**Written Evidence submitted by Lance F Cole**

# FORGOTTEN WARNINGS: INVISIBLE EVIDENCE?

## MEFLOQUINE'S TROUBLED HISTORY 1981-1993

Early warning precursor events & officially framed concerns of 1989 and 1991 indicated specific prior knowledge of military and other prescribing limitations and side effects concerns by mefloquine's manufacturer:

Doctors' early safety concerns have been closely mirrored by subsequent adverse effects claims in civilian and military subjects – suggesting validation of both groups adverse effects claims and indication of alleged risks and potential harms

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**Extent: 3,750 words; plus references and document as Appendix 1**

### 1. Author Details

1 I Lance F. Cole make submission declaring that I was the co-founder and past-Chair of the mefloquine (Lariam) patient support group from 1996, and that group's joint, authored findings from early mefloquine patient support group surveys were published in the medical literature.

2 I have spent over 15 years researching the history of mefloquine hydrochloride. I have worked with qualified experts in the field of mefloquine, and its history. I have advised MPs/Parliamentarians on mefloquine issues and I researched and co-authored the March 1997Adjournment Debate Speech on mefloquine in the House of Commons of Jean Corsten MP (Lab). I have interviewed military recipients of mefloquine from the British Army, Dutch Army, Canadian Army and US Army.

3 I come from a farming and military family based in West Berkshire. I have lived in Asia, West Africa (childhood) and East Africa and ran a family farm in Zimbabwe as well as reporting from the region.

4 I was a Sir William Lyons Scholar and technical journalist; I became a geo-political foreign correspondent based in Asia and Africa (where I took mefloquine as medically advised and prescribed). I am a former national press columnist across political, consumer, safety and technical issues. I previously advised a major military charity to Board level.

5 I have worked as consultant professional researcher and published multi-disciplinary technical/science author. I have undertaken science research works for national academic bodies and have previously acted in a non-scientific, strategic advisory capacity to UK academia and advised a DfID project. My case histories have been cited to UK Government and academic level and I received a 2014-2015 active 'Scotland' protocol security clearance to undertake my research works for a major UK academic body. For related security and professional reasons I do not cite that body herein.

6 I am not medically qualified and do not pretend to be. I simply present my research for consideration, acceptance or dismissal.

7 See statement at base for conflict of interest (none declared) and medical declarations.

**2. Executive Summary**

8 This submission document, submits and evidences key facts regarding the safety and effectiveness of mefloquine hydrochloride (as Lariam™ F. Hoffmann-La Roche / Roche Products Ltd), and its prescribing as prophylaxis to military personnel, and with adjunct relevance to linked and cross-cited supporting evidence in other groups.

9 Herein I specifically cite, the seemingly ignored from current discussion, early warnings for mefloquine safety, and respectfully suggest that this evidence is crucial and relevant and within the Committee's terms of reference (military) as to safety and real-life drug compliance and effectiveness in military contexts.

**Key Messages:**

- 10 That mefloquine's manufacturer F. Hoffmann-La Roche, Basel Switzerland, 'Roche', has allegedly known of actual potential neurological and neuropsychiatric adverse effects and events in detail and classification in officially stated sense, and of viable real concerns expressed by a major body since 17 July 1989, *before* mefloquine was licensed in the UK. Note that Roche and WHO were mefloquine development partners with US Army WRAIR, UNDP, and the World Bank

- 11 That potential warnings of adverse effects of neurological /neuropsychiatric classification were extant in early and pre-licensing mefloquine trials and the literature prior to 17 July 1989. Mefloquine was according to Dr N.J White, previously held in reserve due to its known toxicity.

- 12 That from such concerns, the World Health Organisation (WHO), gathered 18 experts including Roche participants and its consultants in June 1989 and of a 17 July 1989 report, as per findings expressed in internal WHO document as: WHO/MAL/89/1054. (Ref 1) as Appendix 1. The said WHO / Roche-participant document, clearly cites specific adverse events issues and advice of the limitation of mefloquine prophylaxis to certain groups – notably with military relevance (Ref 2).

- 13 That the United Nations did formally remove mefloquine from military prophylaxis in Asia (Cambodia) in 1992 due to concerns over neuropsychiatric adverse effects in soldiers. (Ref 3). Of note the UNDP was with the WHO a Roche partner in mefloquine, it is thus likely that such decision was not unknown by such partners. But did the MoD know of the UN's decision?

