Defence Committee

Oral evidence: An acceptable risk? The use of Lariam for military personnel, HC 567

Tuesday 10 November 2015

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Written evidence from witnesses:

- Roche Products Limited

Watch the meeting – An acceptable risk? The use of Lariam for military personnel

Members present: Dr Julian Lewis (Chair); Richard Benyon; Douglas Chapman; Johnny Mercer; Mrs Madeleine Moon; Jim Shannon; Ruth Smeeth; Phil Wilson

Questions 1–91

Witness[es]: **Dr Frances Nichol**, Head of Drug Safety Quality, and **Mike Kindell**, Lead, Established Products, Roche, gave evidence.

Q1 **Chair:** Welcome to the first session of our inquiry into whether the use of the anti-malarial drug Lariam for service personnel is an acceptable risk. I would like to ask our two witnesses to introduce themselves for the purposes of the record.

Dr Nichol: Good morning. My name is Dr Frances Nichol. I work for Roche Products Ltd, where I am currently the head of UK drug safety. I am a GP by background, and I continue to be a licensed GMC physician.

Mike Kindell: Hello, Committee. My name is Mike Kindell. I lead the established products franchise for Roche in the UK. I am responsible for all aspects relating to the commercial supply of Lariam.

Chair: Thank you very much indeed. We will start our questions with Phil Wilson.

Q2 **Phil Wilson:** Good morning. Can you explain how Lariam works as a defence against malaria?

Dr Nichol: In the context of malaria, Lariam is licensed for both prophylaxis—for preventive use—and the treatment of malaria. Malaria itself, obviously, is a condition that we do not see much of in the UK, but it is a global endemic problem. The figures take a little while to grasp, but the latest figures from the World Health Organisation tell us that there were 214 million cases of malaria last year, of which 500,000 resulted in death. That is what people are receiving prophylactic medication for—against that risk when they travel to malarious areas.

Lariam, as I have said, is indicated for both prophylaxis and treatment, and it works—I will need to explain a little more about what happens when someone contracts malaria, to explain better how it works, if that would be useful. Malaria is spread by a mosquito carrying a parasite called plasmodium. There are lots of different types of parasite, but essentially, when a mosquito that is infected with the plasmodium parasite bites a human, that is when the parasite is transferred. In a non-immune person, the virus first makes its way to the liver, where it starts to replicate. Following replication of the parasite in the liver, it multiplies thousands of times over, and then the parasite is released into the bloodstream, where it hides in the red blood cells. The symptoms of malaria are typically first displayed when the parasite is released into the bloodstream, which is where Lariam works. It works on inhibiting the replication of the parasite in the red cells as it enters that phase of infection.

Typically, the symptoms of malaria at that stage are fever, chills and what is typically described as a general malaise, which can be confused with flu-like symptoms. It is really important that people recognise the symptoms early if they have not had treatment so they can get treatment quickly. Certain forms of malaria can lead rapidly to severe consequences for the patient, which range from anaemia, renal failure—kidney failure and, ultimately, death. Lariam works on the phase when the virus enters the red blood cells and stops it from replicating. Does that help?

Q3 **Phil Wilson:** It does. How does Lariam differ from the other anti-malarial drugs that are available? Are different anti-malarial drugs more effective in different settings and geographies? What are the general conditions of use and the side effects?

Dr Nichol: Okay. There's a lot of information in that question. In terms of other drugs that are available, I need to be careful because I have to be very factual. Obviously, I work for Roche so I will talk about Lariam and less so about some of the other drugs that exist because I don't have detailed knowledge of them, but information is available from the summary of the prescribing characteristics.

There is Lariam, and there is another drug called Malarone, which is a combination of two products called atovaquone and proguanil. Chloroquine is one of the older, longer-standing treatments available, and there are areas across the globe where there is widespread chloroquine resistance. When the guidance is put together for which drugs should be prescribed in certain areas, the World Health Organisation takes into account what is known about the resistance to certain drugs in that area. Chloroquine resistance is a widespread issue, which means that the drugs left as an option for prophylactic treatment are Lariam, Malarone and doxycycline, which is another product.

To come back to your question about differences in dosing, which I think is what you were alluding to—

Q4 **Phil Wilson:** Is it effective in different regions? Can you use it anywhere in the world, or are there specific regions in the world where it is more effective?

Dr Nichol: There are differences. That guidance comes from the WHO, which monitors the resistance patterns on an ongoing basis and releases updates on an annual programme. There is good susceptibility to Lariam in most areas. We know there is Lariam resistance in some areas of south-east Asia. The three drugs I mentioned that are currently used for

prophylaxis, looking at the guidance that is available from the committee that produced this information, are the three options for chloroquine-resistant malaria strains. It is then down to the prescriber to make a decision based on other factors. Would it be useful for me to come back to the prescribing differences?

Phil Wilson: Yes.

Dr Nichol: Lariam, Malarone and doxycycline are prescription-only medications. Therefore, a physician would be expected to assess the risk of prescribing those drugs at the time of seeing the patient, taking into account the risks that the patient is carrying and, as you alluded to, the risks of the area they are going to, how long they are going to be visiting the area and other medications they are on.

Lariam needs to be prescribed in accordance with our SPC, which states that it should be first prescribed 10 days before going on the trip, and then it is prescribed weekly. So the expectation is that the patient would have had two doses of Lariam, one 10 days and another three days before leaving. In the SPC, it states that the purpose of that is to ensure that the patient can adhere to the medication, that they do not have side effects before they leave the country and go on their trip. Then they are expected to take it for a minimum of four weeks on a once weekly basis.

