

What is Wrong with Current SmPCs?

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DIA Product Information Forum, London, June 2011

What is Wrong with Current SmPCs? or *What is Posology?*

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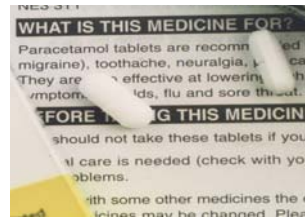
DIA Product Information Forum, London, June 2011

Package Leaflets – for Patients



What do you think about medicine leaflets?

- *They don't inspire you*
- *Priorities are those who wrote it, not patients*
- *People who suffer should help write leaflets*
- Concern about complex language & poor visual presentation
- Patients value information that contains a balance of benefit & harm information



 Raynor et al. *Patient Education & Counseling* 2004

 Raynor et al, *Health Technol Assess* 2007

In this presentation



1. Summary of Product Characteristics

- What is it for?

2. SmPC

- How does it perform?

3. SmPC

- Impact on Package Leaflet

Background – University of Leeds & Luto Research



Consumer medicines information research group:

- Impact of EU legislation & User Testing
- Expressing risks and benefits to patients
- US & Australian medicine leaflets
- Collaborate with **Sydney, Wisconsin, Utrecht & Aarhus**
- Expert advice to policy-makers including European Parliament & FDA

Luto Research - University Spin Out

- Patient information testing service for pharma companies
- Spin outs promoted by University – putting research into practice
- **EPAR Summaries**, clinical trial PIS, IFUs, RMP materials

Principal role remains as an academic

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1. Summaries of Product Characteristics - What are they for?

What is Wrong with Current SmPCs?

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What is the SmPC for?



Serves three masters:

1. Represents the agreed position ...*as distilled through the course of the assessment process*
2. “Basis of information for healthcare professionals on how to use the product safely and effectively”
3. “The Package Leaflet shall be drawn up in accordance with the SmPC”

Too many masters?

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2. Summary of Product Characteristics - How do they perform?

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How useful for health professionals?



We tested two SmPCs with doctors in the UK

- Generalist SmPC: '**Lariam**'; mefloquine
 - anti-malarial
- Specialist SmPC: '**CellCept**'; mycophenolate
 - prophylaxis of transplant organ rejection

Using the process of 'user testing'

- Performance based testing
- Legal requirement for the package leaflet – process the same

Collaboration with Roche

- Roche contracted with Luto Research for testing of the 2 SmPCs
- Project led by
 - Prof Theo Raynor (University of Leeds)
 - Dr Peter de Veene (Roche)

User Testing in Brief



Select 15 key points

- Relevant to safe and effective use

(a) Quantitative aspect

- **Design & pilot a questionnaire which tests:**
 - Finding each piece of information
 - Understanding (express in own words)
- **Recruit 10 people from target group**
 - Interviewed individually
 - Can they find and understand the information?

(b) Qualitative aspect

- **Interview concludes with qualitative questions**
 - What did they like and not like about the document?


Try, Try and Try Again



User Testing is an iterative process

- **Test material**
- **Identify problems**
 - the points people struggled with and their general comments
- **Remedy problems**
 - using research evidence & good practice in writing & design
- **Test again**



 Raynor DK. *Testing, Testing: The Benefits of User-testing Package Leaflets*
Regulatory Affairs Focus 2008

Roche Products Limited

Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW
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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. [Why?](#)

Summary of Product Characteristics last updated on the eMC: 16/09/2009



Lariam

1. NAME OF THE MEDICINAL PRODUCT

Lariam 250mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg mefloquine (as 274.09mg mefloquine hydrochloride).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet. White to off-white cylindrical biplanar tablets, cross scored and imprinted with Roche on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapy and prophylaxis of malaria.

Therapy: Lariam is especially indicated for therapy of *P. falciparum* malaria in which the pathogen has become resistant to other antimalarial agents.

Following treatment of *P. vivax* malaria with Lariam, relapse prophylaxis with an 8-amino-quinoline derivative, for example primaquine, should be considered in order to eliminate parasites in the hepatic phase.

Prophylaxis: Malaria prophylaxis with Lariam is particularly recommended for travellers to malarious areas in which multiple resistant *P. falciparum* strains occur.

For current advice on geographical resistance patterns and appropriate chemoprophylaxis, current guidelines or the Malaria Reference Laboratory should be consulted. Details of which can be found in the British National Formulary (BNF).