- 14 Despite such reports and, expanding claims in the literature 1987-1992, the WHO took no decisive action and fellow Swiss partner, the manufacturer Roche, continued to promote mefloquine for prophylaxis and did so in a study of Steffen et al (Ref 4) sponsored by Roche and structured and framed in manners and protocols of the greatest scientific concern .

- 15 That the subsequent, post-prescribing avalanche of mefloquine prophylaxis adverse effects in military and civilian subjects were predictable and identical to earlier concerns, yet dismissed and decried by the drug's manufacturer and its consultants who blamed 'media hype' and patients 'hysteria' (Ref 5).

- 16 Delineation between 'serious' side effects and 'severe' side effects has been at the core of Roche's mefloquine's ratings and claims about the drug. For mefloquine 'Serious' meant death or hospitalisation/disablement. Hallucinations or a psychotic attack was only 'severe'. A 1996 survey

by MASTA found, not, a 1 in 10,000 'serious' side effect, but a 1 in 140 'severe' temporarily disabling side effect rate (however subjective such events were) and with up to 40 % of mefloquine users citing mild effects – some of which might *now* be considered or cited by Roche as 'prodromal' to a more serious event, but may *not* have been so in 1996 (Ref 6) .

- 17 Of 'Fansidar' – Roche previously had to withdraw this antimalarial drug at the centre of adverse effects claims. The circumstances of Roche's mefloquine story, are worryingly similar and, include fatal toxic epidermal necrolysis after mefloquine (Ref 7). Has this all happened before in terms of claims, denials, blames, debates and very slow admissions by Roche?

**3. Main Submission**

18 The submission herein, does offer vital evidence to the Defence Select Committee, specifically as to the publicly unpublished official World Health Organisation (WHO) document WHO/MAL/89/1054, as issued on 17 July 1989 in Geneva Switzerland and described and entitled thus:

19 'WHO/MAL89/1054 entitled *Central Nervous System Reactions related to the Antimalarial Drug, Mefloquine* WHO/ MAL/89/1054 pp 1-19: World Health Organisation Malaria Unit Report of an informal consultation held in Geneva on 17 July 1989. Research and Technical and Intelligence Malaria Action Programme and the Scientific Working Group on the Chemotherapy of Malaria. UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases. Document supplied by Division of Control of Tropical Diseases (Ref 8).

20 That such document does provide key evidence for the assessment of mefloquine safety, tolerability and prescribing advice for and in military personnel.

21 Therefore I seek to respectfully submit and adduce to the Defence Select Committee evidential material as WHO/MAL/89/1054 of 1989 (as referenced) **AT APPENDIX 1 BELOW** and other materials.

**3.1 1989 WHO document WHO/MAL/89/1054 (Roche participating)**

22 I submit that reliable, official-body, evidence of mefloquine adverse side effects of neurological and neuropsychiatric classifications were known and framed in July 1989 by the World Health Organisation (WHO/MAL/89/1054) in partnership with Roche employees including cited Roche experts and latterly cited consultants.

23 Therein, it is evidenced that prescribing limitations for mefloquine prophylaxis in relation to recipients using '**dangerous equipment**' were 'advised' in the said WHO document on 17 July 1989 that being WHO/MAL/89/1054 at: 5.3 page 9. (Ref 9).

24 That such WHO document with Roche participation suggested prescribing limitations relevant to indicated or implied, 'dangerous equipment', must by any rational, test of reasonableness as de facto claim, implicate and include military equipment and its use.

25 I ask that as an act of rigour and integrity, that this information and its basis, should not be left unadduced to, nor unaddressed by the Defence Select Committee under its terms of reference and should be examined and tested to be accepted or dismissed as a claim or as evidence of reference.

26 That verification of such document's existence as cited is via the fact that WHO and Roche issued an 'interim statement' in July 1989 in the *Weekly Epdemiological Record* August 11 1989 (Ref 10), thus acknowledging the existence of the above cited WHO/MAL/89/1054 meeting and internal report. This cross-references for the observer herein, the factual reality and veracity of the above cited as the report WHO/MAL/89/1054. Such was further cited by Roche in 1990 in the *New England Journal of Medicine* by Drs Sturchler, et al of F. Hoffmann-La Roche CH4002 Basel Switzerland, (Ref 11) thus providing

further (2nd) cross-referencing for validity and veracity purposes to standards of 'proof' in research/legal contexts.