The other medications are different in that they all require to be taken on a daily basis, but they are also different because they do not need to be taken from a period of 10 days in advance; they can be taken closer to the time of leaving. The other ones I think basically say 48 hours before entering the malarious area and they need to be taken for a week after leaving the malarious area.

Q5 **Phil Wilson:** Would you like to add anything?

Mike Kindell: No, I think that covers it very well.

Q6 **Johnny Mercer:** Thank you for that; that is really interesting. How long have you specified that an individual risk assessment should be done for each individual who takes this drug? Was that from the beginning, or did you bring that in in 1996 when the report came out?

Dr Nichol: Okay. Because the legal classification of this product is prescription-only medication, the requirement for a prescribing physician is that they are making that assessment—

Q7 **Johnny Mercer:** Okay. I see what you mean. So that is the process of prescribing. What view would you take of an organisation that essentially did mass distribution? If a group going to an area were told, "There you go, there are your anti-malarials, crack on," would that be in line with the very clear manufacturer's guidelines?

Dr Nichol: In the first part of your question you alluded to the additional, heightened information, which is the information that has been passed around to you in the risk minimisation plan. As more safety data are accumulated for a product—this happens for any product—the emergence of rarer adverse events becomes evident.

Q8 Johnny Mercer: I accept that. The premise of my question is: if there is an organisation that does not do individual risk assessments, is that, or is that not, clearly outside the manufacturer's guidelines?

Dr Nichol: The expectation would be that an individual risk assessment is done by prescribers at the time.

Q9 Johnny Mercer: Okay. That is the expectation, but is that outside your guidelines—yes or no? You have your very clear guidelines. Is that outside or inside?

Dr Nichol: The regulations for prescribing of course are not set by Roche, but a physician, in prescribing, maintains their own conduct under the terms of the GMC.

Q10 Johnny Mercer: When you push out the drug, you have your manufacturer's guidelines and within that you say that it should be prescribed after an assessment. So if an organisation goes outside that, surely they are using the drug outside the guidelines that you stated as the manufacturer of that drug.

Dr Nichol: Yes, the guidelines do say an individual risk assessment should be done, and in the material that we have circulated there is a checklist that the physicians are supposed to go through with each individual—

Q11 Johnny Mercer: Absolutely, and they go through that in detail. But, if that is not done, they are using that outside the guidelines that you, as manufacturers, have laid down—correct?

Dr Nichol: Outside of the terms of the summary of product characteristics.

Q12 Johnny Mercer: Is that correct—yes?

Dr Nichol: Yes.

Q13 Johnny Mercer: And, as I understand it, that checklist has been in place as more and more evidence has come forward.

Dr Nichol: That is correct.

Q14 Johnny Mercer: But, just to be really clear, if they use it outside of those guidelines, in mass distribution, not as a result of an individual check, that is outside the guidelines that you specifically put down as any drug manufacturer does when they release a drug to the market?

Dr Nichol: It is not that it is a guideline; it is the summary of product characteristics, and that is available for all products. This is a required document that the physician should be familiar with.

Q15 Chair: Can I come in for a moment? Can I be a little bit clearer? There seems to be a problem with terminology. The point that Mr Mercer is making is that you make a recommendation as to an assessment that ought to be made in respect of each individual who is going to be given this medication. All he is asking you—this is fairly straightforward—is if that individual assessment is not made, whether the organisation that hands out that drug indiscriminately and en masse is not following your recommendation.

I do not want to quibble about whether it is guidelines or anything else. You are recommending a procedure that should be followed and this is surely a fairly straightforward question, deserving a straightforward answer. If your recommendation is not followed, the organisation that is issuing the drugs en masse, without the individual assessment, is operating in contravention of your recommendation. Surely, that has to be true?

Dr Nichol: Yes, that is true, but the point I am trying to make is that, because of the legal classification of the drug as being prescription-only medication, the prescribing decision sits with the physician. So the expectation would be that a physician sees every individual prior to prescribing any drug that sits under the legal classification.

Q16 Chair: Yes, and if that legal expectation is not fulfilled, the organisation that is not fulfilling that expectation is falling short, is it not?

Dr Nichol: Yes, I would agree.

Chair: Thank you. Jim Shannon.

Q17 Jim Shannon: To follow on from what Mr Mercer said, the Advisory Committee on Malaria Prevention guidance refers to a stringent risk assessment. What do you feel should be in that risk assessment?

Dr Nichol: The documentation that you have in front of you refers to that. There is a tear-out pack in the back of the box and it talks through the consultation. The standard approach of any prescribing physician would be to discuss with the patient their existing risks: the medications they are on, their past medical history, if they have been to malarious areas before and had exposure to drugs before.

I should open my document. You would ask as well about the area they are going to, the duration of travel and their understanding of the risks of each of the products that you would be discussing with them, the options available for them to take and asking their preference for taking a tablet on a daily or weekly basis.

I am a GP by background though I have to say I have not seen patients for 15 years, but the expectation would be that you have a detailed consultation in terms of looking at the patient's existing medical history, asking them, talking through the risks of any of the products that you would be considering prescribing, and going through the checklist, which has now been provided by Roche.

Q18 Jim Shannon: You referred earlier to the first taking of the drug being 10 days before and then three days before. I think you said that in your response to earlier questions. The fact is that whenever service personnel are going to Sierra Leone, let's say, they are probably told maybe three of four days before they deploy. There is a high level of stress at that time and an expectation of uncertainty. At that time of heightened stress, what consideration is given to individuals when it comes to taking the drugs?

Another point is that when you are going away to Sierra Leone, Afghanistan or wherever it may be, you know what you want: you probably want a couple of beers with the boys. Therefore, your mind might not necessarily be focused on the drugs you are taking. It would be the farewell party and minds on other things. What consideration is given to that

sort of thing when it comes to taking the drugs and the effects that has on a person, at a very heightened stressful time?

