Goods Act 1989

TGA Therapeutic Goods Administration

COMMONWEALTH DEPARTMENT OF HUMAN SERVICES AND HEALTH

LARIAM -Revised Product Information



## Application

*(please tick the appropriate box)*

☐ **for Registration (including Benefits Listing) of Drug ProductsPharmaceutical**

☒ **to vary the Conditions of Registration of Drug Products**

*(via Drug Safety and Evaluation Branch)*

- To ensure this form is correctly completed, please refer to the explanatory guide issued for this application form before applying.
- Send **Original** of this form with a cheque for the appropriate fee(s) and an Enterprise Details form if necessary to:



*Note:* Cheques should be made payable to: 'Therapeutic Goods Administration'.

via Courier

**The Business Manager**
**Business Management Unit**
**Therapeutic Goods Administration**
**5th Floor, Alexander Building**
**Furzer Street**
**Phillip ACT**
**Australia**

via Australia Post

**The Business Manager**
**Business Management Unit**
**Therapeutic Goods Administration**
**PO Box 100**
**Woden ACT 2606**
**Australia**

- Send a copy of this form with the Data for Evaluation to:

via Courier

**The Director**
**Drug Safety and Evaluation Branch**
**5th Floor, Alexander Building**
**Furzer Street**
**Phillip ACT**
**Australia**

via Australia Post

**The Director**
**Drug Safety and Evaluation Branch**
**Therapeutic Goods Administration**
**PO Box 100**
**Woden ACT 2606**
**Australia**

8

## Part 1 - General Details

**Sponsor details** ***(if an individual, provide full name; if a corporation, the registered company name under the Companies Code; or business names under which you propose to trade for the purposes of the Therapeutic Goods Act 1989).***

1. **Sponsor's business name** *(max 100 characters)*

ROCHE PRODUCTS PTY LTD

2. **Sponsor's enterprise identification code**

438

3. **Enterprise details**

- Have you attached a completed "Enterprise Details" form? Yes ☐ No ☒

4. **Payment enclosed** *(for payment of relevant fees)*

$ 1200

5. **Sponsor Application and Declaration**

- Sponsors should note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false or misleading in connection with an application for registration of therapeutic goods.

I apply to: *(delete whichever is not applicable)*

- ~~Register (including Pharmaceutical Benefits Listing)~~
- Vary the conditions of registration of

the goods described in this form and declare that the information given is, to the best of my knowledge, current and correct.

To the best of by knowledge, I certify that this application is accompanied by such information and in the required format as will allow the determination of the application (ie. complies with the current AGRD guidelines for preparing applications to market drug products and any associated or supplementary guidelines).
*(Refer to the Guide for details and Note on page 3 of this form).*

RECEIVED 08 MAY 1997 TGA

Signature [redacted] Date 7 5 97 (dd mm yy)

Name *(please print)* [redacted]

Position/ Relationship to Sponsor: REGULATORY AFFAIRS ASSOCIATE

FEES RECEIVED – 9 MAY 1997 Drug Safety and Evaluation Branch

If you are not the Sponsor, have you attached a copy of a current "Instrument of Appointment" authorising you to act as a duly appointed agent of the Sponsor. Yes ☒ No ☐

**Office use Only**

| | | | |
|---|---|---|---|
| Receipt number | 12810 | Charge code | |
| Evaluation fee | 1200 — | Correct fee Yes ☐ No ☐ | |
| Enterprise ID | 438 | | |
| TGAIN | 90516 | | |

ARTG NO.

# Part 2 - Description of Data for Evaluation

6. Application types

- **Application to Register**

**New Chemical or Biological Agent**

| | | |
|---|---|---|
| 1A | new substance | ☐ |
| 1B | new salt or ester | ☐ |

**Other**

| | | |
|---|---|---|
| 2 | new route of administration | ☐ |
| 3 | new combination | ☐ |
| 5 | Pharmaceutical Benefits Listing | ☐ |
| 9 | new strength | ☐ |
| 10 | new dosage form | ☐ |
| 11 | new generic product | ☐ |

**Indications**

| | | |
|---|---|---|
| 4A | addition of new indication | ☐ |
| 4B | deletion of existing indication | ☐ |

**Other (continued)**

| | | |
|---|---|---|
| 12A | formulation | ☐ |
| 12I | packaging | ☐ |
| 12M | other aspect of B1 data | ☐ |
| 12N | change to container | ☐ |

- **Application to Vary Condition**

**Change in Pharmaceutical Data**

| | | |
|---|---|---|
| 12B | specifications - raw material drug | ☐ |
| 12C | specifications - finished product | ☐ |
| 12D | specifications - excipients | ☐ |
| 12E | synthetic route - raw material drug | ☐ |
| 12F | manufacturing procedure - finished product | ☐ |
| 12G | site of manufacture - raw material drug | ☐ |
| 12H | site of manufacture - finished products | ☐ |
| 12I | packaging | ☐ |
| 12J | additional pack size(s) in existing materials | ☐ |
| 12K | shelf life and/or storage conditions | ☐ |
| 12L | labelling | ☒ |
| 12M | other aspects of B1 data | ☐ |

**Other**

| | | |
|---|---|---|
| 2 | new route of administration | ☐ |
| 6 | change in regulatory status | ☐ |
| 7 | change in dosage, dose regimen or maximum daily dose | ☐ |
| 7A | change in patient group | ☐ |
| 13 | not in 1 to 12 | ☐ |

**Change in Product Information**

| | | |
|---|---|---|
| 8A | clinical aspects - safety related | ☒ |
| 8B | clinical aspects - non-safety related | ☒ |
| 8C | preclinical aspects (B2) | ☐ |
| 8D | pharmaceutical aspects (B1) | ☒ |
| 8E | other P1 | ☒ |

8

- Complete the authorisation below, or a copy, for each person you have appointed to submit applications for registration, listing or manufacturing licence on your behalf.
- Send the original authorisation to the *Therapeutic Goods Administration*. A copy of the authorisation should be included with each application (or group of applications) submitted by the authorised person on behalf of the enterprise.

## Instrument of Appointment

- Please print full name where applicable.

I, [redacted]

being a sponsor or company director or company secretary of a sponsor of therapeutic goods in Australia,

hereby appoint [redacted]

as my/the sponsor's duly appointed agent to provide information and make declarations for the purposes of applications as required under the *Therapeutic Goods Act 1989*.

Signature [redacted]

Date 31 / 01 / 95

- **Note:** If an individual person is the sponsor, this instrument is to be signed by that person; if a partnership, by a partner for the partnership; if a corporation, by a director of the company secretary of that corporation.

Specimen signature of appointee [redacted]

Signature of witness [redacted]

Date 31 / 1 / 95

**Company Seal - if a corporation, place an imprint of the Company Seal here.**

The common seal of Roche Products Pty Ltd ACN 000 132 865 is hereto affixed in accordance with its Articles of Association in the presence of:

[redacted]

ROCHE PRODUCTS PTY LIMITED Common Seal A.C.N. 000 132 865

n, Secretary

- When this Instrument is revoked the enterprise must advise the *Therapeutic Goods Administration* in writing of the date of the revocation.

Pin extra pages here

**5** In relation to your sponsorship or manufacture of therapeutic goods, do you trade under any other names or trade marks?

Yes ☑ → Give these trading names/trade marks on separate lines

No ☐ → If No, go to **6**

Roche Diagnostic Systems

Genentech Inc

Nicholas Australia

## Declaration

**6** The following declaration must be signed:

- in the case of a corporation, by a company director or the company secretary,
- in the case of other enterprises, by the owner or one partner

I declare that the above information is correct.

Signature [redacted]

Date 31 / 01 / 95

Name *(please print)* [redacted]

Position/ Relationship to Enterprise COMPANY Secretary

## Authorisations issued

**7** Have you authorised an employee or other person/ company to submit applications under the *Therapeutic Goods Act 1989* on your behalf?

Yes ☑ → Complete "Authorisations" Section overleaf.

No ☐ → forward form to ARTG

## Part 2 - Description of Data for Evaluation *(continued)*

- *Note: If you consider you have not supplied such information as will allow the determination of the application, please attach a separate sheet detailing reasons.*

**7. Details of Data submitted**

| Section | Number of volumes | Number of pages | Number of copies |
|---|---|---|---|
| Pharmaceutical Part II | | | |
| Preclinical Part III | | | |
| Clinical Part IV | 1 | 302 | 1 |
| Summary Part I | | | |
| Bioavailability | | | |
| Product information | | | |
| Other *(specify)* | | | |

- Is this application in support of an application for pharmaceutical benefits listing? Yes ☐ No ☐

**8. Relevant TGA file numbers/control numbers from previous correspondence**

| | | | |
|---|---|---|---|
| 93/33607 | 92/15812 | CO: 006781 | 87/8370 |

**9. Is the product in this application intended to replace an existing ARTG entry?**

Yes ☒ No ☐

Current ARTG Registration No. of the existing entry *(see Guide)*: 43321

**10. Export names**

Do you intend to export this product using a different name from the registration name?

Yes ☐ No ☒ - ***If NO,*** **go to item 11.**

**State the export name(s) to be used for this product**

| | |
|---|---|
| **Export name** | **1.** |
| | **2.** |
| | **3.** |
| | **4.** |
| | **5.** |

**11. Exchange of evaluation reports**

Do you give approval for exchange of evaluation reports with other regulatory agencies for this submission?

N/A

Yes ☐ No ☐

Signature

Date

dd mm yy

Name
*(please print)*

Position/
Relationship
to Sponsor

**Office use only**

**DSEB**

Control number

Application number

## Part 3 - Drug Product Details

**12. Registration name** *(product name in Australia)*

*(max 100 characters)*

LARIAM MEFLOQUINE 250 mg (AS HYDROCHLORIDE) TABLET BLISTER PACK

**13. Code name**

Ro 21-5998/620

**14. Relevant ARTG registration number(s)**

1. 43321 | 2. | 3. | 4.

**15. Category of Therapeutic Goods**

Goods included in this application:

**Drugs only** ☒ - Go to item **16.**

**Drug-Device combination**
*(Drugs supplied in a therapeutic device)* ☐
- attach a supplement for Therapeutic Devices form

**Drugs supplied as a component of a therapeutic device kit** ☐
- attach a supplement for Therapeutic Devices form

| Office use only | | |
|---|---|---|
| | Drug | Device |
| Defn | Y | N |
| Data | Y | |
| ADG | | |

Is a supplement for "Therapeutic Devices form" attached to this page? Yes ☐ No ☐

**16. Pack size and Poisons schedule**

| *(Pack/container sizes in which this product is supplied* | **as per register** SUSDP Schedule No. for this pack size *(if not scheduled write "N")* |
|---|---|
| 1. | |
| 2. | |
| 3. | |
| 4. | |
| 5. | |

## Part 3 - Drug Product Details *(continued)*

**as per register excep.. 22**

**17. Composite Packs**

Is this product a composite pack? **Yes** ☐ **No** ☒ - ***If NO, go to "Dosage Form: details at item 18.***

- ***If YES,*** how many different drug components are there in this pack? ☐

*Note: complete a copy of items 18 to 21 and 23 to 29 for each type of drug component and pin the extra pages to this one.*

- Description of this drug component
*(maximum 50 characters)*

**Office use Only**

**18. Dosage form**

Dosage Form Code

**19. Routes of administration**

1.
2.
3.
4.