**3.2 Participants in WHO/MAL/89/1054**

27 I draw the Defence Select Committee's urgent attention to the cited named list of participants in WHO/MAL/89/1054, page 19 Annex 1. (Ref 12).

- 28 Dr D. Chen Regulatory Affairs and Safety, F. Hoffmann La Roche Ltd. CH-4002 Basel Switzerland

- 29 Dr. L. Strebel, of Roche Drug Safety, Building 52, Room 213 Roche Basel, CH-4002

- 30 Dr R. Steffen (Zurich) who was lead Roche consultant for its Fansidar antimalarial drug, and was undertaking for Roche a key postal survey or study of tourists who were using mefloquine.

- 31 Dr. H.O. Lobel of the US. Centres for Disease Control (CDC) Latterly a close associate in published research of Dr Steffen and who undertook a 1989 Swiss travellers survey and also was cited by Dr Steffen in his Steffen et al mefloquine study, and was a defender (beyond 2000) of mefloquine, including of note, describing side effects claims as: **'**Anecdote and rumour spread by mass hysteria. The scientific data showed us there are no side effects that can be attributed to mefloquine. The long and the short of it is, that studies have shown no difference between mefloquine and a placebo.' *The Washington Post* 10 October 2000

- 32 **British participant**: Cited as Dr. P.A. Phillips-Howard, Department of Epidemiology and Population Sciences London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT. Dr Phillips-Howard subsequently contributed to the mefloquine debate and literature into the 1990s.

33 Dr Phillips-Howard was based at the same hospital where British pro-mefloquine advocate Dr R.H. Behrens (current MoD malaria advisor) has been based during the mefloquine debate and been cited within it, notably as co-author with Dr Steffen (Ref 13) and known to Dr Lobel, and Dr Steffen who were participants in 1989 in the above named WHO/MAL/89/1054 and both were co-founders of the International Society of Travel medicine – a key pro-mefloquiine forum by act of advertisement, publication and spoken presentations.

34 I refer the Committee to statements as so cited as implied by Roche, as Roche's Dr Nichol stated in response to Mr R. Benyon MP at Q59 at oral hearing (Ref 14) – as words 'cumulative' and on-going' about Roche mefloquine knowledge and the company's responses.

35 I cite the document WHO/MAL89/1054 of 17 July 1989 (as at Appendix 1 herein)as evidences that Roche participated in investigation and agreed discussion over just such neurological and neuropsychiatric side effects and therefore allegedly was aware of such potentials <u>long before</u> the drug was released to British military and civilian subjects in the 1990s.

36 It seems that specific knowledge to the point of creating prescribing advice was <u>previously</u> extant, that being so defined on 17 July 1989 in Geneva Switzerland, of the WHO and of issues also raised in 1991 as WHO/MAL/91/1063.

37 Given that in 1992 Roche did formally and publicly in the *New England Journal of Medicine*, (Ref 15) cite its desire that physicians identifying such adverse events, were to report them to the company, and that Roche claimed an 'intensive surveillance', what and where is that vital information from 23 years ago? <u>Why</u> has it taken Roche until recently to significantly update their data, profiles and packet inserts for military prescribers and consumers of their product?

38 Was the MoD aware of such information and the dates of prior knowledge? If not, why not?

**3.3 Previous military warnings over mefloquine**

39 I refer the Committee the following military-related reference which, beyond WHO/MAL89/1054, further challenges the 2015 MoD statement to the BBC 'Lariam Legacy' programme that no major body has ever advised against mefloquine use in a military setting. I refer the Committee to the following evidence:

40 In April 1992, the United Nations in concert with the World Health Organisation removed mefloquine from being recommended as its anti-malarial prophylaxis for UN troops in service in Cambodia.

41 The WHO's Dr A.EG. Rietveld stated that this withdrawal was based mainly on a 'concern about neuropsychiatric side effects'. Such effects were considered of 'particular concern in military personnel.'

42 Cited from a WHO written statement from Dr A.E.G. Rietveld WHO, Geneva, and in the possession of L.F. Cole (copy) (Ref 16)

43 I refer the Committee to the claims of the Dutch troops claiming long term mefloquine related neurological and neuropsychiatric adverse effects circa 1992/1993, and papers by noted pro-mefloquine authors denying linkage to the drug. The Rietveld WHO document referenced above stems from my 1996 interview with the Commanding Officer of the Netherlands Army men so cited and Ms Mieke Sterk MP of the Netherlands Parliament.