Dr Nichol: You make a valid point. The SPC mandates that the drug is taken 10 days before and a second dose three days before, so they should have two doses before going. Somebody leaving at short notice to go to a malarious area would not have had the opportunity to do that. In that case, we would need to look at alternative drugs that can be taken within a shorter period of time and become protective before going to that malarious area. You asked about the considerations taken at the time of going out. I have no experience of how things work in the MoD and I do not feel placed to comment.

Q19 Jim Shannon: I think we are coming back to Mr Mercer's original question. How do we better co-ordinate what happens between the MoD and yourselves on allocating, prescribing and taking the drugs? There is clearly every potential for a fall-down in that process, which concerns us. You referred to the patient alert card, or the prescriber checklist, in your written evidence. Does that correspond with the risk assessment?

Dr Nichol: Yes. I should have said that, at the same time as the prescriber goes through the risk assessment, this also documents that they have given the patient alert card to the patient—this little one here is the patient alert card that is expected to be given to the patient. When the patient receives their packet of Lariam, they will have a patient information leaflet detailed in that, too.

Coming back to the tone of your question, as the manufacturer, obviously we take our responsibilities very seriously in terms of collecting the safety data and making the information available to prescribers not only in the MoD but globally. We actively play no role in the prescribing decision, so these packs are sent out on an ongoing basis, and they are available when anybody looks up the information in the medicines guide on the internet. It is not something that they will be requesting there and then at the time; they wouldn't have access to it in advance.

Q20 Chair: We appreciate that you are not responsible for the way in which the Army prescribes this medication but, in light of the public concern and publicity about cases where there have been severe and sometimes irreversible side effects apparently caused by it, have you had occasion to write to the Ministry of Defence stressing to them the precautions that they ought to be taking, specifically with regard to individual assessments, before prescribing this en masse?

Mike Kindell: We treat all general practitioners in exactly the same way on this, and we have written to all general practitioners with the risk management materials. We haven't actually looked at the military in a different way. Having said that, we have just started to get in touch with them after the most recent article came out in the press.

Q21 Chair: I am a little surprised about that. Obviously, you give your routine advice and recommendations to everyone, but concern about Lariam has been bubbling along for a very long time indeed. Are you telling me that you haven't on any occasion contacted the Ministry of Defence to emphasise to them the importance of this individual assessment in the case of prescribing the drug to a large number of people simultaneously?

Mike Kindell: We haven't contacted the Ministry of Defence as a body, but we will have contacted all the general practitioners who work within the Ministry of Defence.

Chair: I see.

Dr Nichol: The risk management plan materials are updated on an annual basis, so a reminder letter goes out on an annual basis via our warehouse that distributes the product to all the barracks and to where the prescribers are. In addition, whenever a report of an adverse event comes to us from anyone, including from the military, my group has an obligation to follow up that report. Be that report directly from a patient, from a journalist or from the media, we follow up on those reports whenever they come in.

Q22 Chair: But you haven't had any specific meetings with the Ministry of Defence to discuss the use of Lariam by the armed forces?

Dr Nichol: We have reached out to the MoD, and we haven't yet had a meeting.

Q23 Jim Shannon: The background information that we have indicates that the MoD stated that the summary of product characteristics has been updated on 20 occasions since 1999. That indicates to me and the Committee that there were some concerns about safety that gave reason to update Lariam. What changes have been made on those 20 occasions in the 16 years since 1999? They have been made for a purpose. What is that purpose?

Dr Nichol: I don't think it is 20. I would need to double check the detail. Lariam has been around for 30 years. The Lariam SPC, as is true for all products, is updated on a regular basis.

Q24 Jim Shannon: The Ministry of Defence states that it was updated 20 times so I presume that that is factually correct. If it is, we are trying to figure out the reasoning.

Dr Nichol: We need to check but I can certainly tell you the gist of why things are updated. When any product comes to market it does so with a limited amount of data. Then the number of the population who are prescribed that product increases. The expectation is that adverse events are reported. That can be done through clinical trials, non-interventional studies and real-life prescribing. From a global perspective, all of those adverse events come to our individual affiliates and go to our global safety database. That information is collated on a regular basis. The safety science team will do a signal detection—we look at the data coming in from each individual case and update the information depending on what comes in.

Q25 Jim Shannon: Sorry to interrupt. You refer to adverse responses to Lariam. I want to ask you what those responses have been so we have some understanding. If it was thought that it was necessary to change the Lariam, and that was done, we need to know why that happened and what changes they felt were necessary. You talk generically but you do not go into specifics.

Dr Nichol: Yes. I can do. Sorry, I was just giving some background. Apologies if that was not helpful. The Lariam SPC has been updated primarily to pull out the preponderance of what we have classified as neuropsychiatric effects including a combination of common side effects such as dizziness, nausea, and bad dreams. That has been added in as it has become evident that that experience is common. It tends to be mild and to settle. The most

important things that have been called out are the more serious elements of the neuropsychiatric effects. There has been shown to be an increased risk of depression, psychosis, hallucinations and terrors, which are disturbing and debilitating for people. We have called that out in the information that you have, to the extent of indicating in the label that anybody who has a history of or currently has depression or anxiety should not be prescribed the product, which is key for the individual risk assessment that you referred to earlier. My colleague has just passed me a note that says there were 18 changes since 2005. Those were mostly minor, except the change that I referred to in 2013 when the black box to indicate the neuropsychiatric adverse events was added.

Q26 **Mrs Moon:** When were the patient alert cards and the checklist for the prescription of Lariam issued?