Lariam SmPC Testing 1: - the original



15 Key points tested with General Practitioners

Finding the information

- Doctors' ability to navigate around the document was poor
- 9/15 points not found, or found with difficulty, by 2 or more doctors

Understanding

- 5/15 points were not understood by 2 or more doctors

Qualitative comments

- Comments included that the SmPC was '*muddled*'
- *Information buried*
- *Search backwards and forwards*

Revising the Lariam SmPC:



Problem points of information

- | | |
|------------------------------|-----------------------------------|
| • Pregnancy | • Identifying side effects |
| • Driving and using machines | • Reducing side effects with food |
| • Lactose intolerance | |

Common themes

- Information not where expected; headings not useful
- Repetition - a problem with the sections on interactions, pregnancy, and driving
- Who is it addressing?

4. CLINICAL PARTICULARS

4.1 Therapeutic indications


Therapy and prophylaxis of malaria.

Therapy: **Lariam** is especially indicated for therapy of *P. falciparum* malaria in which the pathogen has become resistant to other antimalarial agents.

Following treatment of *P. vivax* malaria with **Lariam**, relapse prophylaxis with an 8-amino-quinoline derivative, for example **primaquine**, should be considered in order to eliminate parasites in the hepatic phase.

Prophylaxis: Malaria prophylaxis in areas in which multiple resistant strains are present.

For current advice on geographical resistance patterns or the Malaria Reference Laboratory, see the British National Formulary.



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2. What **Lariam** is used for

2.1 Indications

Lariam is used to treat or prevent malaria.

To treat malaria

- Lariam** is particularly recommended to treat *P. falciparum* which has become resistant to other anti-malarial agents.
- It can also be used for treatment of *P. vivax* malaria. However, you need to also consider relapse prophylaxis with an 8-amino-quinoline derivative e.g. **primaquine**. This is to eliminate parasites in the hepatic phase of malaria.

Cross-resistance between **mefloquine** and **halofantrine** has been seen.

If there is no improvement 48 to 72 hours after a full treatment course, consider alternative treatments.

Tell patients that re-infection or re-appearance of malaria is possible after effective anti-malarial therapy.

For prophylaxis of malaria

- Malaria prophylaxis with **Lariam** is particularly recommended for travellers to areas with malaria where there are multiple resistant *P. falciparum* strains.
- Check current guidelines in the British National Formulary (BNF) or from the malaria reference laboratory for current advice on:
 - geographical resistance patterns
 - appropriate chemoprophylaxis


4.7 Effects on ability to drive and use machines

Mefloquine can cause dizziness or disturbed sense of balance. It is consequently recommended not to drive or carry out tasks demanding fine co-ordination and spatial discrimination during treatment with **mefloquine**. Patients should avoid such tasks for at least 3 weeks following therapeutic use, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported up to three weeks after the use of **Lariam**.

Prophylactic use

Caution should be exercised with regard to driving, piloting aircraft and operating machines, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported during and up to three weeks after use of **Lariam**.

In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug (see section 4.8 Undesirable Effects).



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4.5 Effects on ability to drive and use machines

While taking **Lariam**

Mefloquine can cause dizziness or a disturbed sense of balance. It is recommended not to drive or carry out tasks demanding fine co-ordination and spatial discrimination during treatment or prophylaxis. This includes driving, piloting aircraft and operating machines.

After taking **Lariam**

Patients should not undertake such tasks for at least 3 weeks following therapeutic use. This is because dizziness, a disturbed sense of balance or neuro-psychiatric reactions have been reported up to three weeks after the use of **Lariam**.

In a small number of patients it has been reported that dizziness, vertigo or loss of balance may continue for several months after stopping the drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

lactose

crospovidone

maize starch

ammonium-calcium alginate

poloxamer (polyoxyethylene-polyoxypropylene copolymer)

talc

magnesium stearate

4. Contra-indications and precautions

4.1 Contra-indications

Do not use Lariam if the patient has:

- known hypersensitivity to mefloquine or related compounds e.g. quinine
- severe liver function impairment and needs malaria prophylaxis - there is no experience in such patients
- history of psychiatric problems (including depression) and needs malaria prophylaxis - Lariam may precipitate these conditions
- history of epilepsy and needs malaria prophylaxis - Lariam may precipitate convulsions. May be used for treatment if there are very good reasons (see also Section 4.2 Special warnings)
- rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption - this is because Lariam contains lactose.