Admin. Route Code

*(max 150 characters)*

**20. Visual identification of dosage form**

**21. Type of container in which this dosage form is to be supplied**

Container code

**22. Proposed indications**

*(max 500 characters)*

Malaria treatment: LARIAM is indicated for the treatment of acute attacks of malaria due to *P.falciparum* infection resistant to conventional antimalarial drugs.
Following therapy of mixed *P.falciparum/P.vivax* malaria with LARIAM relapse prophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate liver forms of *P.vivax.*
Malaria Prophylaxis: For travellers to countries with documented chloroquine and antifolate combination (FANSIDAR/Maloprim) resistant *P.falciparum* malaria, who are considered to be at high risk for malaria in view of their residence or travel through rural areas (between the dusk to dawn period).
For travellers hypersensitive to sulphonamides and sulphones, who are considered to be at high risk for malaria in view of their residence or travel through rural areas, (between the dusk to dawn period) in countries with high level chloroquine-resistant *P.falciparum* malaria.

IX

## Part 3 - Drug Product Details *(continued)*

**as per register**

**23. Sterility**

Is this product or any of its components supplied sterile? Yes ☐ No ☐

| | | | | | |
|---|---|---|---|---|---|
| Steam | ☐ ST | Ethylene oxide | ☐ EO | Filtration | ☐ FT |
| Gamma irradiation | ☐ GR | Dry heat | ☐ DH | Other | ☐ OT |

*If OTHER, please specify (max 100 characters)*

**24. Proposed storage and shelf life**

- State the proposed temperature of storage of the product. *(Tick the appropriate box).*

(i) Store below minus 18 degrees Celsius (deep freeze) ☐

(ii) Store below minus 5 degrees Celsius (freeze ☐

(iii) Store below 8 degrees Celsius (refrigerate ☐

(iv) Store at 2 to 8 degrees Celsius (refrigerate - do not freeze) ☐

(v) Store below 25 degrees Celsius ☐

(vi) Store below 30 degrees Celsius ☐

- State below whether any special additional storage precautions are necessary.

- State the proposed shelf life of the product. *(Tick the appropriate box).*

1 year ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ other ☐ *(please specify)*

**25. Source of material**

**Was material of human or other animal origin used at any stage in the manufacture and/or formulation of these goods?** Yes ☐ No ☐ Not applicable ☐

*If YES, identify species*

| 1. | 2. | 3. |
|---|---|---|

## Part 3 - Drug Product Details *(continued)*

**26. Printed product material supplied ***

*(Tick one or more boxes as relevant)*

| | | |
|---|---|---|
| Container label | | CL |
| primary pack label | | PP |
| package insert | X | IN |
| promotional material | | PM |
| product information | X | PI |
| other *(please specify)* | | OT |

* Attach to this page.

3

## Part 4 - Formulation Details

**as per register**

**27. Active Ingredients**

*Note:* *Attach additional pages as required.*
*Names used must be those published in the Australian approved Names List, unless no appropriate name exists in the lists.*

| | | | | Office use Only |
|---|---|---|---|---|
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |
| Name | | | | |
| Quantity | | Units | | |

**Office Use Only**

Number of active ingredients *(including equivalence statements)* listed for this drug component *(last page only)*

## Part 4 - Formulation Details *(continued)*

as per re[illegible]er

**28. Excipients**

*Attach additional pages as required.*

*Names used must be those published in the Australian Approved Names Lists, unless no appropriate name exists in the lists.*

*Note: List proprietary ingredients, the formulations of which have not been or will not be revealed to you by your supplier(s) on page 11.*

**Office use Only**

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Name**

Quantity Units

**Office Use Only**

Number of non-proprietary excipient ingredients listed for this drug component *(last page only)*

## Part 4 - Formulation Details *(continued)*

**as per register**

**29. Proprietary ingredients -** **the formulations of which have not been or will not be revealed to you by your supplier(s)**

*Attach additional pages as required.*

*(max 65 characters)*

**Office use Only**

**Proprietary ingredient name**

Name of supplier

Supplier's Enterprise identification Codes *(if known)*

Proprietary ingredient ARTG number *(if known)*

**Proprietary ingredient name**

Name of Supplier

Supplier's Enterprise identification Codes *(if known)*

Proprietary ingredient ARTG number *(if known)*

**Proprietary ingredient name**

Name of supplier

Supplier's Enterprise identification Codes *(if known)*

Proprietary ingredient ARTG number *(if known)*

**Proprietary ingredient name**

Name of supplier

Supplier's Enterprise identification Codes *(if known)*

Proprietary ingredient ARTG number *(if known)*

**Proprietary ingredient name**

Name of supplier

Supplier's Enterprise identification Codes *(if known)*

Proprietary ingredient ARTG number *(if known)*

- Number of Proprietary ingredients listed for this drug component
- How many completed "Enterprise Details" forms have you attached for proprietary ingredient suppliers?
- Have you requested the suppliers of proprietary ingredients to advise the Australian Register of Therapeutic Goods of the composition of the proprietary ingredient on a "Notification of a Proprietary ingredient" form? Yes ☐ No ☐

## Part 5 - Manufacturer Details

as per re er

### Principal Manufacturer Details

*Note:* *Attach a copy of this section for each additional manufacturer.*

*(max 100 characters)*

30. **Principal manufacturer's business name**

31. **Principal manufacturer's licence number** *(if applicable)*

32. **Principal manufacturer's enterprise identification Code**

**Office Use Only**
Site Code

### Alternative principal manufacturers

*Note:* *Attach a copy of this section for each additional manufacturer.*

*(max 100 characters)*

33. **Alternative principal manufacturer's business name**

34. **Alternative principal manufacturer's licence number** *(if applicable)*

35. **Alternative principal manufacturer's enterprise identification code**

**Office Use Only**
Site Code

### Sub-manufacturers

*Note:* ***Attach a copy of this section for each additional sub-manufacturer.***

*(max 100 characters)*

36. **Sub-manufacturer's business name**

37. **Sub-manufacturer's licence number** *(if applicable)*

38. **Sub-manufacturer's enterprise identification code**

**Office Use Only**
Site Code

39. **Step in manufacturer**

## Part 6 - Overseas Manufacturer Details

**40.** Is evidence from a relevant overseas authority attached to establish that the principal manufacturer of the goods is of an acceptable standard?

N/A ☒ Yes ☐ No ☐ → *Attach a separate sheet giving reasons*

**41.** If documentation of the standard of the overseas manufacturer has previously been supplied as part of a successful application for registration or listing, state ARTG registration/listing number for the product here.

ARTG number

**42.** If acceptable documentation is not available, do you agree to pay the cost of an inspection of the principal overseas manufacturer by Australian inspectors if deemed necessary by the Secretary?

Yes ☐ No ☐ → *Attach a separate sheet giving reasons.*

**43.** Has the overseas manufacturer agreed in writing to such an inspection?

Yes ☐ No ☐ → *Attach a separate sheet giving reasons.*

ROCHE PRODUCTS PTY. LIMITED
ACN 000 132 865

4-10 INMAN ROAD, DEE WHY, N.S.W.
POSTAL ADDRESS: P.O. BOX 255, DEE WHY 2099, AUSTRALIA
TELEPHONE: 9982 0222 • TELEFAX AUSTRALIA WIDE: (02) 9981 3229 • TELEFAX INTERNATIONAL: (61 - 2) 9981 5708

97.400.2

Medical/DC

7 May 1997

The Business Manager
Business Management Unit
TGA
PO Box 100
Woden ACT 2606



Dear Sir

**Category 1 Application to Vary the Conditions of Registration of mefloquine (Lariam®) Update of the Product Information**

We wish to apply to update the Lariam Product Information to reflect current knowledge. Since the last PI update in 1993, knowledge concerning the efficacy and safety of the mefloquine has been extended. To this end, we propose a number of amendments, the most significant of these being to the "Dosage and Administration" and "Adverse Reactions" sections of the document.

The Lariam Product Information was under constant negotiation between March 1990 and May 1993.

Following a TGA request subsequent to a WHO "alert", Roche applied to include a number of warning statements in the Lariam PI in March 1990. At the 154th ADEC meeting, the treatment dose of 1250 mg was approved with a recommendation (Resolution 4198) that the "TGA should seek further information concerning the use and safety of the 1500 mg dose. The company replied in September 1992 upholding the position concerning the 1500 mg dose, stating that a treatment dose of 1250 mg in non-immune individuals was inadequate. In December 1993, the TGA delegate rejected the 1500 mg (25 mg/kg) dose because there was no demonstrable increase in efficacy to outweigh the increased incidence of side effects at the higher dose. The company maintains that the 1500 mg dose is appropriate and necessary, especially in areas where resistance is most prevalent, such as the border areas of Thailand, Cambodia and Myanmar. We propose to amend the PI in this regard.

The ADEC at their 156th meeting encouraged the company to submit data to support indications and doses in paediatric patients. This application includes data to extend Lariam usage to children under 14 years of age.

In December 1992, ADEC (Resolution 5012) recommended that Lariam prophylaxis be extended up to 3 months. Roche submitted a PI with this change in January 1993 including dosing for 2 weeks after leaving the area. The TGA accepted these amendments in April of that year. We would like the time limit on prophylaxis to be abolished and provide supporting evidence that long-term prophylactic use of Lariam is not associated with significant long-term side effects. In addition, we would like to extend the dosing period to 4 weeks after leaving the endemic area in line with current WHO recommendations.

Please find included under this cover:

- a copy of the Application for Registration of Drugs with an Instrument of Appointment for the undersigned.
- a cheque drawn for $1200 being for one application fee.
- Part IV Volume 1 1 copy

Part IV consists of a draft Product Information and a draft Consumer Product Information. A "document compare" is also provided highlighting the differences between the approved Product Information and the draft Product Information provided with this submission. This volume also contains all the references used to support the various changes to the Product Information.

There is no new pharmaceutical chemistry (Part II) or pre-clinical data (Part III) in this submission.

Thank you for your consideration of this application.

Yours faithfully
ROCHE PRODUCTS PTY LTD

[redacted]
Regulatory Affairs Associate

IN CONFIDENCE

EXTRACT FROM AUSTRALIAN DRUG EVALUATION COMMITTEE MINUTES

SECTION No. 719.6

MEETING No. 1991/4 (154th)

DATE 15 + 16 AUG 91

Document 3

39

## ITEM 16 MEFLOQUIN HYDROCHLORIDE - LARIAM - ROCHE

16.1 The Committee considered an application by Roche Products Pty Ltd to change the dosage regimen and certain product information for the currently approved Lariam Tablets, containing Mefloquine Hydrochloride 250mg.

16.2 Background:

Mefloquine hydrochloride was considered at the 120th and 125th Meetings of ADEC and approved for the treatment of acute attacks of malaria due to resistant Plasmodium falciparum infection and for short term prophylactic use (up to one month). The currently approved product information recommends (1) for treatment: a total dose of 1250-1500mg in divided doses in one day for non-immune adults and (2) for prophylaxis:250mg once a week.

The dosage submitted for approved is a maximum of 1250mg or 20mg/kg for non-immune patients.