44 I refer the Committee to the following references:

45 Dr G.D. Shanks in 'The Rise and Fall of mefloquine in South East Asia' published in 1994 in *Military Medicine* (Ref 17) observed that drug development (of mefloquine) was 'compromised by rapid biological response from the cited parasite'.. and ...by 'military concerns'.

46 January1995 UK Civil Aviation Authority (CAA) statement: 'Mefloquine's side effects profile is significant...This drug is not recommended as a prophylactic.' (Ref 18).

47 Has the Committee ascertained why the French Army refused to accept or prescribe mefloquine?

48 Is the Ministry of Defence aware of the above evidence trail? If not why not?

**3.4 Doctors early warning letters**

49 I refer the Committee to the referenced list of doctors mefloquine adverse effects reports in the literature as mefloquine was being launched and UK licensed. These describe repeated neuropsychiatric events (mainly) after prophylactic dose mefloquine. They are a vital element of precusor evidence to mefloquine safety events. I provide some examples thus:

50 1987 Dr Bernard, *La Presse Medicale 1987; 16:1654-55*

51 1989 Drs Patchen, Campbell and Williams *New England Journal of Medicine 1989*; 321:1415-16;

52 1989, Dr Rouviex *Annals of Internal Medicine;* 1989; 110:577-578

53 1989 Dr Bjorkman *Lancet 1989; 2:865*

54 1990 Dr Folkerts *Neverenarzt 1991; 635.*

55 1990 Dr Ajana *Semaine de Hopitaux 1990 ; 66; 17; 918.*

56 1990 Dr Roder *Therapie* 1990:46; 5,

57 1990/92 Dr Gascon *Medicina Clinica 1990:95:7 & Medicina Clincia: 1993:101:13.*

58 1993 Dr M. Buke; *Lancet* 6 June 1993; 341 (8860): 1605-6.

**3.5 Further WHO concerns 1991**

59 I refer the Committee to the publicly unpublished internal, WHO/MAL91/1063 of 1991 and its views that: 'Mefloquine side effects reports were a cause for concern' and that the WH )should examine all available reports in more detail and develop a surveillance system to obtain further information notably to determine the frequency of neuropsychiatric reactions.(Ref 19).

60 I further refer the Committee to the 1983 WHO Scientific Group on the Chemotherapy of Malaria under the title 'Advances in malaria chemotherapy: (Internal) Report of a WHO scientific group (Ref 20) which categorically states that mefloquine is distributed in tissue compartments and that neuropsychiatric adverse effects need to be investigated.

61 I submit that the Committee may wish to ask, as these classified neuropsychiatric symptoms were identified prior to 1984, and as officially cited in 1989 by WHO/MAL/89/1054 of 1989, and WHO/MAL/98/1063, in 1991, were known, how did the Roche's Steffen study suddenly 'find' that the drug was tolerable and 'serious' reactions were 1 in 10,000?

62 And why were the known neuropsychiatric effects not cited or framed in the much quoted and cited and supposedly defining, Dr Steffen's Roche-sponsored key study of 1990-1992 which claims mefloquine safety and effectiveness? (Ref 21)

**3.6 Roche's key mefloquine '1 in 10,000 'serious' adverse effects Steffen 'study', was it safe science?**

63 Within this Steffen et al, its basis of claim is via self-diagnosis by tourists in filling-in Roche Malpro 1 & Malpro 2 postal questionnaires. Yet Malpro 1 made no mention of the (previously known) potential neuropsychiatric mefloquine effects, and Malpro 2 only asked about depression – not the range of mefloquine symptoms now, finally, deemed 'prodromal' by Roche. Of course self diagnosis of a neuropsychiatric condition is a contradiction in terms. So why did Roche rely on it in their foundation study questionnaire used to promote mefloquine?

64 It is this Steffen et al study (published in *The Lancet*) in 1993 that is the basis of Roche's claims that mefloquine is highly effective and safe with a 1 in 10,000 adverse effects rate.

65 Vital questions were asked in the medical literature of the Roche-Steffen study and its claims, notably the assumptions over the 50 per cent non-response rate of the Steffen study and, its unusual probability rate of 0.01%. I thus refer the Defence Select Committee to the references of Milford et al (Ref 22), and Croft et al (Ref 23) to evidence the above statement concerning the Steffen et al study.