Dr Nichol: These, I believe, we issued for the first time in 2013 to correlate with the update on the label.

Q27 **Mrs Moon:** So prior to 2013, what would individual patients have been given and what checklist would the prescribing officer have to follow?

Dr Nichol: The checklist didn't exist prior to 2013 in this way. The patients would have been given the information available in the patient information leaflet in the box.

Q28 **Mrs Moon:** You mean the piece of paper that you pull out of the box.

Dr Nichol: Yes, that's right. This relates to new requirements in European law and a new process called the risk minimisation plan.

Q29 **Mrs Moon:** Thank you. You are clear in your advice that Lariam should not be taken if there is an "active or a history of psychiatric disturbances such as depression, anxiety disorders, schizophrenia or other psychiatric disorders".

Dr Nichol: Should not be taken.

Q30 **Mrs Moon:** Yes. So what advice do you give on how to test against those criteria?

Dr Nichol: We don't give specific advice other than to take a full detailed history because this is a prescription-only medication. It is not an over-the-counter drug. It is not a drug that is being given out by pharmacists. It is being done in a one-on-one setting with qualified physicians who know how to ask and illicit the appropriate responses from their patients in an individual setting.

Q31 **Mrs Moon:** When did you issue the specific advice that it should not be taken if there is a history of or an active psychiatric disturbance?

Dr Nichol: As you said, there have been a lot of changes. The specific wording to which you are referring came in in 2013. Prior to that, the label already said "not to be issued for active depression". I believe that that label came into place in 2009.

Q32 **Mrs Moon:** So from 2009 to 2013 the advice related only to active depression as a contraindication.

Dr Nichol: I believe so, but I would want to confirm that detail to be absolutely sure.

Q33 Mrs Moon: That would be fine. The Committee would be more than happy if you could give us a timeline of the advice that was given to prescribing practitioners as to the contraindications for the use of Lariam during its history.

Dr Nichol: Absolutely, we can put that together.

Q34 Mrs Moon: It would be extremely helpful to see any guidance that was issued to both the prescribing physician and patient receiving it.

Dr Nichol: *indicated assent*.

Q35 Mrs Moon: There is a separate issue as to whether or not, within the Ministry of Defence, the patient or individual prescribed the medication would ever get the leaflet. That is part of our concern.

Do you have any records of how many adverse reports Roche received from the Ministry of Defence or its prescribing physicians?

Dr Nichol: We do have records. As I have indicated, all the adverse events that occur from UK prescriptions would come to my group, and the same database is replicated across all the Roche subsidiaries. In terms of issuing that data, I have looked at it and I can see that there are reports coming from the military. We also have reports in which reference is made to the military—where we have picked up reports from the literature and from journalists' reports as well. I do not have an absolute number to hand. Again, I would want to be very clear if it's the number that you want—if you would like an absolute number of all the reports.

Q36 Mrs Moon: Thank you. It would also be helpful if we had it broken down by year.

Dr Nichol: Yes, absolutely.

Q37 Mrs Moon: Thank you very much. Given the concerns that there have been about this drug for some time, what research have you undertaken on the long-term negative effects of using it? Not just the immediate impact, but over the longer term.

Dr Nichol: A lot of research in ongoing globally. As we have indicated, Lariam is prescribed to a large population of patients all around the world—those patients who are at highest risk, living in endemic areas. There has been significant research, and most of the research that is currently ongoing relates to women of child-bearing age and pregnant women. It also relates to using the drug with HIV and other medications. Significant research is also available from database researches—from the GP UK database—looking at the incidence of new cases of depression versus the other available drugs. So there is a lot of research.

Q38 Mrs Moon: Is this research undertaken by Roche, or by other organisations?

Dr Nichol: A mixture of both, in that some of it is supported by Roche. Most of the research that Roche supports has been in relation to tropical diseases in and around the African area, which is where the majority of the product is used.

Q39 Mrs Moon: Can we have a copy of the research that you are talking about, broken down by that which is funded and undertaken by Roche and that from other organisations?

Dr Nichol: *indicated assent*.

Q40 Mrs Moon: Can I take you back to the amazing work done by *The Independent* in highlighting the problem here? In October 2013, Roche wrote to doctors in the UK warning of instances of "hallucinations, psychosis, suicide, suicidal thoughts and self-endangering behaviour" and that Lariam "may induce potentially serious neuropsychiatric disorders". Does that refer to individuals with an existing history or does it warn that Lariam can trigger an unforeseen episode? You previously said that there are risks if someone has had depression, anxiety disorders, schizophrenia and so on, but was the 2013 guidance about that group with pre-existing conditions or was it about triggering them in individuals?

Dr Nichol: I believe it relates to both. Obviously, someone who has had a past history is, by nature, irrespective of the drug they are on, at increased risk of having a recurrent episode, but certainly the guidance—let me get this right. The evidence as it was pulled together would have captured information based on those who have had events, and based on the fact that they have had events, they should not be prescribed the drug at any point.

Q41 Mrs Moon: Sorry, can I get this clear in my head? When you say that individuals should not be prescribed Lariam, are you talking about those with pre-existing conditions?

Dr Nichol: They should not be prescribed it, yes.

Q42 Mrs Moon: So were you also alerting that there should be observation and monitoring of those with no pre-existing conditions, since it could trigger hallucinations, psychosis, suicide, suicidal thoughts and so on?

Dr Nichol: It says in the information that the patient should be informed of these increased risks with Lariam, and that should they become aware of any of those features—a change in mood or in personality—they are advised to immediately contact the doctor and stop taking it. That is called out in the guidance as well.

Q43 Mrs Moon: So you were saying that it could trigger these events.