Following a WHO "alert" (8 August 1989), on the dosage and adverse reactions to mefloquine, Roche were approached to revise the Australian product information in relation to safety related statements and to provide comments on the maximum dose as recommended by WHO. In response, the company proposed a number of changes to their product information document, including a change in dosage regimen. The latter aspect was presented to the Committee for consideration.

16.3 The WHO alert advised that severe neurological reactions, including severe depression, psychotic episodes and seizures have been associated with mefloquine use. Amongst other recommendations, the alert recommended that the treatment dose of mefloquine should not exceed 15mg/kg or 1000mg mefloquine base, whichever is greater.

16.4 The clinical evaluator reported that over the last ten years no dose-ranging studies have been done in non-immune populations. WHO sponsored studies in semi-immune populations had shown a dose of 500-750mg as efficacious. The evaluator cited a WHO compilation of data from 17 clinical research projects in the treatment of P.falciparum malaria in semi-immune and non-immune subjects. Most of the subjects had been treated at 750mg (215 subjects) and 1000mg (235 subjects), with cure rates of 96.7% and 97.4% respectively. Of the 181 subjects treated at 1250-1500mg the cure rate was 99.4%. There appeared to be a marginal improvement in cure rates between 750mg and 1500mg. The few treatment failures at the lower doses could be ascribed to both differences in immunity and bodyweight, however there is insufficient information to confirm this.

The evaluator recommended a dose of 1250mg for Australian non-immune patients over 70kg bodyweight. The dose of 1500mg should not be recommended because of the potentially greater risk of adverse effects. It was further recommended that the section on semi-immune patients under Dosage and Administration in the

product information should be deleted, since it is irrelevant to Australia at the present time. Certain safety related changes were also recommended for the product information.

16.5 In the Pre-ADEC Consultation document, Roche advised that the parent company had re-examined the dosage recently and had retained the treatment dosage for non-immune patients of 1250mg in divided doses for patients of up to 60kg and 1500mg for patients over 60kg. The Company argued that Australia has a large migrant population from Thailand and Vietnam, hence the above recommendation from the clinical evaluator should not be accepted. The wording should read "For patients who have lived in malaria endemic areas". A further issue was the original approval for limitation of prophylactic treatment to one month. This had been accepted by ADEC on the advice of the Communicable Diseases Committee of NH&MRC, as a means of limiting the development of resistance. Roche Basle has suggested limiting prophylactic use to a maximum of three months. This is the time limit in the UK. The FDA does not limit prophylactic usage and mefloquine is the drug of choice for US Peace Corps workers in chloroquine-resistant areas.

16.4 The Departmental adviser noted that insufficient data were available in 1985 to set on optimum dose of mefloquin for the treatment of P.falciparum malaria, and as is usual with antimalarials, the adverse reaction profile was confused by the disease symptomatology. The overview supported a dose of 1250mg for non-immune patients.

16.5 The Committee received documentation from the Company concerning a "Revised Dosing Regimen for Malaria Prophylaxis with Mefloquine", published by the Malaria Br., Div. of Parasitic Diseases, Centre for Infectious Diseases, CDC, dated 14 September 1990. The document stated: "The new regimen consists of a single dose of mefloquine to be taken weekly, starting one week before travel. Prophylaxis should be continued weekly during travel in malarious areas and for four weeks after a person leaves such areas".

16.6 The members considered the conflicting recommendations concerning the deletion and extension of the Product Information, as it pertained to the Australian population. It was agreed that many Asian migrants may be semi-immune to P.falciparum, but such immunity relapses with time, hence the wording suggested by the Company should be extended thus: from "For patients living in malaria endemic areas" to "For patients who have recently arrived from malaria endemic areas..."

Concerning the recommended upper range of dosage for non-immune patients, the Members reviewed the data in the Clinical Evaluator's report and the Company's "Comments on the WHO maximum Recommended Treatment Dose". The Departmental adviser reiterated that the original submissions concerning dosage had been inadequate and the current submission was poor. In view of the toxicity reported for Mefloquine, concern was expressed at the high dosage of 1500mg. Potential toxicity at this dosage should be balanced against the life-threatening nature of a P.falciparum

attack and the merits of a single day dosage regimen. The evaluator's comment of "a marginal improvement in cure rates between 750mg and 1500mg" was considered. The question of an "adequate" dose in patients with high body weight was addressed. Since patients with malaria should be monitored by a daily malaria count, a suggestion was made that "in patients with body weight greater than 60-70kg, a dose of 1250mg may be suboptimal and if serial clearance has not occurred after 24hr, then a higher dose should be given." This recommendation was considered suitable for controlled conditions within Australia, but may not be suitable instruction for travellers taking mefloquine overseas. In conclusion, it was agreed to approve the 1250mg dosage, with a request to the TGA to research further information on the 1500mg dose.

The Committee did not have evaluable data on the duration of prophylaxis and resolved to seek the advice of the National Health and Medical Research Council. This body should be requested to comment on the relevance of the current wording in the Product Information, as shown: "Malaria Prophylaxis: Prophylaxis of malaria with Larian should be initiated one week before arrival in a malarious area."

16.7 It was therefore resolved:-

RES NO 4196 **ROCHE PRODUCTS PTY LTD SHOULD BE ADVISED THAT THE COMMITTEE HAD NO OBJECTION TO THE PROPOSED CHANGE TO THE CURRENTLY APPROVED PRODUCT INFORMATION FOR LARIAM TABLETS, CONTAINING MEFLOQUIN 250MG, TO A MAXIMUM DOSE OF 1250MG FOR NON-IMMUNE PATIENTS, SUBJECT TO THE INSERTION OF THE ADDITIONAL WORDING "WHO HAVE RECENTLY ARRIVED FROM ENDEMIC AREAS", AND THE APPROVAL OF THE MODIFIED PRODUCT INFORMATION BY THE THERAPEUTIC GOODS ADMINISTRATION.**

**IT WAS RECOMMENDED FURTHER THAT:**

(1) RES NO 4197 **THE MALARIA SUBCOMMITTEE OF THE NH&MRC SHOULD BE REQUESTED TO COMMENT ON THE DURATION OF THE CURRENTLY APPROVED PROPHYLACTIC DOSAGE REGIMEN FOR MEFLOQUINE AND**

(2) RES NO 4198 **THE THERAPEUTIC GOODS ADMINISTRATION SHOULD SEEK FURTHER INFORMATION CONCERNING THE USE AND SAFETY OF THE 1500MG DOSE.**

IN CONFIDENCE

EXTRACT FROM AUSTRALIAN DRUG EVALUATION COMMITTEE MINUTES

| | |
|---|---|
| SECTION No. | 719.7 |
| MEETING No. | 156 |
| DATE | 5th DEC. 1991 |



ITEM 3B1-3 MALARIA DRUGS

## A Background information presented to the meeting

3B1-3.1 The meeting noted that the Malaria Panel of the Communicable Diseases Standing Committee of the NH & MRC would be considering the issue of the prophylactic dosage regimen of mefloquin hydrochloride. Comment should be available for the April 1992 meeting of the ADEC. The matter of the use and safety of the 1500 mg dose (Resolution 4198) was under investigation within the TGA.

3B1-3.2 The meeting received a minute from Dr R Hall, Director, Communicable Disease Section on product information for mefloquin and doxycycline, as quoted:

> "At the present, dosage schedules for mefloquine do not include paediatric recommendations as the safety of mefloquine for malaria chemoprophylaxis in children has been the subject of field trials. However, WHO now recommends mefloquine as the prophylactic of choice for children in areas where multi-drug resistant malaria is present and mefloquine is registered in France for use in children 150mg/week for children weighing between 10 and 25 kg). Could the ADEC examine the paediatric use of mefloquine.
>
> Currently, doxycycline has not been approved in Australia for use in malaria chemoprophylaxis. However, its use as a short-term (less than 8 weeks) prophylactic is well documented. Could the ADEC examine this situation with a view to to having malaria included as an indication in the product information for doxycycline."

## B Discussion

3B1-3.3 The meeting agreed that in the spirit of the Baume Report, the Chairman should invite the Companies to submit evaluable data to support the indications and dosage regimens for paediatric use for mefloquine and the use of doxycline in malaria. The meeting therefore resolved:

IN CONFIDENCE

EXTRACT FROM AUSTRALIAN DRUG EVALUATION COMMITTEE MINUTES

| | |
|---|---|
| SECTION No. | 79.7 |
| MEETING No. | 156 |
| DATE | 5th DEC. 1991 |



THE COMMITTEE'S ATTENTION HAS BEEN DRAWN BY THE DIRECTOR, COMMUNICABLE DISEASE SECTION, NH&MRC, TO THE DEFICIENCIES IN THE PRODUCT INFORMATION OF MEFLOQUINE, (LARIAM TABLETS, ROCHE PRODUCTS PTY LTD) CONCERNING PAEDIATRIC DOSES. SINCE MANY AUSTRALIAN FAMILIES VISIT MALARIOUS AREAS AND THE WHO NOW RECOMMENDS MEFLOQUINE AS THE PROPHYLACTIC OF CHOICE FOR CHILDREN WHERE MULTI-DRUG RESISTANT MALARIA IS PRESENT, IT IS CLEARLY IN THE PUBLIC INTEREST THAT THE PRODUCT INFORMATION SHOULD PROVIDE CLEAR INSTRUCTION ON PAEDIATRIC USE OF MEFLOQUINE. THE COMMITTEE HAS RECOMMENDED THAT THE CHAIRMAN SHOULD ENCOURAGE THE COMPANY TO SUBMIT DATA TO SUPPORT INCLUSION OF PAEDIATRIC DOSES AND DOSAGE REGIMENS IN THE PRODUCT INFORMATION. THE MATTER SHOULD BE ADDRESSED IN THE CHAIRMAN'S REPORT TO THE MINISTER.

RES NO 4283

THE COMMITTEE'S ATTENTION HAS BEEN DRAWN BY THE DIRECTOR, COMMUNICABLE DISEASE SECTION, NH&MRC, TO THE WIDESPREAD USE BY AUSTRALIANS VISITING MALARIOUS AREAS, OF DOXYCYCLINE FOR MALARIA PROPHYLAXIS. THE COMMITTEE HAS NOTED THAT "MALARIA PROPHYLAXIS" IS NOT AN APPROVED INDICATION FOR DOXYCYCLINE, HENCE THERE IS NO PRODUCT INFORMATION ABOUT THIS INDICATION. IN THE PUBLIC INTEREST, THE CHAIRMAN SHOULD ENCOURAGE THE VARIOUS COMPANIES WHICH MARKET DOXYCYCLINE TO PROVIDE TIMELY EVIDENCE TO SUPPORT "MALARIA PROPHYLAXIS" AS AN APPROVED INDICATION FOR THIS DRUG. THE MATTER SHOULD BE ADDRESSED IN THE CHAIRMAN'S REPORT TO THE MINISTER.

RES NO 4284

IN CONFIDENCE

EXTRACT FROM AUSTRALIAN DRUG EVALUATION COMMITTEE MINUTES





ITEM 2.5 MEFLOQUIN - MALARIA PROPHYLAXIS

2.5.1 The 154th (1991/4) Meeting of the Australian Drug Evaluation Committee had sought the opinion of the Malaria Subcommittee of the NH & MRC on the duration of the currently approved prophylactic dosage regimen for mefloquine. At the same time, the Therapeutic Goods Administration was requested to seek further information concerning the use and safety of the 1500mg dose.