**3.7 Mefloquine, the most effective drug?**

66 I submit to the Committee that mefloquine may not have been as effective as claimed in selected tests and trial groups, and suffers from adverse effects leading to discontinuation in-use and of note in-country, likely to render the patient at risk from malaria, notably falciparum malaria risk. This 'compliance' factor was a long unrealised factor in lower rates of adherence to the drug. Mefloquine resistance was also cited in the literature as early as 1992. A mefloquine dosing regime change was also ordered after question in the literature over steady state protective blood levels of the drug upon departure.

67 Norrbohm et all notably stated in 1999 at Montreal that: "Reported mild side effects to mefloquine prophylaxis have greatly impeded its use in travellers to malaria endemic areas, where mefloquine represents the optimal drug from efficacy point of view."(Ref 24). Other such reports exist.

68 So, cases of malaria may dramatically *increase* if the adverse effects of a drug lead to in-country withdrawal via lower compliance by users due to such side effects. This is a key mefloquine issue and I urge the Committee not to be swayed by marketing led claims based upon the Steffen et al study that created a “only mefloquine works” and “malaria is worse” and “whatever the risks of mefloquine you must take it” assumptions. The medical literature contains many questions of mefloquine's original claims of efficacy and safety.

69 The issue of suspected but causally unproven deaths from mefloquine adverse effects notably as suicides, remains unresolved. Changes by Roche in the USA to mefloquine warnings about 'suicide' were made in 2002. Of note from 1997-2001 the US FDA had tracked 11 suicides and 12 suicides attempts during or after mefloquine use. Roche has made reputed financial settlement with the widow of Charles Perry a White House staff member following his suicide after mefloquine ingestion, but denied liability.

70 Malaria is a dangerous disease and travellers must take the appropriate prophylaxis, providing it is safe, reliable and not subject to very serious adverse effects reports and, compromised effectiveness, with such being denied for years by the manufacturer and blamed upon the media hype or mass hysteria.

**3.8 Fansidar by Roche**

71 Is the Defence Select Committee aware that a previous Roche antimalarial drug named **'Fansidar'** was also at the centre of several years debate prior to withdrawal. Doctors have stated in the literature that the mefloquine story may create similar consequences, as cited notably Dr Ian Perry in the *BMJ* on 24th June 1996 (Ref), and Drs McBride, Lawrence, Pape and Reid, in *The Lancet* on 11 Jan 1997 (Ref 34).

**3.9 Mefloquine and 'mood changes' contraindication**

72 According to Roche Products UK on 2nd February 1996, in its press release statements, you should not take Lariam if you had a pre-existing condition that included a 'history of **mood changes,** fits or psychiatric illness.' (Ref 27). Given recent changes and references by Roche in the data, to 'generalised anxiety disorder' (a familiar battle or conflict zone issue) as a melfoquine contradiction, can we expect 'mood changes' to soon be added? As with other changes by Roche, it has taken them decades to enact

**4. Concluding remarks**

73 The issue is, what happened, why, when, and were precursor events, warnings, actions, declarations and outcomes, assessed, declared and actioned in manners of sufficient rigour, transparency, responsibility, and of adequate product warning, timings and structural and ethical integrity?

74 Have advisory and prescribing authorities such as the UK Malaria Advisory Council really been vigilant? Has the MoD simply gone along with an assumed and deeply flawed perceived wisdom?

75 Why have the earlier concerns and officially framed 1980s and 1990s warnings over adverse effects, their classifications and advice of prescribing limitation been apparently left undeclared or uncited? As no chemical changes to mefloquine's formula were known to be made by Roche after launch, can we wonder if the 'change' in mefloquine's toxicity risk, was created *statistically* (Steffen et al) rather than chemically?

76 Continued support of the use of this drug may have very significant personal health implications for recipients, no matter how great the threat of malaria and falciparum malaria in-country/in-theatre.

77 In the UK One (1) mefloquine fatality by toxic epidermal necrolysis is admitted. Other fatal outcomes from suicide, cardiac, brain and other events may be extant. The problem is, we simply do not know and have not been told. Are these risks that should ever have been accepted, or ignored?

78 The issue of medical care costs for mefloquine reactees (currently borne by the NHS and State) is a

'live' issue for military and civilian claimants, as is that of compensation..Where are Roche's proposals to address its responsibilities as a global corporate citizen? Will, like Fansidar, the drug be quietly withdrawn with no liabilities admitted

79 I respectfully ask that the Defence Select Committee accepts this submission and its referenced content into the Committee's process and for further information on the mefloquine safety and efficacy issues to be submitted or heard, in order that an accurate history of mefloquine for the military can be known and adjudged prior to any finding or view being made.