Dr Nichol: It is associated with an increased risk of neuropsychiatric events. That is correct.

Q44 Mrs Moon: For those who previously had no experience of them—no previous history of depression, psychosis, psychiatric disturbances, anxiety disorders, schizophrenia or other psychiatric disorders.

Dr Nichol: Compared with the other drug that is available—looking at the study that was referred to in our summary of product characteristics that compares Lariam with the other most commonly prescribed anti-malarial, Malarone, which we call out because it is the most obvious choice that doctors would be making, that study states that the risk of the conditions grouped together under the term "neuropsychiatric event" is 29% versus 14% for the Malarone drug. So it is saying that there is an increased risk of these events. Patients who have had a psychiatric history should not be receiving the drug, and patients who are prescribed the drug because it is the appropriate drug for them based on all the other discussions that have taken place should be aware that there is an increased risk of neuropsychiatric events with that product, versus the other one that exists, and they should act if they start to experience anything indicative of that.

Q45 Mrs Moon: What research triggered that alert in 2013? Could you highlight that for us when you send us the list of research? That would be helpful.

Dr Nichol: Yes.

Q46 Chair: Would it be fair to say that your position is that this drug, handled responsibly, can be and is a life-saver but must be tailored to individual circumstances before it is prescribed?

Dr Nichol: I think that is a very accurate way of representing how Lariam is used in terms of being a life-saver across the world, but yes, it must be handled appropriately.

Mike Kindell: And that emphasises the importance of the consultation with each patient.

Q47 Chair: And therefore, while reiterating that you are not responsible for the way in which the MoD and the medical staff within the MoD prescribe your product, does this not raise an obvious problem when the person who is prescribed the drug may have some history of psychiatric illness or depression, for example, but may feel unable to disclose that to the person proposing to prescribe Lariam to them for fear of damaging their career?

Mike Kindell: I would think that is certainly a very much hypothetical risk, yes.

Q48 Chair: More than just hypothetical.

Mike Kindell: It is a risk, yes.

Q49 Chair: So, in other words, you are a soldier and you know that you have had some episode or some anxieties in the past, but you really would feel pretty inhibited before saying to the Medical Officer in your regiment, "I really shouldn't take this stuff, because it could have a very serious effect on me."

Mike Kindell: I think that is a fair statement.

Chair: Thank you.

Q50 Douglas Chapman: Good afternoon. The written evidence you submitted sets out a number of cautions and conditions for use of Lariam. At any stage, has your advice to the user distinguished between civilian and military use? I know that you have produced this helpful card, but have you had anything purely for a military setting?

Dr Nichol: No, there has not been any distinction.

Q51 Douglas Chapman: You are a huge international company with a reputation that goes before you and I suspect that you want to do everything to try to protect that reputation. I understand that you are not the user intermediary for this particular drug, but, in terms of your previous answer and given some of the concern around the use or Lariam, does it not concern you that you have not been able to secure a meeting with the MoD at least to talk through what the concerns might be, how they can be resolved and how we can make our serving personnel safer in the field after they return? Is that not something that should have been at the top of your list? Should the MoD not have been dragged kicking and screaming to the table to make sure that their personnel were protected in the way that a normal employee would be protected?

Mike Kindell: I think, as I said, historically we have treated all GPs the same, so we have treated GPs who work in the MoD the same as any other GPs and given them all the information. But, if there is a way that we can work with the MoD to improve the distribution of the risk management material, we are willing to do so.

Q52 Douglas Chapman: You will be aware of the work of Dr Remington Nevin, who has argued that Lariam exposes military staff to "certain unique risks not encountered with most civilian use of the drug." I notice in your evidence that 15% of the distribution of Lariam is to the military, so by my calculation 85% of it is used for other purposes. You also mentioned some of the feedback you were getting from MOs in the military and so on. Do you get the same level of feedback from GPs or anyone else who prescribes this drug?

Dr Nichol: I know I have not given out the absolute numbers yet, but in terms of the rough percentages of adverse events for Lariam that come into the UK database, which is a small section of the total database, I believe that last year approximately 90% of the AEs—sorry, adverse events—came from civilian cases of Lariam and approximately 10% of what we have coming into the drugs safety database came from military-associated cases.

Q53 Douglas Chapman: Have you made any further specific assessment of the use of Lariam by the MoD in other military situations? Have you conducted any other specific assessments on the use of Lariam in military situations?

Mike Kindell: Worldwide?

Douglas Chapman: Yes, but specifically with the MoD in the UK.

Mike Kindell: Not really, no. We do supply about 15,000 units of Lariam to the MoD annually. We supply about 100,000 in total, so about 15%-odd of our sales go to the MoD. Looking at that data, it is dangerous to conflate both the numbers, because clearly in the MoD you are more likely to go into high-risk malaria areas for long periods of time, whereas in the civilian population it is likely to be much shorter than that.

Q54 Ruth Smeeth: Good afternoon. Following on from Mr Chapman's questions, Dr Nevin states that the US special operations command has issued a formal order prohibiting the use of mefloquine among its personnel, because it acknowledged that consideration must be given of the impact of the medication on the population. Were you consulted on that decision, and did that decision influence your advice on the drug, which changed in 2013?

Mike Kindell: No, we were not consulted on that decision. In the US Lariam went off patent about 2004, I believe. Lariam is no longer sold by Roche in the States. The reason for that is that there is a number of generic entries in the market, so they would probably have consultation with the generic companies; they did not have consultation with Roche.

Q55 Ruth Smeeth: On that basis, given that they did not consult, have any armed forces anywhere in the world consulted with you or put similar restrictions in place on the use of Lariam?