2.5.2 A response (dated 15 August 1992) from Dr R Hall, Malaria Panel, Communicable Diseases Section, was considered by the ADEC. The document indicated that: "1. The Panel considered the issue of long term use of mefloquine remained incapable of being resolved due to the paucity of the current data available. 2. The Panel continued to be concerned by the frequency of reports of adverse events associated with the prophylactic use of mefloquine and with the severity of these effects in some cases. 3. Notwithstanding the above, the Panel considered that mefloquine should be recommended as the drug of choice for people unable to tolerate the "first line" drug doxycycline and that its use for up to 3 months, in adults, was acceptable."

2.5.4 A Member noted that the presently approved Product Information for mefloquine, as provided from the MIMS Annual, did not include any advice on the duration of therapy for 2 weeks after leaving the malarious area. This should be rectified by the Company.

2.5.5 In response to a Member's enquiry, the Acting Director, Evaluation Unit 1, reported that the recommended review of the 1500mg dose for mefloquine was in progress.

2.5.6 The Meeting accepted this various advice and resolved to advise the Minister and the Secretary that:

RESOLUTION NO 5012

THE COMMITTEE ACCEPTED THE ADVICE OF THE MALARIA PANEL, NH & MRC, THAT DESPITE THE PAUCITY OF SATISFACTORY DATA AND THE FREQUENCY OF REPORTS OF ADVERSE EVENTS, THE USE OF MEFLOQUINE AS A PROPHYLACTIC IN MALARIA FOR UP TO 3 MONTHS, IN ADULTS, WAS ACCEPTABLE. AS THIS WAS IN KEEPING WITH THE SUBMISSION BY ROCHE PRODUCTS PTY LTD AT THE 154TH MEETING (1991/4), THE PRODUCT INFORMATION FOR LARIAM TABLETS SHOULD BE MODIFIED ACCORDINGLY.

THE SECTION ON "MALARIA PROPHYLAXIS" SHOULD PROVIDE GUIDANCE TO TRAVELLERS RETURNING FROM MALARIOUS AREAS, BY ADVISING THEM TO CONTINUE MEFLOQUINE TREATMENT FOR A FURTHER TWO WEEKS.

IN CONFIDENCE

EXTRACT FROM AUSTRALIAN DRUG EVALUATION COMMITTEE MINUTES

SECTION No. 719.9

MEETING No. 1993/6 (1657)

DATE 2-3 DEC 1993

23

**ITEM 4.15 MEFLOQUINE - LARIAM - ROCHE PRODUCTS PTY LTD 1500mg DOSE APPLICATION.**

4.15.1 Background:

Mefloquine (LARIAM, Roche) was considered at the 120th and 125th Meetings of ADEC and approved for the treatment of acute attacks of malaria due to resistant Plasmodium falciparum infection, and for short term prophylactic use (up to one month) in adults and children of more than 45kg body weight. The approved treatment dose was 750 to 1500mg, dependent on body weight less than or greater than 60kg, and the immune status of the patient.

In August 1989, a WHO "alert" reported the occurrence of serious psychiatric and neurological adverse events in association with mefloquine use. These included severe depression, psychotic episodes and seizures. WHO recommended a maximum treatment dosage of "15mg/kg or a total dose of 1000mg mefloquine base, whichever is the greater".

Comment was sought from Roche, the response was evaluated by TGA, and the matter was considered by ADEC at its 154th Meeting. The sponsor sought the retention of a maximum dose of 1250mg in non-immune patients, pointing out that this was the approved dosage in the USA. The clinical evaluator noted that a compilation of WHO studies had shown a clear dose-response effect, although the improvement in cure rates from 750mg to 1250-1500mg was small (96.7% for the former, versus 99.4% for the latter). ADEC had no objection to the proposed maximum dosage of 1250mg in non-immune patients, subject to the insertion into the PI of the additional wording "who have recently arrived from endemic areas". The currently approved PI incorporates this maximum dosage and wording.

ADEC recommended further that the TGA "should seek further information concerning the use and safety of the 1500mg dose." Roche had responded, stating the company's belief that "there is sufficient evidence that a dose of 1250mg in non-immune subjects weighing more than 60kg is inadequate". Whilst noting the WHO maximum recommended dose of 1000mg, the company also pointed out the conclusion of a WHO scientific group in 1990 that "data from non-immune subjects weighing more than 60kg are insufficient to conclude that this (1000mg) regimen will result in radical cure in all cases". The Meeting considered the evaluation of the submitted data.

4.15.2 The clinical evaluator had not recommended approval of the sponsor's request for an increase in the maximum dose of mefloquine from 1250 to 1500mg for the treatment of multi-drug-resistant malaria, in non-immune patients weighing over 60kg, on the grounds that there was insufficient evidence of increased benefit from the

higher dose. The evaluator noted that data on non-immune subjects were not sufficient to support an increase in the maximum dose. The data were insufficient also to conclude that a dose of 1250mg in patients weighing more than 60kg will result in complete cure in all cases. The evaluator suggested the addition of the following paragraph to the section of the Product Information entitled "Dosage and Administration":

> "Data on the treatment of non-immune patients weighing more than 60kg are insufficient to conclude that a dose of 1250mg will result in radical cure in all cases. Close medical follow-up must therefore be assured after treatment."

4.15.3 The TGA delegate supported this proposal, based on the limited data available. The increased risk of adverse events was considered to outweigh any increase in benefit with the higher dose. The advice and comment of the ADEC was requested.

4.15.4 The Committee considered the two studies submitted to support this application. The first study was conducted in semi-immune patients living in camps along the Thai-Burmese border. This open prospective trial compared mefloquine 15 mg/kg (n=90) with 25 mg/kg (n=92) in patients > 60 kg. The higher dosage was more efficacious but was linked with an increased incidence of adverse reactions. The second study was an open uncontrolled study and included some patients who could reasonably be assumed to be non-immune. The study involved 17 patients in Germany who had returned from Africa, and 3 Africans from endemic malarial areas, on tour in Germany. In this group, there was a 100% response, despite the fact that 25% of the patients vomited.

4.15.5 The Meeting had difficulty in reaching conclusions on the proposed changes, due to the limited data and the deficiencies in the studies. For example, 29 Thai patients in the 15 mg/kg group and 7 in the 25 mg/kg group had negative smears at days 7-9, but had relapsed by day 28. Despite the "paired randomisation", the mean baseline parasite burden within each age subgroup was lower in the group treated with the higher dose. These difficulties in interpretation were compounded by an average body weight less than 70 kg and by the pre-treatment of a significant proportion of the adults in the 25 mg/kg group with mefloquine, sulfadoxine and pyrimethamine at doses of 15/30 and 1.5 mg/kg respectively from 2 to 8 weeks prior to the trial. In the German trials, late recurrences of illnesses (>13 days) were not followed up; only 3 of the patients had been in regions with antifolate-resistant malaria and none had visited areas with known low-grade mefloquine resistance. This patient population therefore did not correspond to that in which mefloquine treatment is approved in Australia.

4.15.6 The Members noted that the present Australian dosage is an average between the two dosages tested (20 mg/kg). Any increased efficacy from increasing the dose from 20 to 25 mg/kg had not been defined but it seemed, from the data presented, that increasing the dose to 25 mg/kg would be associated with increased adverse reactions. Additionally, due to reliance on spontaneous reporting and/or difficulties in determining the number of treated patients, it was difficult to derive an absolute incidence of serious adverse events from the submission of published studies. Estimates in the submission ranged from 49 per 100,000 (15 mg/kg, Thailand), to 79 per 100,000 (25mg/kg, Thailand), and 920 per 100,000 (250-2000 mg, Europe).

4.15.7 The Company had argued (Pre-ADEC documentation 19 October 1993) that: "At the frequency level of 0.079% (79 per 100,000), these serious adverse events are considered as rare complications of mefloquine therapy". The Company had stated that the benefit of use of high dose mefloquine in a life threatening condition would appear to outweigh the risk of serious neurological adverse events. The Committee noted that the neurological and gastro-intestinal side effects had been considered and accepted in past discussions on the drug.

4.15.8 The ADEC received advice that the Swedish Medical Products Agency (19 October 1993) had considered the risks of dose-dependent side effects and, on balance, had approved the manufacturer's recommendation of the higher dose. However, the prescribing of this dosage for self-treatment of malaria was not approved, because of the risk of dose-dependent side effects, and was preserved for patients with verified malaria. A Member recalled that this type of approach had been considered by the ADEC previously, but had been rejected as an option.

4.15.7 In summary, the Members agreed that the existing dosage (1250 mg maximum) should remain until adequate data are available to justify a higher dose. The Minister and the Secretary should be advised that:-

RESOLUTION NO 5309

THE APPLICATION BY ROCHE PRODUCTS PTY LIMITED TO CHANGE THE MAXIMUM DOSAGE FOR LARIAM TABLETS, CONTAINING MEFLOQUINE, AS THE HYDROCHLORIDE, FROM 1250 MG DAILY TO THE HIGHER DOSE OF 1500 MG DAILY, SHOULD BE REJECTED ON THE GROUNDS OF INSUFFICIENT EVIDENCE FOR ENHANCED EFFICACY AND AN INCREASED INCIDENCE OF ADVERSE REACTIONS AT THE HIGHER DOSE LEVEL.

# LARIAM®

*mefloquine*

**Consumer Product Information**

## What is in this leaflet

This leaflet answers some common questions about LARIAM tablets. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking LARIAM tablets against the benefits they expect it will have for you.

**If you have any concerns about taking this medicine, ask your doctor or pharmacist.**

**Keep this leaflet with the medicine.** You may need to read it again.

## What LARIAM is taken for

LARIAM is used to for the treatment and prevention of *Plasmodium falciparum* malaria resistant to other anti-malarial therapy.

Malaria is an infectious disease which is widespread in tropical and subtropical areas of Africa, Latin America, Asia and countries around the Pacific. There are different forms of malaria, each of them caused by a specific parasite transmitted to humans by the bite of the Anopheles mosquito.

The symptoms of malaria may often be mild. However, malaria should be suspected if, after one week in a malarial area, you suffer unexplained fever with or without other symptoms such as headache, aching limbs, weakness, shaking, chills, and, sometimes diarrhoea, vomiting and cough. These symptoms can easily be confused with influenza.

If these symptoms are caused by the most dangerous form of malaria caused by the falciparum parasite, and they are not treated in time, severe organ damage, loss of consciousness and death can occur within a short period. The less dangerous forms of malaria, which are not life-threatening, can break out months or even years after the end of a stay in a malarial area.

Early diagnosis is critical for successful treatment. Anyone suspected of malaria should seek medical attention promptly and request that a blood sample be taken and examined microscopically for malaria parasites.

Most tourists and business travellers will normally be able to receive medical attention. However, if this is not readily available, anti-malarial drug treatment can be self-administered ('stand-by treatment').

Consult your doctor about the need to carry 'stand-by treatment' on your trip. Medical advice should still be sought after self-administered drug treatment.

There are many different types of medicines used to treat malaria. LARIAM belongs to a family of medicines called quinolones. These medicines work by destroying specific forms of malarial parasites.