*3 December 2015*

**5. Author's declaration and conflict of interest statement**

80 I declare that I have no financial, or employment links to any legal or pharmaceutical body and that I am not funded in mefloquine research by anyone.

81 I have always openly declared that I took advised and prescribed mefloquine as prophylaxis on three occasions in the 1990s and was hospitalised on the third occasion in 1994. My use of prescribed mefloquine and my claimed side effects have been medically and legally verified by independent experts. I continue to suffer some degree of physical and neurological post-mefloquine effects.

82 I have been allegedly subject to potentially defamatory claims and comments about me by representatives of Roche to others. I expect Roche to once again attempt to undermine my reputation and claims, but I believe my claims and researches (and those of others) are now validated and vindicated by Roche's mefloquine admissions and data changes.

**References:**


Ref 1 WHO/MAL89/1054 *Central Nervous System Reactions related to the Antimalarial Drug, Mefloquine* pp 1-19:
Ref 2 WHO/MAL/89/1054 at: 5.3 page 9.
Ref 3 Rietveld Dr A.E.G.WHO, Geneva. Correspondence to ZEMBLA TV Netherlands and in the possession of L.F. Cole (copy).
Ref 4 Steffen R, Fuchs E, Schildeknecht J, Naef U, Schlagenhauf P, et al Mefloquine compared with other antimalarial chemoprohylactic regimens in tourists visiting East Africa. *Lancet* 1993:341:1299-303
Ref 5 Holladay N. MD Roche Products UK Ltd. *Nursing Times* 12 June 1996
Ref 6 Barrett et al. *BMJ*; 1996 Aug 31;313:7056:525-8
Ref 7 McBride SR, Lawrence CM, Pape SA, Reid CA, Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, UK.*Lancet* 1997 349 (9045) 101.
Ref 8 WHO/MAL89/1054 *Central Nervous System Reactions related to the Antimalarial Drug, Mefloquine* WHO/ MAL/89/1054 pp 1-19
Ref 9 WHO/MAL/89/1054 at: 5.3 page 9 'Guidelines'.
Ref 10 WHO Interim Statement *Weekly Epdemiological Record* Vol 64 August 11,1989:247-8.
Ref 11 Drs Sturchler, et al of F. Hoffmann-La Roche CH4002 Basel Switzerland, *NEJM*, Vol 322: No24:1752-1753. 14 June 1990.
Ref 13 Behrens, R. Keystone, J. Steffen, R. Malaria Chemoprophylaxis. WHO *International Travel & Health*: 7 Feb 2002.
Ref 14 Mr R. Benyon MP at Q59 at oral hearing HC Defence Select Committee 10 November 2015, House of Commons London.
Ref 15 Drs Sturchler, et al of F. Hoffmann-La Roche CH4002 Basel Switzerland. *NEJM* Vol 322: No24, 1752-1753.14 June 1990.
Ref 16 Rietveld Dr A.E.G.WHO, Geneva. Correspondence to Zembla TV and in the possession of L.F. Cole (copy).
Ref 17 Shanks. G.D. *Military Medicine* 1994 Apr;159(4):275-281.
Ref 18 UK Civil Aviation Authority (CAA);AIC2/11995.12 January 1995

Ref 19 WHO/MAL91/1063, WHO: 1991. Geneva .
Ref 20 WHO Technical Report Series Ref: 711 (1).1 January 1984.Geneva
Ref 21 Steffen R, Fuchs E, Schildeknecht J, Naef U, Schlagenhauf P, et al Mefloquine compared with other antimalarial chemoprohylactic regimens in tourists visiting East Africa. *Lancet* 1993:341:1299-303.
Ref 22 Milford et al. *Lancet*; 1993: 342;8869.
Ref 23 Croft AM, BMJ;318: 1998 1139-40
Ref 24 Norrbohm, O. Vepsalainen, S. Bjorkman ,A. Presentation on mefloquine side effects at 6th Annual Conference of the ISTM Montreal 6 June 1999.
Ref 25 Perry I. *British Medical Journal*1995;310(6995):1673 24th June 1995
Ref 26 McBride SR, Lawrence CM, Pape SA, Reid CA, Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, UK. *Lancet* 1997 349 (9045) 101.
Ref 27 Roche Products UK of 2nd February 1996 Official Output)
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