Mike Kindell: Not that I am aware of. Certainly, with my consultation with other affiliates, that communication has not happened.

Q56 Ruth Smeeth: So the only public concerns would be in America and here for military use?

Mike Kindell: To my knowledge. All the militaries will have different protocols. As Frances alluded to before, there is a number of different products you can use for the prophylactic treatment of malaria. Different militaries would put different priorities on different medicines.

Q57 Johnny Mercer: Sorry, Mr Kindell, are you unaware of the feeling and mindset in Australia towards this drug within the Australian military? You say you have not had representations from anyone outside the US or UK, but there is quite a significant body of evidence in Australia. Has that not come across?

Mike Kindell: Sorry, I was not aware of the Australian situation.

Q58 Chair: Basically, your case is that when it is no longer a question of your own firm selling this drug in other countries, obviously there is no reason why you would be up to speed on what these other countries are doing. Is that what you are saying to us?

Mike Kindell: We sell to a wholesaler, generally speaking, and the wholesaler sells the product on. In the UK we can understand, because we are very close to it, so that is why we have been able to evaluate exactly what we sell to the MoD. It is a little bit more difficult in other countries. I do believe the actual use of Lariam in other countries for the military is much lower than in the UK.

Q59 Richard Benyon: You are looking at somebody who has had malaria, a few years later took Lariam and had an adverse effect from it. I was never given one of these cards. It was probably prior to that; it was the second part of 2013, which is when I think you said it came in. I would not have said that I was somebody who would have flagged up any of those concerns, although I think feelings of mistrust towards others probably precludes all Members of Parliament.

Are you aware that people who live and work in malarial areas in Africa are amazed that this drug is still prescribed as a popular prevention against malaria, particularly those in the tourist industry, who pretty regularly have to deal with the adverse side effects of people suffering neurological conditions as a result of taking this drug?

Dr Nichol: Obviously, the information that has become available is based on the cumulative use of the product. It is not just independently assessed by Roche as the manufacturer, but goes through regulatory approval as well. On an ongoing basis we are providing information to the regulator agencies that license the drug. It is in conjunction with the discussion in the UK with the MHRA that we have modified the label, because you are absolutely right that there is an increased risk of these events. That is why the benefit-risk ratio—the balance of risk to the benefit of taking the drug—is still believed to be valuable and important in this global endemic, if it is prescribed to the right people, so that would apply globally as well. That is why the information has been added. The drug is still believed to have an advantageous position and is important in having the choice of prescribing because, as was said, there are resistance areas and there are other indications that doctors in any parts of the world would have to take into consideration when

prescribing a drug to a patient. Obviously, the drug will not do anything if it is not taken so the patient needs to be able to tolerate it.

Q60 Richard Benyon: In your written evidence you state that adverse effects should be reported directly to manufacturers or via the MHRA. How do the MoD and other countries' Defence Departments share this information? I think you have already said that the US is dealt with through distributors there. Are you a receptacle of all the adverse reports about effects of this drug?

Dr Nichol: It is interesting because malaria is a reportable condition in the UK but, in terms of gathering drug safety information after a drug is licensed, there is no mandate for prescribers to report. The European legislation over the past few years has heightened the need for the patients themselves to report directly but there is no mandate for prescribers per se to report. There is—this is not just for Lariam but for all drugs—an under-reporting of adverse events generally. Not everybody goes and tells the doctor.

Richard Benyon: I am one of them. I didn't report it. I just stopped taking it.

Dr Nichol: So that exists for all drugs. The importance of gathering the information—on the route of things coming in, if somebody were to report an adverse event to the MHRA, they share that report information with us, as the manufacturer. If the report were to come directly to us as the manufacturer, we share it with the MHRA and with our global database and other regulators. That is the route, but it does not mean that every single adverse event that occurs from any of our products comes to us. It requires the prescribers to contact us and tell us, and patients as well.

Q61 Richard Benyon: Have you heard any evidence that Lariam causes or is a trigger for PTSD? The MoD has said that there is no evidence per se and that the similarity of the symptoms has resulted in some people making an incorrect connection. Do you have any evidence of a link between Lariam and PTSD, and are you aware of any research being conducted in this area?

Dr Nichol: Again, I have done a lot of reading over the past few weeks. I believe that analysis was done on post-traumatic stress disorder. In terms of having the information directly to hand just now, I would rather give you some more detailed information afterwards if that would be useful.

Richard Benyon: Thank you. That would be very useful.

Q62 Chair: Before coming to Johnny Mercer, may I just ask you a question relating specifically to the US? I understand they have banned the use of Lariam there. Is there any evidence that more service personnel have caught malaria in the armed forces of that country as its Government have decided not to prescribe Lariam?

Mike Kindell: Not that I am aware of. I do not know of the evidence. It may be there but I am not aware of it. Maybe we can have a look.

Q63 Chair: That would suggest that there are possible alternatives to Lariam that could be used without rendering the individuals more likely to catch malaria.

Dr Nichol: There are alternatives to Lariam—the other ones that I mentioned at the start. Other drugs can be prescribed. Obviously, different drugs are licensed in different countries. Just to clarify, me and Mike both work for the UK affiliate so we do not have to hand all the information or the stats, nor had we prepared for this meeting with a US perspective.

Q64 Chair: But can you think of any reason why, in the UK, we would want to prescribe Lariam rather than one of the alternatives if the alternatives do not make it any more likely that the service personnel will catch malaria?