Your doctor may have prescribed LARIAM for another purpose. **Ask your doctor if you have any questions why LARIAM has been prescribed for you.**

This medicine is available only with a doctor's prescription.

LARIAM is not addictive.

## Before you take LARIAM

### *When you must not take it*

**Do not take LARIAM if:**

- **you have had an allergic reaction to LARIAM or any ingredients listed at the end of this leaflet**
- **you have had an allergic reaction to quinine or quinidine**
- **you plan to have a live typhoid vaccination.**

**Do not take LARIAM if the packaging is torn or shows signs of tampering.**

**Do not take LARIAM if the expiry date (EXP) printed on the pack has passed.**
If you take this medicine after the expiry date has passed, it may not work as well.

**If you are not sure if you should start taking LARIAM, contact your doctor.**

**Do not give LARIAM to a child under 3 months of age or weighing less than 5 kg, unless advised by the child's doctor.**
Safety and effectiveness in very young children have not been established.

### *Before you start to take it*

Your doctor must know about all the following before you start to take LARIAM.

**Tell your doctor if:**

1. **if you are pregnant or plan to become pregnant.**

   LARIAM is generally not recommended for use during pregnancy. If there is a need to take LARIAM during your pregnancy, your doctor will discuss with you the risks and benefits of using it.

2. **you are breastfeeding or intend to breastfeed**
   LARIAM passes into breast milk. Its effect on breast-fed infants is not known.

3. **you have or have had any medical conditions, especially the following:**

- **fits or seizures (epilepsy, convulsions)**
- **psychiatric disturbances particularly mood disturbances (e.g. anxiety, depression)**
- **liver disease**

4. **if you are allergic to any other medicines, foods, dyes or preservatives.**

### *Taking other medicines*

**Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy, supermarket or healthfood shop. Some medicines and LARIAM may interfere with each other. These include:**

- medicines used to treat or prevent malaria such as chloroquine
- quinine, a medicine used to treat cramps and malaria
- quinidine, a medicine used to treat heart problems
- halofantrine, a medicine used for the treatment of malaria. Halofantrine and LARIAM cannot be taken together.
- medicines used to treat fits (epilepsy) such as valproic acid, carbamazepine, phenobarbital or phenytoin
- medicines used to lower blood-sugar (treat diabetes)
- medicines used to prevent blood clots.

These medicines may be affected by LARIAM, or may affect how well it works. You may need to take different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

**You should not be vaccinated against typhoid with live vaccine while taking LARIAM.** Oral live typhoid vaccinations should be completed at least three days before the first dose of LARIAM.

Your doctor and pharmacist has more information on medicines to be careful with or avoid while taking LARIAM.

## How to take LARIAM

### *How much to take*

**Follow all directions given to you by your doctor and pharmacist carefully.**
They may differ from the information contained in this leaflet.

**Take LARIAM exactly as your doctor has prescribed.** Your doctor will tell you how many LARIAM tablets to take each day.

**Treatment of malaria**

For adults the total dose is 5 to 6 tablets.

Your doctor will tell you the correct dose to give your child.

**Prevention of malaria**

For adults the dose is 1 tablet of LARIAM once weekly. Take the first tablet at least one week before you arrive in the malarial area. Take one tablet each week that you are in a malarial area always on the same day and for 4 weeks after you have left the area.

Your doctor will tell you the correct dose to give your child.

### *How to take it*

Swallow the tablets with a full glass of water. If you or your child cannot swallow the tablets, they may be crushed and mixed with water before giving them.

### *When to take it*

Take LARIAM after meals.

### *How long to take LARIAM*

Treatment or prevention of malaria with LARIAM ends when you have taken the prescribed number of tablets.

**Do not use LARIAM for longer than your doctor says.**

### *If you forget to take LARIAM*

**If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to. Otherwise, take it as soon as you remember and then go back to taking it as you would normally.**

**Do not take a double a dose to make up for the dose that you missed.**

If you are not sure whether to skip the dose, talk to your doctor or pharmacist.

### *In you take too much (o[illegible]dose)*

**Immediately telephone your doctor or Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much LARIAM. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.**

**If you are not sure what to do, contact your doctor or pharmacist.**

## While you are taking LARIAM

### *Things you must do*

**If you become pregnant while taking LARIAM, tell your doctor immediately.**

Women of child-bearing potential should use an effective contraception while using LARIAM.

**If you are taking LARIAM for the treatment of malaria, tell your doctor if you feel it is not helping your condition.**

**Tell all doctors, dentists and pharmacists who are treating you that you are taking LARIAM.**

### *Things you must not do*

**Do not stop taking LARIAM or lower the dose without first checking with your doctor. Do not let yourself run out of medicine over the weekend or on holidays.**

**Do not give LARIAM to anyone else even if they have the same condition as you.**

**Do not use LARIAM to treat other complaints unless your doctor says to.**

### *Things to be careful of*

**Be careful driving or operating machinery until you know how LARIAM affects you.**

LARIAM may cause dizziness or loss of balance in some people. Make sure you know how you react to LARIAM before you drive a car, operate machinery, or do anything else that could be dangerous if you are dizzy or feel unsteady. If you experience these effects, do not drive.

### *Further Information*

The best protection against malaria is to avoid mosquito bites. The mosquito that causes malaria mainly bites between dusk and dawn. Therefore the following precautional measures are recommended:

- during this period, wear clothes that cover as much of your skin as possible
- apply mosquito repellent to your uncovered skin and to your clothes
- when sleeping in rooms which are not protected against mosquitoes, use an effective mosquito net well tucked under the mattress. Additional protection is provided by smoke spirals insect sprays and candles.

## Side Effects

**Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking LARIAM.**

LARIAM helps most people but it may have unwanted side effects in a few people. All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

If you are taking LARIAM for the treatment of malaria, you may not be able to distinguish between the side effects of the drug and the disease itself.

- It is possible that you may experience some side effects after you have stopped taking LARIAM.

**Ask your doctor or pharmacist to answer any questions you may have.**

**Tell your doctor if you notice any of the following and they worry you:**

- dizziness, light-headedness or unsteadiness (loss of balance)
- headache
- difficulty sleeping, strange dreams
- stomach upset including nausea (feeling sick), vomiting
- diarrhoea, pain in the stomach
- drowsiness, sleepiness

These side effects are generally mild and may decrease with continued use of LARIAM.

**Tell your doctor immediately if you experience:**

- a seizure (fit)
- sudden or severe skin rash or redness of the skin

These are serious side effects. You may need urgent medical attention. Serious side effects are rare.

**If any of the following happen while you are taking LARIAM to prevent malaria, stop taking LARIAM and tell your doctor immediately or go to casualty at your nearest hospital:**

- change in mood, for example, depression, restlessness, confusion, feeling anxious or nervous.

**Other side effects not listed above may also occur in some patients. Tell your doctor if you notice anything else that is making you feel unwell.**

**Ask your doctor or pharmacist if you don't understand anything in this list.**

Do not be alarmed by this list of possible side effects. You may not experience any of them.

## After using LARIAM

### Storage

**Keep your tablets in the blister pack until it is time to take them.**
If you take the tablets out of the blister pack they will not keep well.

**Keep the tablets in a cool dry place where the temperature stays below 30°C.**

**Do not store LARIAM or any other medicine, in a bathroom or near a sink.**
**Do not leave it in the car or on window sills.**
Heat and dampness can destroy some medicines.

**Keep it where children cannot reach it.**
A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

### Disposal

**If your doctor tells you to stop taking LARIAM, or the tablets have passed their expiry date, ask your pharmacist what to do with any that are left over.**

## Product Description

### What LARIAM looks like

The tablets are white, round, and marked with 'Roche 250'. They are cross-scored so that they can be easily broken into halves or into quarters.

### Ingredients

LARIAM does not contain sucrose, gluten, tartrazine or any other azo dyes.

**Active ingredient** - mefloquine

- each LARIAM tablet contains 250 mg mefloquine as mefloquine hydrochloride.

**Inactive ingredients** -

- microcrystalline cellulose
- lactose
- maize starch
- crospovidone
- ammonium calcium alginate
- talc [553]
- magnesium stearate [470]
- Poloxamer 3800.

LARIAM comes in packs of 8 tablets.

### Distributor

LARIAM is distributed by:

Roche Products Pty Limited
ACN 000 132 865
4 - 10 Inman Road
Dee Why NSW 2099

Australian Registration Number

- 43321.

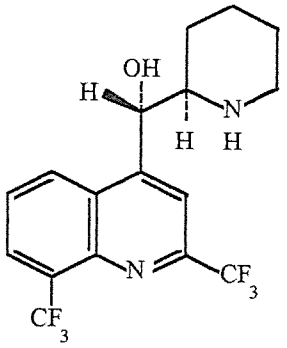
This leaflet was prepared ....

**LARIAM**
**(mefloquine hydrochloride)**

007

~~COMPOSITION~~

~~Chemically, mefloquine i~~LARIAM contains DL - erythro - alpha - 2 - piperidyl - 2,8 - bis (trifluoromethyl) - 4 - quinoline methanol (mefloquine) which has the following formula: ~~. The structural formula of mefloquine hydrochloride is shown below.~~




~~It~~Mefloquine is an odourless, bitter-tasting, white crystalline powder of molecular weight 414.78. It is soluble in methanol and ethanol but practically insoluble in water. A 1% aqueous suspension has a pH of 5.6.

(1) LARIAM tablets contains ~~as~~ the active substance 250 mg mefloquine in the form of mefloquine hydrochloride (274.09 mg). Lariam tablets also contain the excipients poloxamer 3800, microcrystalline cellulose, lactose, maize starch, crospovidone, ammonium calcium alginate, talc and magnesium stearate.

## PHARMACOLOGY

### Actions

Mefloquine is an antimalarial belonging to the quinoline-methanol group of drugs and is structurally related to quinine. Its effectiveness in the treatment of malaria is due essentially to destruction of the asexual intraerythrocytic forms of the human ~~malarial pathogens~~ parasites *Plasmodium falciparum, P. vivax, P. malariae* and *P. ovale*.~~ It~~ (2) Mefloquine is also effective against ~~*Plasmodium falciparum* infections~~ malaria parasites resistant to other antimalarials such as chloroquine and other 4-amino-quinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

Laboratory animal studies have shown that resistance to mefloquine can be readily induced in the malarial parasite and that this resistance is stable during passage through the insect vector. Mefloquine resistance has also been seen in a few clinical isolates from patients receiving mefloquine. Cross-resistance can be shown between mefloquine and quinine.

(3) ~~Strains~~ Resistance ~~resistant~~ of *P.falciparum* to mefloquine ~~have~~ has been reported mainly ~~(e.g.~~ in parts of (4) ~~Indochina~~ South-East Asia~~)~~. Cross-resistance between mefloquine and halofantrine has been observed.

Mode of Action: The basic mode of action of mefloquine has not yet been elucidated. However a number of studies of its actions in biochemical systems have been made.

Like quinine, mefloquine is able to form complexes with haemin. The ability to co-ordinate with haemin seems to correlate with the antimalarial activity of the compound. But, unlike chloroquine, quinacrine and quinine, mefloquine does not intercalate with DNA. Thus interaction with DNA does not seem to be involved in the antimalarial action of mefloquine.