Do not use halofantrine (for prophylaxis or treatment) at the same time, or after, Lariam. (See Section 4.3: Interactions)

4.8 Undesirable effects

At the doses given for acute m symptoms of the disease itself prophylaxis is comparable to the mefloquine adverse events is

Because of the long half-life of than several weeks after discon that dizziness or vertigo and lo

Patients should be advised to concerning or neuropsychiatric particularly if neuropsychiatric prophylaxis can then be evalu

The following adverse events (cannot be estimated from the

Blood and Lymphatic System

Psychiatric Disorders: Sleep di depression, mood swings, pan paranoid reactions.

There have been rare reports has been established.

Nervous System Disorders: Di memory impairment, sensory Isolated cases of encephalopa

Hepatobiliary disorders: Trans

Skin and Subcutaneous Tissue hyperhidrosis. Isolated cases reported.

Musculoskeletal and Connectiv

5.2 List of adverse events

The following adverse events have been reported, although their absolute frequencies are not known:

Psychiatric:

- panic attacks
- depression, mood swings
- agitation, restlessness, anxiety
- confusional state, hallucinations
- sleep disorders (insomnia, abnormal dreams)
- aggression, psychotic or paranoid reactions.

There have been rare reports of suicidal thoughts and suicide, but no relationship to Lariam administration has been established.

Blood and lymphatic system:

- leucopenia or leucocytosis and thrombocytopenia.

Nervous system:

- headache
- drowsiness
- memory impairment
- syncope, convulsions
- dizziness and loss of balance
- isolated cases of encephalopathy have been reported.
- sensory and motor neuropathies (including paraesthesia, tremor and ataxia)

Liver and biliary:

- transient elevation of transaminases.


Skin and subcutaneous tissue:

- alopecia
- hyperhidrosis

4.2 Posology and method of administration
Curative treatment

The recommended total therapeutic dose of **mefloquine** for non-immune patients is 20 – 25mg/kg. A lower total dose of 15mg/kg may suffice for partially immune individuals.

The recommended total therapeutic dosages of **Lariam** tablets relative to body weight and immune status are presented in the following table.*



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5. Side effects

5.1 Overview of undesirable effects

At the doses given for acute malaria, adverse reactions to **Lariam** may not be distinguishable from symptoms of the disease itself. The overall incidence of adverse events reported during **mefloquine** prophylaxis is comparable to that reported for other **chemoprophylactic** regimens.

Tell patients taking **Lariam** for prophylaxis to talk to a doctor if any concerning symptoms develop. They should do this before they take the next weekly dose.

Neuro-psychological adverse events

Most **mefloquine** adverse events are **neuro-psychological**.


- Because of the long half-life, adverse reactions may happen or persist for more than several weeks after stopping the drug.
- If psychiatric disturbances occur, **Lariam** should be stopped and an alternative prophylactic or treatment agent recommended.

Minimising side effects

Splitting the total daily dose into 2 or 3 parts may reduce the chance of side effects or make them less severe.

- For example 3+1, 3+2 or 3+2+1 tablets taken 6 to 8 hours apart.

Lariam SmPC Testing 2:
- Revised wording in original layout



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10 more General Practitioners

Finding the information


- Doctors' ability to navigate around the document was again poor
- 7/15 points not found, or found with difficulty, by 2 or more doctors

Understanding


- 4/15 points were not understood by 2 or more doctors

Qualitative comments

- *Its not particularly easy to use but its very, very necessary, the information that's in there*
- *[Pregnancy] mentioned in 2 totally different sections, might be worthwhile combining the two*
- *Important points should perhaps be aggregated on front page*