Dr Nichol: Again, it comes down to a prescribing decision. Generally, when you are making a decision to prescribe any treatment there is usually a choice of more than one drug. That is helpful for most prescribers because you are able to individualise your choice based on the needs of the patient in front of you. In terms of the efficacy of treatment, for the other options that are available—I mentioned the combined drug, Malarone, earlier and doxycycline—grouped together all the evidence suggests that each of those drugs has a similar efficacy for the treatment of malaria, so it is not the efficacy that differentiates the drugs but more the choice based on the patient's contraindications, their medication, perhaps to some extent their desire to take a once-weekly tablet versus a once-every-day one, and the duration of their exposure in the malarious area. Those would be the reasons why it would be useful to have an option of drugs available in front of the prescriber.

Q65 Chair: Why do you think Lariam keeps getting all this bad press for having such serious side effects in individual cases, rather than some of these other drugs, unless it is the case that Lariam is more likely to cause these adverse effects than other drugs?

Dr Nichol: It is already stated in the summary of product characteristics that Lariam has a higher preponderance of causing the neuropsychiatric side effects we have referred to. It is for that reason that those patients with a history of illnesses should not be prescribed it. That is why it is there as a contraindication and called out very specifically on the label.

Q66 Chair: I am still not quite clear why anyone would choose to prescribe Lariam rather than one of the alternatives. There must be some reason for that. Is it expense? Is it that the alternatives might be more likely to cause problems that Lariam would not cause? What possible reason is there?

Dr Nichol: Okay. The serious side effects that we are talking about are rare, and the common side effects tend to be tolerable. Obviously other drugs have side effects as well. I don't want to go through the list of them, but they all have side effects. Indeed, common side effects listed for Malarone include insomnia, dizziness and depression.

Q67 Chair: Yes, but if Lariam has more, presumably in a rational world most people would choose one of the alternatives when prescribing.

Dr Nichol: Yes. It is the other factors. It depends on the person. I guess the main difference in a prescribing decision relates to how frequently the drug can be taken. Lariam is required to be taken only once a week, and the individual is instructed to take it at the same time every week. We have data for Lariam that goes out to 12 months of usage. The other drugs don't have the same length of data for usage. But yes, it would depend on the risk and the situation that the person is going to.

Chair: Okay, we will leave it at that.

Q68 Johnny Mercer: Mr Kindell, you mentioned 100,000 units a year worldwide and 15,000 to the UK. How long is that contract projected to go on? Is it year by year?

Mike Kindell: It is not a contract as such. We simply supply Lariam to the wholesaler. They buy the product from us and the MoD will go to them and buy what they want from the wholesaler, so there is no contract as such in place.

Q69 Johnny Mercer: Okay, great. Are you aware of the Journal of the Royal Navy Medical Service report entitled "The adverse effects of mefloquine in deployed military personnel"? You said—understandably, because you are the drug manufacturer—that you haven't done research specifically into military personnel. Some organisations have done that, such as the Royal Navy. Are you aware of that piece of research that was released last year?

Dr Nichol: Yes.

Q70 Johnny Mercer: You are. I therefore find it quite hard to marry up the statement you just made, Dr Nichol, about rare side effects with the data from that study that indicated that 54% of 111 troops suffered an adverse reaction—that doesn't seem particularly rare to me—and 100% of the women suffered an adverse reaction. What would you say about data like that?

Dr Nichol: I am familiar with the paper. Having reached out to the MoD, it is things like that paper that would be really useful for us to discuss with them and understand the methodology.

Q71 Johnny Mercer: Did the MoD bring that paper to you?

Dr Nichol: No, they didn't.

Q72 Johnny Mercer: As a manufacturer, is that something you would have expected to happen if you saw a set of results like that?

Dr Nichol: Yes. The first thing I have to do, having seen that paper, is—all of those events will become reportable in our adverse event database, and our immediate reaction is that we need to contact the author, to get as much information as we can about those reports. That is already in place—

Q73 Johnny Mercer: Sorry to interrupt you, but we have limited time and I really want to put a couple of these points out. You talk about reportable incidents. When Staff Sergeant Bales from the US killed 16 people on 11 March 2012 in Kandahar, were you informed of him using your product at that time?

Dr Nichol: I don't think I am allowed to speak about individual cases.

Q74 Chair: That is for legal reasons, I take it.

Dr Nichol: Yes.

Q75 Johnny Mercer: You mentioned fits as one of the side effects. How many times have fits been reported as such?

Dr Nichol: Again, if you want specific numbers—

Q76 Johnny Mercer: Is it generally quite a large number? Is it what you expect or more than you expect, or do you not know the number?

Dr Nichol: Again, because patients are all different, it will depend on their previous history—what drugs they are on and that kind of thing—but it is called out. I can refer to it if you want the information from the SPC. Seizure disorder is called out in terms of saying: "In patients with epilepsy, mefloquine may increase the risk of convulsions."

Q77 Johnny Mercer: Okay. I just have two more questions. Mr Kindell, you said that you were unaware of any other militaries interrogating this. In *The Independent*—public, open-source material—it talks about Germany, the Netherlands, Denmark and Canada having either banned the use of Lariam or used it as a last resort.

Mike Kindell: Sorry, I misunderstood the question—I thought you meant what their policy is with regard to Lariam in terms of the volumes they use. That is the bit I don't know.

Q78 Johnny Mercer: You don't know what their policy is?

Mike Kindell: No, I don't know how much Lariam they actually prescribe. I know that lots of countries have different policies, and Lariam is moving down the list. In America, it is used as a last resort, when nothing else is there. I guess this comes back to the whole story of Lariam. Lariam has been around for a very long time. When it first came out, it saved hundreds of thousands of lives. As time moves on, new medications come in with similar efficacies and different side-effect profiles, and that assessment gets done. In more and more cases now, it is being used where you cannot use something else, and I think that dialogue is happening in other countries as well.