Mefloquine does not exert antifolic activity and its antimalarial action is not antagonised by p-aminobenzoic acid.

**~~PHARMACOKINETICS~~ harmacokinetics**

~~Absorption: Following oral doses of 250 mg mean peak plasma levels of approximately 300 ng/ml were observed. They were reached approximately 14 hours after administration.~~
Absorption

(5) Plasma concentrations peak 6-24 hours (median, about 17 hours) after a single dose of mefloquine.
(6) Maximum plasma concentrations in µg/L are roughly equivalent to the dose in milligrams (for example, a
(7) single 1000 mg dose produces a maximum concentration of about 1000 µg/L). At a dose of 250 mg once weekly, maximum steady state plasma concentrations of 1000-2000 µg/L are reached after 7-10 weeks.

~~Bioavailability: The absolute bioavailability of mefloquine is not known. However, relative to an oral solution the bioavailability of mefloquine from LARIAM tablets was determined to be 87 ± 11%.~~
Bioavailability

(8) The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is
(9) not available. The bioavailability of the tablet formulation compared with an oral solution was over 85%.
(10) The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability.

~~Distribution:~~
Distribution

(9) ~~The~~ In healthy adults, the apparent volume of distribution ~~has been calculated as~~ is approximately ~~19~~ 20 L/kg body weight, indicating extensive tissue distribution. Mefloquine is taken up largely in the liver but also into the lungs, muscles, brain and retina. The concentration in erythrocytes is approximately twice that in the
(9) plasma. About ~~98.2%~~ 98% of mefloquine is bound to plasma proteins. Clinical experience suggests a
(11) minimal suppressive plasma concentration of mefloquine in the order of 600 µg/L.

(12) Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see Precautions, Use in lactation).

(13)
~~Metabolism:~~ Metabolism
(14) ~~Animal studies have demonstrated that several metabolites of mefloquine are formed, the major metabolite being the cinchonic acid derivative. In addition to the acid, other known metabolites are the corresponding alcohol, a mefloquine derivative with a hydroxy group in the piperidine moiety and the mefloquine lactam~~
(15) ~~(6-keto-piperidine derivative).~~ Two metabolites have been identified in humans. The main metabolite, 2,8-
(16) *bis*-trifluoromethyl-4-quinolone carboxylic acid, is inactive in *P. falciparum*. In ~~human beings~~ a study in
(17) healthy volunteers, the ~~cinchonic~~ carboxylic acid metabolite appeared in ~~the~~ plasma 2–4 hours after ~~administration of LARIAM~~ a single oral mefloquine dose. Maximum plasma concentrations, which were about 50% higher than those of mefloquine, were ~~and~~ reached ~~its maximum concentration~~ after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. ~~During the first 12 weeks the mean concentration~~ The area under the plasma concentration-time curve (AUC) of the ~~acid~~ main
(18) metabolite was 2 to 5 times ~~greater~~ larger than that of ~~mefloquine~~ the parent drug. ~~The metabolite has a longer half life than mefloquine and is not active against the malarial parasite.~~ The other metabolite, an
(19) alcohol, was present in only minute amounts.
~~Elimination:~~

Elimination

The ~~average~~ mean elimination half-life of mefloquine in caucasians is ~~is 21 days~~ 3 weeks. Total clearance, which is essentially hepatic, is in the order of 30 mL/min. Clinical studies carried out to date have shown that only a minute proportion of the active ingredient is excreted unchanged in the urine. In volunteers, urinary excretion of unchanged mefloquine and its main metabolite accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine. Animal studies suggest that mefloquine is primarily excreted via the bile and faeces as unchanged drug and metabolites.

## INDICATIONS

Malaria treatment: LARIAM is indicated for the treatment of acute attacks of malaria due to *P.falciparum* infection resistant to conventional antimalarial drugs.

Following therapy of mixed *P.falciparum/P.vivax* malaria with LARIAM relapse prophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate liver forms of *P.vivax*.

Malaria Prophylaxis: For travellers to countries with documented chloroquine and antifolate combination (FANSIDAR/Maloprim) resistant *P.falciparum* malaria, who are considered to be at high risk for malaria in view of their residence or travel ~~(of up to 3 months duration)~~ through rural areas (between the dusk to dawn period).

For travellers hypersensitive to sulphonamides and sulphones, who are considered to be at high risk for malaria in view of their residence or travel ~~(of up to 3 months duration)~~ through rural areas, (between the dusk to dawn period) in countries with high level chloroquine-resistant *P.falciparum* malaria.

## CONTRAINDICATIONS

Hypersensitivity to mefloquine ~~and quinine~~or related compounds (e.g. quinine and quinidine) or any of the excipients in LARIAM.

~~The use of LARIAM is presently contraindicated in patients with renal insufficiency or severe impairment of liver function as no experience has been gained in such patients.~~

LARIAM should not be prescribed for prophylaxis in ~~Patients~~ persons with a ~~past~~ history of ~~psychiatric disturbances~~ psychosis or convulsions. ~~should not be prescribed LARIAM prophylactically.~~

## ~~WARNING~~
## PRECAUTIONS

~~As mefloquine is related structurally to quinine, its use in patients with cardiac disease should be avoided as data on the cardiac effects of mefloquine are at present inadequate to establish safety.~~

~~Animal studies indicate that mefloquine can induce retinopathy. There are no data on the ophthalmological effects of mefloquine in human beings.~~

## ~~PRECAUTIONS~~

010

(27) Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine must not be given simultaneously with or subsequent to LARIAM. No data are available on the use of LARIAM after halofantrine.

(28) ~~Caution should be exercised with regard to~~Persons experiencing dizziness, loss of balance or other disorders of the central or peripheral nervous system should be cautious with regard to activities requiring alertness and fine motor co-ordination such as driving, piloting aircraft and operating machines~~, since dizziness, disturbed sense of balance on neuropsychiatric reactions have been reported during and up to 3 weeks after use of LARIAM.~~

During prophylactic use, if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued.

In patients with epilepsy, mefloquine, especially when used in high doses may increase the risk of convulsions. Therefore in such patients LARIAM should be used only for curative treatment and only if there are compelling medical reasons (see **Interactions with Other Drugs**).

(29) In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels.

(30) ~~Women of childbearing potential who are travelling to malaria-endemic areas in which multi-drug resistant *P.falciparum* is found should use an effective contraceptive throughout the therapy and for at least 3 months after taking the last dose of mefloquine.~~

### Use in Pregnancy (Category B3)

~~Pregnancy Category B3.~~

The use of LARIAM in the treatment of malaria is accepted because the small risk to the fetus is outweighed by the benefits to the mother and fetus.

Prophylaxis in high risk situations is also justified.

(30) Women of childbearing potential should use an effective contraceptive during malaria prophylaxis with LARIAM.

### Use in Lactation

(31) Mefloquine is excreted into breast milk in small amounts, the activity of which is not known. ~~Since no data on~~
(32) ~~drug levels in breast milk after high dosage (curative treatment) or prolonged administration (prophylaxis) is available, LARIAM should not be used by nursing mothers or breast feeding should be discontinued.~~
(33) Circumstantial evidence suggests that adverse effects do not occur in breast-fed infants whose mothers are taking LARIAM.

### Paediatric Use

(34) ~~At present data are inadequate to establish the safety of mefloquine in children below the age of 14 years.~~ Experience with LARIAM in infants less than 3 months old or weighing less than 5 kg is limited.

## Interactions with Other Drugs

(35) Concomitant administration of LARIAM ~~must not be administered concurrently with~~ and other related compounds (e.g. quinine, ~~or~~ quinidine and chloroquine) may produce electrocardiographic abnormalities and ~~since this~~ could increase the risk of convulsions (see Dosage and administration, Treatment). ~~In severe cases, however, patients may be treated initially for one or more days with quinine given intravenously and~~ (36) ~~subsequently with LARIAM. Aggravation of side-effects can be largely precluded by delaying administration of LARIAM until at least 12 hours after the last dose of quinine.~~

(37) ~~Patients taking LARIAM while taking valproic acid had loss of seizure control and lower than expected valproic acid blood levels~~In patients taking an anticonvulsant (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of LARIAM may reduce seizure control by lowering the plasma levels of the anticonvulsant. ~~Therefore, patients concurrently taking antiseizure medication and~~ (38) ~~LARIAM should have the blood level of their antiseizure medication monitored and the dosage adjusted accordingly.~~ Dosage adjustments of anticonvulsant medication may be necessary in some cases (see Precautions).

(39) ~~Concomitant administration of LARIAM and quinine, quinidine or drugs producing beta-adrenergic blockade may produce electrocardiographic abnormalities or cardiac arrest.~~

(40) There is evidence that the use of halofantrine after mefloquine causes a significant lengthening of the QTc interval. Clinically significant QTc prolongation has not been found with mefloquine alone. Theoretically, (41) co-administration of other drugs known to later cardiac conduction (e.g. anti-arrhythmic or -adrenergic blocking agents, calcium channel blockers, antihistamines or H1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval. Evidence suggests that co-medication with such drugs is not contraindicated. ~~Drug-drug interactions with LARIAM have not been~~ (42) ~~explored in detail. There is one report of cardiopulmonary arrest, with full recovery, in a patient who was taking a beta-blocker (propranolol). Although no cardiovascular action of mefloquine hydrochloride, a~~ (43) ~~myocardial depressant, has been observed during clinical trials, parenteral studies in animals show that it possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval~~ (44) ~~reported with quinine. The effect of mefloquine hydrochloride on the compromised cardiovascular system has not been evaluated. The benefits of LARIAM therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.~~

When LARIAM is taken at the same time or shortly before oral live typhoid vaccines, attenuation of the immunisation induced by such vaccines cannot be excluded. ~~Therefore~~ Vvaccinations ~~of this type~~ with (45) attenuated live bacteria should be completed~~/terminated~~ at least three days before the first ~~intake~~ dose of LARIAM, keeping in mind that LARIAM prophylaxis should be started one week before arrival in a malarious area.

No other drug interactions are known. Since interactions with oral antidiabetics and oral anticoagulants have not been tested, the relevant parameters should be checked when LARIAM is taken for malaria prophylaxis.

## ADVERSE REACTIONS

012

(46) ~~Clinical:~~ At the doses used for treatment of acute malaria ~~infections, the symptoms possibly attributable to drug administration~~ adverse reactions to LARIAM may not be distinguishable from those symptoms ~~usually attributable to~~of the disease itself.

(47) ~~Among subjects who received mefloquine for prophylaxis of~~ The most common adverse reactions to malaria prophylaxis, namely nausea, ~~the most frequently observed adverse experience was~~ vomiting and. ~~D~~dizziness, (48) are generally mild and may decrease with prolonged use, in spite of increasing plasma drug levels. ~~, syncope,~~ (49) ~~extrasystoles and paraesthesia were also reported less frequently.~~ In a large study of tourists receiving various prophylactic antimalarials, about 22% of the subjects taking LARIAM reproted adverse events, a rate similar (50) to that for chloroquine.