Lariam 250mg Tablets
Summary of Product Characteristics




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Key information

- Lariam is used to treat or prevent malaria, particularly:
 - treating *P. falciparum* resistant to other anti-malarials
 - prophylaxis in areas with multiple resistant *P. falciparum*.
 See Section 2 below for more information. Always check guidelines before prescribing anti-malarials.
- See the tables in Section 3 for the dose regimes.
 - For **treatment**: spread doses through the day, after a meal.
 - For **prophylaxis**: once a week on the same day; 1 to 3 weeks before and 4 weeks after leaving the affected country.
- Do not use for prophylaxis in severe liver problems, a history of psychiatric problems or epilepsy (see Section 4.1).
- When treating malaria, use with caution in people with epilepsy or cardiac conduction disorders (see Section 4.2).
- Lariam interacts with some other medicines including quinine and similar drugs, ketoconazole and anti-convulsants. Also, do not use halofantrine at the same time or after Lariam. (See Section 4.3 for more information)
- Do not use in pregnancy (particularly the first trimester) unless the benefits outweigh the risks. Contraception should be used during treatment, and 3 months after treatment. Women should not breast-feed while taking Lariam. (See Section 4.4 for more information)
- In acute malaria, side effects may be very similar to the disease itself.
- The most common side effects are **neuro-psychological** – if psychiatric problems happen, stop Lariam. When taken for prophylaxis, patients who get side effects should see a doctor, before taking the next weekly dose. (See Section 5 for more information on side effects)
- Lariam can cause dizziness or balance problems which can last up to 3 weeks after stopping. Sometimes they may last for months after.

See over for the full information about **Lariam**.



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1. NAME OF THE MEDICINAL PRODUCT
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
3. PHARMACEUTICAL FORM
4. CLINICAL PARTICULARS
 - 4.1 Therapeutic indications
 - 4.2 Posology and method of administration
 - 4.3 Contraindications
 - 4.4 Special warnings and precautions for use
 - 4.5 Interaction with other medicinal products and other forms of contraception
 - 4.6 Pregnancy and lactation
 - 4.7 Effects on ability to drive and use machines
 - 4.8 Undesirable effects
 - 4.9 Overdose
5. PHARMACOLOGICAL PROPERTIES
 - 5.1 Pharmacodynamic properties
 - 5.2 Pharmacokinetic properties
 - 5.3 Preclinical safety data
6. PHARMACEUTICAL PARTICULARS
 - 6.1 List of excipients
 - 6.2 Incompatibilities
 - 6.3 Shelf life
 - 6.4 Special precautions for storage
 - 6.5 Nature and contents of container
 - 6.6 Special precautions for disposal and other hazards
7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORISATION NUMBER(S)
9. DATE OF FIRST AUTHORISATION/RENEWAL
10. DATE OF REVISION OF THE TEXT
- LEGAL STATUS

In this SPC

1. General information
2. What **Lariam** is used for
3. Dose and how to use
4. Contra-indications and precautions
5. Side effects
6. Overdose
7. Pharmacological properties
8. Formulation and storage
9. Marketing authorisation holder

Lariam SmPC Testing 3: - Revised wording & revised layout



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10 more General Practitioners

Finding the information

- Doctors' ability to navigate around the document was poor
- 8/15 points not found, or found with difficulty, by 2 or more doctors

Understanding

- 7/15 points were not understood by 2 or more doctors

Qualitative comments

- *Its probably taught me something. I didn't know that information would have been there*

CellCept SmPC Testing 1: - the original



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15 Key points tested with Specialist Hospital Doctors

Finding the information

- Doctors' ability to navigate around the document was poor
- 11/15 points not found, or found with difficulty, by 2 or more doctors

Understanding

- 1/15 points were not understood by 2 or more doctors

Qualitative comments

- *Haven't ever looked at CellCept SPC although have prescribed for years*
- *I can't confidently tell you I have ever looked at an SPC*
- *There's actually lot more information in here than we tend to give credit for*

3. Package Leaflets and Impact of SmPC

What is Wrong with Current SmPCs?

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Impact of SmPC on PL

SmPC is comfort blanket for some regulators and regulatory affairs staff. Resistance to moving information points to where patients will look on the PL

- **Duplication of contra-indications**
 - Interactions
 - Pregnancy
- **Side effect information in Section 2 'Before taking...'**
 - Serious side effects deemed needing to be stated up front
- **No benefit information in SmPC**
 - Prime desire of patients

Key points



- **SmPCs serve 3 purposes**
 - Do we need a bespoke version for health professionals?
- **Two SmPCs tested performed poorly**
 - Particularly for doctors finding relevant information
- **User Testing identified where there were problems**
 - Solutions could be applied, as for PLs
- **Key solutions relate to headings, sub-headings**
 - Placement of information where doctors expect it
- **Revised versions showed some improvements**
 - Qualitative results particularly informative
 - Key information section widely liked
 - Could be used more if easier to use and doctors knew of value
- **Improving the SmPC could improve the PL**

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