Q79 Johnny Mercer: Absolutely. Finally, if you were the parent of a serviceman or servicewoman who had pre-existing conditions and took this medication, how would that make you feel?

Mike Kindell: They should have had a proper assessment.

Q80 Chair: But how can they have a proper assessment when they would have to disclose to their own Medical Officer the fact that they had this pre-existing problem but might feel, for career reasons, unable to make that disclosure?

Mike Kindell: Speaking for myself, I completely empathise with that position.

Q81 Johnny Mercer: I think it would be fair to say that our—or certainly my—general problem is absolutely not with the manufacturer. You place a product on the market, and that is the way it operates, but it should be used within those guidelines. What we are trying to wheedle out today—I think we have been quite successful—is that if it is not used within those guidelines, like any medication that has side effects, it is going to cause adverse problems. Some families clearly feel that their lives have been quite significantly affected by this. I don't want you to think that I have a personal crusade against the company; it is nothing to do with that at all. It is about representing the families who, for one reason or

another, rightly or wrongly feel that this has not been used properly and have lost husbands and sons to it.

Dr Nichol: We do understand, and of course, in any situation where there is a significant, and in some cases fatal, outcome, if I were in that situation, I would certainly want to ask questions and understand if all the appropriate assessments had been made.

Q82 Mrs Moon: Are the contraindications that you highlight always immediate? Might it be that someone starts off taking the drug and it is fine, but that the conditions emerge as the drug accumulates within their system? Is it always immediate? Can I just get that clear?

Dr Nichol: It will vary. Again, because everyone is different, they react to drugs differently. It is not always immediate; it might build up over time.

Q83 Mrs Moon: I know you said that it is a drug that you take once a week, which is clearly helpful if you are in a working situation in which remembering to take something every day is difficult. What about if you fail to take the medication on the prescribed day, and what about when you cease taking the medication? Are there risks if you forget, and are there risks when you stop? Can you say a little about that?

Dr Nichol: If you forget, there is some guidance in the SPC that says you should take it as soon as possible but not take a double dose if you have forgotten for a whole week. If you come off the medication without completing the whole course, theoretically you haven't fully protected yourself against the malaria to which you have been exposed.

Q84 Mrs Moon: How often have you had side effects reported as a result of people not taking the medication on a regular basis or when they stop the medication?

Dr Nichol: The data do not come to us in a way for us to be able to analyse it in that way. There is evidence, however, that people are experiencing some of the side effects while taking it and that the side effects can be prolonged for some period of time after they stop taking the medication. That in part answers your question, I think.

Q85 Mrs Moon: Have you had any reported episodes where someone has been taking the medication, has managed to cope with the medication and then, sometime after they have stopped, experienced the side effects?

Dr Nichol: I am not aware of any reports like that.

Q86 Chair: Are you satisfied with what you know about the way in which your product is prescribed within the UK armed forces, or do you feel that you don't know enough about it?

Dr Nichol: I would say from my own experience of preparing to come to this Committee over the past few weeks that it is true that I don't feel that I know enough about how it is being prescribed. We could say the line that it is down to the prescriber to make that decision but, as a company, we certainly feel a responsibility to engage with the MoD—we have made reference to that—to try to understand a bit better. We cannot influence the prescribing decision one way or another. A journal reference was mentioned earlier, and I would be interested in speaking to the author to better understand the methodology and how it is prescribed.

Q87 Chair: If in a future session with representatives of the MoD, for example, we manage to tease out a lot of detail about how it is prescribed, would you then be willing to write to us with a commentary on the adequacy, or otherwise, of the way you think that that practice is being carried out?

Dr Nichol: I would be prepared to write a commentary in the context of my role at Roche, but clearly I am not a prescriber in the UK. For something like that, you might want to consider getting an independent review of the appropriateness of the prescriptions.

Q88 Chair: Yes, but, as a firm, you laid down all these recommendations and restrictions on how your product ought to be prescribed, and therefore you are presumably in a position to comment knowledgably, when told how it is being prescribed, on the adequacy or otherwise of those processes, aren't you?

Mike Kindell: All of those processes are outlined in the SPC, so it is there in the public domain.

Q89 Chair: So you are telling us that we ought to draw our own conclusions?

Mike Kindell: No, it is there, so an independent person could do that. I suppose that is my point.

Dr Nichol: To answer your question—yes, we can do an assessment of their prescribing policy, if that is made available to us, in accordance with the SPC.

Chair: That is precisely what I am asking.

Dr Nichol: We do not have sight of that prescribing policy.

Q90 Chair: No, but we hope that we might be able to bring something out in the course of our investigations, and then it would be extremely helpful to the Committee if you were willing to do that. It is clear that we are going to have to look more closely at what happens in the armed forces in relation to the warnings that you, the manufacturer, give. You have stressed the importance of the individual's personal circumstances being properly assessed before this drug is prescribed, and I feel that a great deal of light has been shone into some rather dark corners on this very worrying phenomenon of people suffering a great deal from side effects of this drug.

Finally, Dr Nichol, you said earlier that Roche had reached out to the Ministry of Defence and that you were hoping that a meeting would take place. It would be good to know whether you have had any response at all from the Ministry of Defence. Have they offered you any dates? Have they refused? Have they suggested conditions under which such a meeting would be held?

Dr Nichol: We have just reached out to them in response to the information that came to light and my assessment of the paper that I saw over the weekend. We have to give them time to respond to that request.

Q91 Chair: Will you kindly keep us informed of what happens next?

Dr Nichol: Yes.

Mike Kindell: Yes.

Chair: It just remains for me to thank you both. It is not an easy job to appear before a Committee for such a protracted period on such a delicate and important subject. We are very grateful to you.