(51) ~~Among subjects who received mefloquine for treatment, t~~The most frequently observed adverse ~~experiences~~ events ~~included:~~ are ~~dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhoea, skin rash,~~ (52) ~~abdominal pain, fatigue, loss of appetite and tinnitus~~ nausea, vomiting, dizziness or vertigo, loss of balance, (53) headache, somnolence, sleep disorders (insomnia, abnormal dreams), diarrhoea and abdominal pain. ~~Those side effects occurring less frequently included bradycardia, hair loss, emotional problems, pruritus, asthenia,~~ (54) ~~transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been~~ (55) ~~reported.~~

(56) ~~Two serious adverse reactions were cardiopulmonary arrest in one patient shortly after ingesting a single prophylactic dose of mefloquine while concomitantly using propranolol (PRECAUTIONS), and~~ (57) ~~encephalopathy of unknown aetiology during prophylactic mefloquine administration. The relationship of encephalopathy to drug administration could not be clearly established.~~

(58) ~~The following additional adverse reactions have been reported during post-marketing surveillance: vertigo, visual disturbances and central nervous system disturbances (e.g. psychotic manifestations, hallucinations, confusion, anxiety and depression, memory disturbances), tachycardia, paraesthesia, erythema multiforme and~~ (59) ~~Stevens-Johnson Syndrome.~~

(60) ~~Laboratory: The most frequently observed laboratory alterations which could be possibly attributable to drug administration were decreased haematocrit, transient elevation of transaminases, leucopenia and~~ (61) ~~thrombocytopenia. These alterations were observed in patients with acute malaria who received treatment doses of the drug and were attributed to the disease itself.~~

(62) ~~During prophylactic administration of mefloquine to indigenous populations in malaria-endemic areas, the following occasional alterations in laboratory values were observed: transient elevation of transaminases, leucocytosis or thrombocytopenia.~~

(63) ~~During curative or prophylactic treatment with mefloquine transient cardiac conduction alterations as well as peripheral neuropathy have also been observed.~~

(64) ~~In rare cases, the adverse reactions mentioned above have been observed more than one week after the last dose.~~

(65) ~~During prophylactic use, if signs of unexplained anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be stopped.~~

~~NOTE: In animals mefloquine has been associated with increases in ALT, AST, alkaline phosphatase, and BUN. Similar changes in clinical studies if they occurred, could not be dissociated from the effects of malaria infection. Repeated administration of mefloquine to male rats adversely affected fertility~~

Less frequently reported adverse events:

*Central and peripheral nervous system:* sensory and motor neuropathies (including paraesthesia), convulsions, visual disturbances, tinnitus and vestibular disorders, anxiety, restlessness, depressive mood, forgetfulness, confusion, hallucinations and psychotic or paranoid reactions.

*Cardiovascular system:* circulatory disturbances (hypotension, hypertension, flushing, syncope), tachycardia or palpitation, bradycardia, irregular pulse, extrasystoles and other transient cardiac conduction alterations.

*Skin:* rash, exanthema, erythema, urticaria, pruritus, hair loss.

*Musculo-skeletal system:* muscle weakness, muscle cramps, myalgia, arthralgia.

*General symptoms:* asthenia, malaise, fatigue, fever, chills, loss of appetite.

*Laboratory abnormalities:* transient elevation of transaminases, leukopenia or leukocytosis, thrombocytopenia.

Isolated cases of erythema multiforme, Stevens-Johnson syndrome, AV-block, and encephalopathy have been reported.

Because of the long half-life of mefloquine, adverse reactions to LARIAM may occur or persist up to several weeks after the last dose.

## DOSAGE AND ADMINISTRATION

Mefloquine has a bitter and slightly burning taste. LARIAM tablets should be swallowed whole, preferably after a meal, with at least one glass of liquid. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

*Malaria Treatment*: ~~Adults and children of more than 45 kg bodyweight:~~

~~(i) Non-immune patients recently arrived from endemic areas.~~

~~The recommended total dosage of LARIAM, 1,250 mg according to bodyweight, should be administered as follows:~~

~~A loading dose of 3 tablets (750 mg), followed 6 to 8 hours later by 2 tablets (500 mg).~~

The recommended total therapeutic dose of mefloquine for non-immune patients is 20-25 mg/kg. This corresponds to a total dose of 1250-1500 mg mefloquine (5-6 LARIAM tablets) in patients weighing over 45 kg.

~~ii) Semi-immune patients~~

~~For patients in malaria endemic areas, a~~ A ~~smaller~~ lower total ~~dosage~~ dose of ~~LARIAM~~ 750-1000 mg ~~–~~mefloquine (3-4 LARIAM tablets) in partially immune patients weighing over 45 kg ~~is sufficient~~ may suffice. This corresponds to a lower dose of 15 mg/kg. (See following table). ~~since they have usually developed partial immunity. Adults weighing 60 kg receive an initial dose of 3 tablets, followed by 1 tablet 6 to 8 hours later.~~

79 *Recommended total therapeutic dosages of LARIAM tablets relative to bodyweight and immune status **

| | Non-immune patients | Partially immune patients |
|---|---|---|
| < 20 kg ** | ¼ tablet / 2.5-3 kg | ¼ tablet / 4 kg |
| | 1 tablet / 10-12 kg | 1 tablet / 16 kg |
| 20-30 kg | 2-3 tablets | 1½ -2 tablets |
| 30-45 kg | 3-4 tablets | 2-3 tablets |
| 45-60 kg | 5 tablets | 3 tablets |
| > 60 kg *** | 6 tablets | 4 tablets |

80 * Splitting the total curative dosage into 2-3 doses (e.g. 3 + 1, 3 + 2, or 3 + 2 + 1) taken 6-8 hours apart may reduce the occurrence or severity of adverse effects.

81 ** Experience with LARIAM in infants less than 3 months old or weighing less than 5 kg is limited.

82 *** There is no specific experience with total dosages of more than 1500 mg in very heavy patients.

83 A second full dose should be given to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30-60 minutes after a dose, an additional half dose should be given.

84 After treatment of *P. vivax* malaria, relapse prophylaxis with an 8-aminoquinolone derivative (e.g. primaquine) should be considered in order to eliminate liver forms.

85 If a full treatment course ~~has been administered without clinical cure,~~ with LARIAM does not lead to improvement within 48-72 hours, alternative treatments should be ~~given~~ considered. ~~Similarly if previous~~

86 ~~prophylaxis with mefloquine has failed, LARIAM should not be used for curative treatment.~~

87 When breakthrough malaria occurs during LARIAM prophylaxis, carefully evaluate which antimalarial to use for therapy (see Precautions, Interactions with other drugs).

88 LARIAM can be given for severe acute malaria after an initial course of intravenous quinine lasting at least 2-3 days. Interactions leading to adverse events can largely be prevented by allowing an interval of at least 12 hours after the last dose of quinine.

89 In areas with multiresistant malaria, initial treatment with artemisinin or a derivative, if available, followed by LARIAM is also an option.

*Malaria Prophylaxis*:

90 Prophylaxis of malaria with LARIAM should be initiated at least 1 week before arrival in a malarious area.

~~The following dosage schedule is given as a guide:~~

91 ~~LARIAM can be used for up to 3 months in the prophylaxis of malaria.~~

| | ~~Dosage~~ | ~~Course of Prophylaxis~~ |
|---|---|---|
| ~~Adults and children of more than 45kg bodyweight~~ 92 | ~~1 tablet~~ 93 | ~~Stated dose to be given once weekly, always on the same day.~~ 94 ~~First dose one week before departure. Further doses at weekly~~ 95 ~~intervals during travel in malarious areas and for 2 weeks after leaving the area.~~ |

(96) If this is not possible, a loading dose should be given; in adults weighing over 45 kg this is one LARIAM tablet (250 mg) daily for 3 days, followed by 1 tablet weekly. When a traveller is taking other medication it (97) may be desirable to start prophylaxis 2-3 weeks prior to departure in order to ensure that the combination of (98) drugs is well tolerated. Weekly doses should always be taken on the same day of the week. To reduce the (99) risk of malaria after leaving an endemic area, prophylaxis must be continued for 4 additional weeks.

(100) 1. Adults and children weighing over 45 kg
In persons over 45 kg, the prophylactic dose is 250 mg of mefloquine (one tablet) once weekly.

(101) 2. Children and adults weighing less than 45 kg
The weekly dose decreases in proportion to bodyweight:

| | |
|---|---|
| 31 - 45 kg | ¾ tablet |
| 21 - 30 kg | ½ tablet |
| up to 20 kg | ¼ tablet |

(102) Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited.

(103) When prophylaxis with LARIAM fails, doctors should carefully evaluate which antimalarial to use for therapy (see Precautions, Interactions with other drugs).

(104) ~~The tablets should be swallowed whole with plenty of liquid~~

## OVERDOSAGE

Symptoms: In cases of overdosage with LARIAM, the symptoms mentioned under ADVERSE REACTIONS may be more pronounced.

Treatment: The following procedure is recommended: Induce vomiting or perform gastric lavage as appropriate. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances.

## PRESENTATION

Packs of 8 tablets (cross-scored) each containing 250 mg mefloquine.

## DISTRIBUTOR

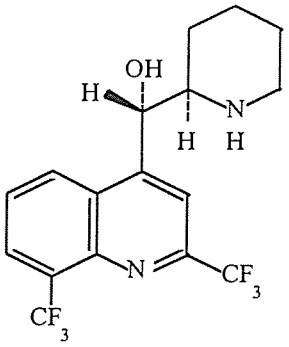
ROCHE PRODUCTS PTY LTD
ACN 000 132 865
4 - 10 Inman Road
Dee Why NSW 2099

TGA Approval date: ~~31 May, 1993~~

**LARIAM**
**(mefloquine hydrochloride)**

016

LARIAM contains DL - erythro - alpha - 2 - piperidyl - 2,8 - bis (trifluoromethyl)- 4 - quinoline methanol (mefloquine) which has the following formula:




Mefloquine is an odourless, bitter-tasting, white crystalline powder of molecular weight 414.78. It is soluble in methanol and ethanol but practically insoluble in water. A 1% aqueous suspension has a pH of 5.6.

LARIAM tablets contain the active substance 250 mg mefloquine in the form of mefloquine hydrochloride (274.09 mg). Lariam tablets also contain the excipients poloxamer 3800, microcrystalline cellulose, lactose, maize starch, crospovidone, ammonium calcium alginate, talc and magnesium stearate.

## PHARMACOLOGY

### Actions

Mefloquine is an antimalarial belonging to the quinoline-methanol group of drugs and is structurally related to quinine. Its effectiveness in the treatment of malaria is due essentially to destruction of the asexual intraerythrocytic forms of the human malarial parasites *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Mefloquine is also effective against malaria parasites resistant to other antimalarial such as chloroquine and other 4-amino-quinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

Laboratory animal studies have shown that resistance to mefloquine can be readily induced in the malarial parasite and that this resistance is stable during passage through the insect vector. Mefloquine resistance has also been seen in a few clinical isolates from patients receiving mefloquine. Cross-resistance can be shown between mefloquine and quinine.

Resistance of *P. falciparum* to mefloquine has been reported, mainly in parts of South-East Asia. Cross-resistance between mefloquine and halofantrine has been observed.

Mode of Action: The basic mode of action of mefloquine has not yet been elucidated. However a number of studies of its actions in biochemical systems have been made.

Like quinine, mefloquine is able to form complexes with haemin. The ability to co-ordinate with haemin seems to correlate with the antimalarial activity of the compound. But, unlike chloroquine, quinacrine and quinine, mefloquine does not intercalate with DNA. Thus interaction with DNA does not seem to be involved in the antimalarial action of mefloquine.

Mefloquine does not exert antifolic activity and its antimalarial action is not antagonised by p-aminobenzoic acid.

## Pharmacokinetics



Absorption

Plasma concentrations peak 6-24 hours (median, about 17 hours) after a single dose of mefloquine. Maximum plasma concentrations in μg/L are roughly equivalent to the dose in milligrams (for example, a single 1000 mg dose produces a maximum concentration of about 1000 μg/L). At a dose of 250 mg once weekly, maximum steady state plasma concentrations of 1000-2000 μg/L are reached after 7-10 weeks.

Bioavailability

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formulation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20 L/kg body weight, indicating extensive tissue distribution. Mefloquine is taken up largely in the liver but also into the lungs, muscles, brain and retina. The concentration in erythrocytes is approximately twice that in the plasma. About 98% of mefloquine is bound to plasma proteins. Clinical experience suggests a minimal suppressive plasma concentration of mefloquine in the order of 600 μg/L.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see Precautions, Use in lactation).

Metabolism

Two metabolites have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinolone carboxylic acid, is inactive in *P. falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2-4 hours after a single oral mefloquine dose. Maximum plasma concentrations, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3-5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in only minute amounts.

Elimination

The mean elimination half-life of mefloquine in caucasians is 3 weeks. Total clearance, which is essentially hepatic, is in the order of 30 mL/min.

Clinical studies carried out to date have shown that only a minute proportion of the active ingredient is excreted unchanged in the urine. In volunteers, urinary excretion of unchanged mefloquine and its main metabolite accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine. Animal studies suggest that mefloquine is primarily excreted via the bile and faeces as unchanged drug and metabolites.

16

018

## INDICATIONS

Malaria treatment: LARIAM is indicated for the treatment of acute attacks of malaria due to *P.falciparum* infection resistant to conventional antimalarial drugs.

Following therapy of mixed *P.falciparum/P.vivax* malaria with LARIAM relapse prophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate liver forms of *P.vivax*.

Malaria Prophylaxis: For travellers to countries with documented chloroquine and antifolate combination (FANSIDAR/Maloprim) resistant *P.falciparum* malaria, who are considered to be at high risk for malaria in view of their residence or travel through rural areas (between the dusk to dawn period).

For travellers hypersensitive to sulphonamides and sulphones, who are considered to be at high risk for malaria in view of their residence or travel through rural areas, (between the dusk to dawn period) in countries with high level chloroquine-resistant *P.falciparum* malaria.

## CONTRAINDICATIONS

Hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine) or any of the excipients in LARIAM.

LARIAM should not be prescribed for prophylaxis in persons with a history of psychosis or convulsions.

## PRECAUTIONS

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine must not be given simultaneously with or subsequent to LARIAM. No data are available on the use of LARIAM after halofantrine.

Persons experiencing dizziness, loss of balance or other disorders of the central or peripheral nervous system should be cautious with regard to activities requiring alertness and fine motor co-ordination such as driving, piloting aircraft and operating machines

During prophylactic use, if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued.

In patients with epilepsy, mefloquine, especially when used in high doses may increase the risk of convulsions. Therefore in such patients LARIAM should be used only for curative treatment and only if there are compelling medical reasons (see Interactions with Other Drugs).

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels.

**e in Pregnancy (Category B3)**



The use of LARIAM in the treatment of malaria is accepted because the small risk to the fetus is outweighed by the benefits to the mother and fetus.

Prophylaxis in high risk situations is also justified.

Women of childbearing potential should use an effective contraceptive during malaria prophylaxis with LARIAM.

**Use in Lactation**

Mefloquine is excreted into breast milk in small amounts, the activity of which is not known. Circumstantial evidence suggests that adverse effects do not occur in breast-fed infants whose mothers are taking LARIAM.

**Paediatric Use**

Experience with LARIAM in infants less than 3 months old or weighing less than 5 kg is limited.

**Interactions with Other Drugs**

Concomitant administration of LARIAM and other related compounds (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and could increase the risk of convulsions (see Dosage and administration, Treatment).

In patients taking an anticonvulsant (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of LARIAM may reduce seizure control by lowering the plasma levels of the anticonvulsant. Dosage adjustments of anticonvulsant medication may be necessary in some cases (see Precautions).

There is evidence that the use of halofantrine after mefloquine causes a significant lengthening of the QTc interval. Clinically significant QTc prolongation has not been found with mefloquine alone. Theoretically, co-administration of other drugs known to alter cardiac conduction (e.g. anti-arrhythmic or β-adrenergic blocking agents, calcium channel blockers, antihistamines or $H_1$-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval. Evidence suggests that co-medication with such drugs is not contraindicated.

When LARIAM is taken at the same time or shortly before oral live typhoid vaccines, attenuation of the immunisation induced by such vaccines cannot be excluded. Vaccinations with attenuated live bacteria should be completed at least three days before the first dose of LARIAM, keeping in mind that LARIAM prophylaxis should be started one week before arrival in a malarious area.

No other drug interactions are known. Since interactions with oral antidiabetics and oral anticoagulants have not been tested, the relevant parameters should be checked when LARIAM is taken for malaria prophylaxis.

## ADVERSE REACTIONS

020

At the doses given for acute malaria, adverse reactions to LARIAM may not be distinguishable from symptoms of the disease itself.

The most common adverse reactions to malaria prophylaxis, namely nausea, vomiting and dizziness, are generally mild and may decrease with prolonged use, in spite of increasing plasma drug levels. In a large study of tourists receiving various prophylactic antimalarials, about 22% of the subjects taking LARIAM reproted adverse events, a rate similar to that for chloroquine.

The most frequently reported adverse events are nausea, vomiting, dizziness or vertigo, loss of balance, headache, somnolence, sleep disorders (insomnia, abnormal dreams), diarrhoea and abdominal pain.

Less frequently reported adverse events:
*Central and peripheral nervous system:* sensory and motor neuropathies (including paraesthesia), convulsions, visual disturbances, tinnitus and vestibular disorders, anxiety, restlessness, depressive mood, forgetfulness, confusion, hallucinations and psychotic or paranoid reactions.
*Cardiovascular system:* circulatory disturbances (hypotension, hypertension, flushing, syncope), tachycardia or palpitation, bradycardia, irregular pulse, extrasystoles and other transient cardiac conduction alterations.
*Skin:* rash, exanthema, erythema, urticaria, pruritus, hair loss.
*Musculo-skeletal system:* muscle weakness, muscle cramps, myalgia, arthralgia.
*General symptoms:* asthenia, malaise, fatigue, fever, chills, loss of appetite.
*Laboratory abnormalities:* transient elevation of transaminases, leucopenia or leucocytosis, thrombocytopenia.

Isolated cases of erythema multiforme, Stevens-Johnson syndrome, AV-block, and encephalopathy have been reported.

Because of the long half-life of mefloquine, adverse reactions to LARIAM may occur or persist up to several weeks after the last dose.

## DOSAGE AND ADMINISTRATION

Mefloquine has a bitter and slightly burning taste. LARIAM tablets should be swallowed whole, preferably after a meal, with at least one glass of liquid. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

*Malaria Treatment*:

The recommended total therapeutic dose of mefloquine for non-immune patients is 20-25 mg/kg. This corresponds to a total dose of 1250-1500 mg mefloquine (5-6 LARIAM tablets) in patients weighing over 45 kg.

A lower total dose of 750-1000 mg mefloquine (3-4 LARIAM tablets) in partially immune patients weighing over 45 kg may suffice. This corresponds to a lower dose of 15 mg/kg. (See following table).

***Recommended total therapeutic dosages of LARIAM tablets relative to bodyweight and immune status ****

| | Non-immune patients | Partially immune patients |
|---|---|---|
| < 20 kg ** | ¼ tablet / 2.5-3 kg<br>1 tablet / 10-12 kg | ¼ tablet / 4 kg<br>1 tablet / 16 kg |
| 20-30 kg | 2-3 tablets | 1½ -2 tablets |
| 30-45 kg | 3-4 tablets | 2-3 tablets |
| 45-60 kg | 5 tablets | 3 tablets |
| > 60 kg *** | 6 tablets | 4 tablets |

* Splitting the total curative dosage into 2-3 doses (e.g. 3 + 1, 3 + 2, or 3 + 2 + 1) taken 6-8 hours apart may reduce the occurrence or severity of adverse effects.

** Experience with LARIAM in infants less than 3 months old or weighing less than 5 kg is limited.

*** There is no specific experience with total dosages of more than 1500 mg in very heavy patients.

A second full dose should be given to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30-60 minutes after a dose, an additional half dose should be given.

After treatment of *P. vivax* malaria, relapse prophylaxis with an 8-aminoquinolone derivative (e.g. primaquine) should be considered in order to eliminate liver forms.

If a full treatment course with LARIAM does not lead to improvement within 48-72 hours, alternative treatments should be considered. When breakthrough malaria occurs during LARIAM prophylaxis, carefully evaluate which antimalarial to use for therapy (see Precautions, Interactions with other drugs).

LARIAM can be given for severe acute malaria after an initial course of intravenous quinine lasting at least 2-3 days. Interactions leading to adverse events can largely be prevented by allowing an interval of at least 12 hours after the last dose of quinine.

In areas with multiresistant malaria, initial treatment with artemisinin or a derivative, if available, followed by LARIAM is also an option.

*Malaria Prophylaxis:*

Prophylaxis of malaria with LARIAM should be initiated at least 1 week before arrival in a malarious area.

If this is not possible, a loading dose should be given; in adults weighing over 45 kg this is one LARIAM tablet (250 mg) daily for 3 days, followed by 1 tablet weekly. When a traveller is taking other medication it may be desirable to start prophylaxis 2-3 weeks prior to departure in order to ensure that the combination of drugs is well tolerated. Weekly doses should always be taken on the same day of the week. To reduce the risk of malaria after leaving an endemic area, prophylaxis must be continued for 4 additional weeks.

1. Adults and children weighing over 45 kg
   In persons over 45 kg, the prophylactic dose is 250 mg of mefloquine (one tablet) once weekly.

2. Children and adults weighing less than 45 kg
   The weekly dose decreases in proportion to bodyweight:

| | |
|---|---|
| 31 - 45 kg | ¾ tablet |
| 21 - 30 kg | ½ tablet |
| up to 20 kg | ¼ tablet |

Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited.

..hen prophylaxis with LARIAM fails, doctors should carefully evaluate which antimalarial to use for therapy (see Precautions, Interactions with other drugs).

## OVERDOSAGE

Symptoms: In cases of overdosage with LARIAM, the symptoms mentioned under ADVERSE REACTIONS may be more pronounced.

Treatment: The following procedure is recommended: Induce vomiting or perform gastric lavage as appropriate. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances.

## PRESENTATION

Packs of 8 tablets (cross-scored) each containing 250 mg mefloquine.

## DISTRIBUTOR

ROCHE PRODUCTS PTY LTD
ACN 000 132 865
4 - 10 Inman Road
Dee Why NSW 2099

TGA Approval date: