An Roinn Sláinte
DEPARTMENT OF HEALTH

PAC-R-1041

26th July 2013

Correspondence 3B.3
Meeting 93 – 19/09/2013

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Committee Secretariat
Committee of Public Accounts
Leinster House
Dublin 2

Dear Ms Maguire

Further to your correspondence dated 1st February 2013, I attach for your attention briefing in relation to the drug Tamiflu.

Please accept my apologies for the delay in responding to your request.

Yours sincerely

Dr Ambrose McLoughlin
Secretary General

Briefing for the Committee of Public Accounts

Briefing regarding Tamiflu (oseltamivir)

Summary

Tamiflu is an antiviral medicine manufactured by Roche Pharmaceuticals which is authorised for use in the prevention and treatment of influenza, including pandemic influenza.

Tamiflu is authorised for use in all Member States of the EU, following a centralised evaluation carried out by the European Medicines Agency (EMA). Under the EU centralised authorisation procedure, a single application for authorisation of a medicine is submitted to the EMA, which carries out the evaluation. If a centralised authorisation is granted by the European Commission to a medicinal product, that product is authorised for placing on the market in all EEA countries, including Ireland. It is compulsory to use the EU centralised procedure for authorisation of human medicines for the treatment of number of specified conditions, including viral diseases.

During the H1N1 (swine-flu) pandemic in 2009/2010, Governments, including the Irish Government, purchased Tamiflu for the treatment of pandemic flu. In April 2009, the Health Service Executive (HSE) procured almost 2 million doses of antivirals for use in an influenza pandemic at a cost of €27.9 million. This was in response to a recommendation made by the Pandemic Influenza Expert Group at the request of the National Public Health Emergency Team. The antivirals not used during the 2009 pandemic have continued to be used in the subsequent influenza seasons and have a shelf-life of a further two years.

The request for briefing arises from correspondence received by the Committee of Public Accounts which raises questions regarding the effectiveness of Tamiflu in the prevention and treatment of influenza. The correspondence to the Committee refers to research undertaken by the Cochrane Collaboration which, based on available data, has suggested that the effectiveness of Tamiflu in the prevention and treatment of influenza has been overstated. In addition, in the correspondence to the Committee it is stated that some of the clinical trial data regarding Tamiflu is unpublished and has not been released and suggests that the Government should seek a refund of taxpayers' monies on that basis.

Following ongoing engagement with the Cochrane Collaboration, in April 2013 Roche agreed to release all clinical trial data relating to the product Tamiflu over the coming months. In the interim,

the Cochrane Collaboration has been seeking clinical trial data regarding Tamiflu from the EMA. The EMA, has not, as yet been in a position to release the clinical trial data held by it as part of the Tamiflu authorisation process because in the course of separate ongoing legal proceedings pending before the General Court of the EU, the EMA was ordered to suspend certain procedures for granting access to documents submitted by marketing authorisation holders about their medicines.

The UK Committee of Public Accounts held a hearing on the issue in June 2013 to take evidence on the National Audit Office Report on *Access to clinical trial information and the stockpiling of Tamiflu* which was published in May 2013.

In 2012 the European Medicines Agency, published a report on Tamiflu as part of the renewal of the product's European authorisation for Tamiflu effectiveness. The EMA continues to be of the opinion that the benefit risk profile of Tamiflu remains positive, i.e. that the benefits of the product outweigh the risks associated with the product; consequently, Tamiflu continues to be authorised as a medicine at EU level. It should also be noted that neither WHO nor the European Centre for Disease Control, both leaders in public health have changed their antiviral guidance on foot of the review of Tamiflu by the Cochrane Collaboration. In April 2013, the Pandemic Influenza Expert Group (PIEG) recommended that Ireland maintain an antiviral stockpile.

1. Background to the authorisation of medicinal products in the EU

For a medicine to be placed on the EU or Irish market, the product must be authorised. Medicinal products placed on the market in EU Member States must either be authorised nationally by the relevant medicines competent authority of the Member State (the Irish Medicines Board in the case of Ireland) or centrally at EU level by the European Commission following evaluation by the European Medicines Agency. Manufacturers must submit evidence regarding the medicine's efficacy, safety and quality as part of the application for authorisation, including information on clinical trials carried out on the product to demonstrate its efficacy and safety.

Under the EU centralised authorisation procedure, a single application for authorisation of a medicine is submitted to the EMA, which carries out the evaluation. If a centralised authorisation is granted by the European Commission to a medicinal product, that product is authorised for placing on the market in all EEA countries, including Ireland.

2. Background to the authorisation of Tamiflu

Tamiflu (brand name for the antiviral medicine oseltamivir) is authorised for use in the prevention and the treatment of influenza, including pandemic influenza.

Tamiflu was granted a marketing authorisation by the European Commission in 2002 following a favourable centralised evaluation of the product by the European Medicines Agency, based on clinical trial data submitted by the marketing authorisation holder, Roche.

In 2007 the EMA renewed the marketing authorisation for Tamiflu with a number of conditions attached. These conditions related to monitoring of the product's safety profile, but did not affect the benefit-risk profile of the product, which remained positive (i.e. that the benefits of the product outweighed the risks associated with the product).

Under the EU pharmaceutical legislative framework, it is compulsory to use the EU centralised procedure for authorisation of human medicines for the treatment of number of conditions, including viral diseases. Consequently, it was not open to the Irish Medicines Board or Ireland to evaluate or grant an application for a marketing authorisation to Tamiflu at national level because it was compulsory that Tamiflu be authorised as a medicine under the EU centralised procedure by the European Commission following evaluation by the European Medicines Agency.

3. Usage of antiviral medicines

Antiviral medicines are an important adjunct to vaccine and infection control in the control of influenza. Influenza antiviral prescription medicines can be used to treat or to prevent influenza. Early antiviral treatment can reduce the risk of complications from influenza e.g. pneumonia, respiratory failure and death, shorten duration of illness among acutely ill patients and reduce morbidity and mortality among patients with severe infection.

The Health Protection Surveillance Centre is responsible for drawing up Irish guidance regarding antiviral usage, setting out the Irish recommendations for the antiviral treatment and prophylaxis (prevention) of seasonal influenza. This draws on guidance already issued by organisations such as the World Health Organisation (WHO). In areas where adequate evidence is not available the recommendations rely on expert consensus opinion.

It is recommended by the Health Protection Surveillance Centre that antiviral treatment is commenced as early as possible for any patient with suspected or confirmed influenza who:

- Is hospitalised,
- Has severe complications or progressive illness,
- Is at higher risk from influenza complications.

Antiviral treatment can also be considered for any previously healthy symptomatic outpatient (not at high risk) with confirmed or suspected influenza on the basis of clinical judgement. Ideally, treatment should be initiated within 48 hours of illness onset.

Clinical judgement on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since symptom onset is important when considering the initiation of antiviral therapy for high risk outpatients. Where possible, antiviral therapy should be started as soon as possible after illness onset. The greatest benefit is achieved when antiviral therapy is commenced within 48 hours of illness onset. However, antiviral therapy may still be beneficial in patients with severe complicated or progressive illness and in hospitalised patients when administered more than 48 hours of illness onset.

Empiric antiviral treatment is often necessary and providers should not delay initiation of treatment while awaiting confirmatory diagnostic test results or if specimens are not obtained. Patients with suspected influenza should complete antiviral treatment for a full treatment course regardless of negative initial test results unless an alternative diagnosis can be established and clinical judgement suggests that influenza is an unlikely diagnosis.

4. Use of Tamiflu during the H1N1 (swine flu) Pandemic in 2009/2010

Many governments, including the Irish Government, purchased Tamiflu for the treatment of pandemic flu. This decision was guided by the World Health Organisation (WHO) guidance on pandemic preparedness which stated that antivirals are effective for both prophylaxis ad early treatment of influenza and that they could reduce influenza- related complications, hospitalisations and, potentially death rates.

Prior to the emergence of HINI as a specific threat in April 2009, the HSE procured almost 2 million doses of antivirals for use in an influenza pandemic at a cost of €27.9 million.

5. EMA – current status of authorisation

In 2012 the EMA published a report on the renewal of the authorisation for Tamiflu in which it made references to recent research published by the Cochrane review regarding concerns about the effectiveness of Tamiflu. However the report concluded that:

"Although the effect of oseltamivir is considered modest, data available since the last renewal have confirmed that oseltamivir is efficacious in the prevention and treatment of influenza. Oseltamivir has been shown to shorten the clinical course of influenza, especially influenza caused by A viruses, by approximately one day. Oseltamivir is also effective in preventing influenza both in the seasonal prophylaxis and in post-exposure setting. Furthermore, oseltamivir has been recognised as a valuable option in a potential pandemic influenza outbreak.

The overall safety profile of Tamiflu since the last renewal has remained unchanged.

Benefit-risk balance of oseltamivir remains positive in the approved indications.".

In a letter to the European Medicines Agency in December 2012, researchers with the Cochrane Collaboration, an independent not-for-profit organisation which carries out systematic reviews of primary research in healthcare, have expressed the view that Tamiflu had an aspecific mode of action and that:

"[t]he data found in EMA's holding of Tamiflu clinical trial data provided by the drug's manufacturer present no credible evidence that oseltamivir affects complications or prevents person to person spread of influenza".

In February 2013 the EMA responded on the basis of the clinical trial data and evidence submitted to the EMA at the time of authorisation of Tamiflu in 2002. The EMA did not agree with the Cochrane researcher's view that Tamiflu has an aspecific mode of action and responded that:

"[t]he benefit-risk of Tamiflu in the granted indications is considered positive by the CHMP and no regulatory actions have been envisaged at this stage".

6. Recent requests for access to Tamiflu clinical trials data

In February 2013, researchers from the Cochrane Collaboration made a request to the EMA for the original documents of 10 clinical studies submitted to the EMA by Roche as part of the application for Tamiflu authorisation and which were referred to in the EMA's response.

On 10 July 2013, the EMA responded that it is not in a position to release the clinical trial data sought by the Cochrane researchers because, in the course of separate ongoing legal proceedings pending before the General Court of the EU, the EMA was ordered to suspend certain procedures for granting access to documents submitted by marketing authorisation holders about their medicines. This decision is currently being appealed by the Cochrane Collaboration researchers.

The request is part of a wider call for greater transparency in clinical trial data. In 2012 the EMA agreed to commence publishing all clinical trial data on its website. The EMA is currently engaged in a legal action brought by two pharmaceutical companies seeking to challenge the EMA's decisions to grant access to non-clinical and clinical information (including clinical-study reports) submitted by companies as part of marketing-authorisation applications.

In July 2012 the European Commission adopted a proposal for a regulation to replace the existing legislation on clinical trials. A key part of the new Regulation will be to increase the transparency of clinical trials conducted in the EU, including the publication of trial results in a publicly accessible database.

Through the British Medical Journal, Roche has been requested to publish all clinical trial data relating to Tamiflu for independent scrutiny. In April 2013 Roche informed the Cochrane Collaboration that it will release the reports of all clinical trials on Tamiflu which Roche has sponsored over the coming months.

7. Ongoing UK review relating to Tamiflu

In the UK the National Audit Office (NAO) published a review ***"Access to clinical trial information and the stockpiling of Tamiflu"*** on 21 May 2013. The purpose of the review was to report whether medicines regulators and the UK National Institute for Health and Care Excellence (NICE) had access to the clinical trials evidence they require when assessing the clinical and cost-effectiveness of Tamiflu and other medicines for use in the NHS, and whether the Department of Health stockpiled Tamiflu for influenza pandemics on the basis of clinical evidence.

The UK Committee of Public Accounts held a hearing in June 2013 to take evidence on the NAO Report. A group of six cross-party MPs has urged the Chair to demand that Roche repay the money

to the Government if the Committee finds that Roche concealed clinical trials evidence regarding the product.

7. Conclusion

Tamiflu (oseltamivir) is a medicine which is authorised for use in the prevention and the treatment of influenza, including pandemic influenza. Tamiflu was purchased, stockpiled and supplied by Governments to patients during the H1N1 (Swine-flu) Pandemic in 2009 / 2010.

Tamiflu is authorised by the European Commission for placing on the market in EEA countries following evaluation of its efficacy, safety and quality by the European Medicines Agency.

A Cochrane review of Tamiflu has raised questions regarding the effectiveness of Tamiflu in the prevention and treatment of influenza.

The European Medicines Agency carried out a review of Tamiflu as part of the renewal of the product's authorisation in 2012. The EMA continues to be of the opinion that the benefit risk profile of Tamiflu remains positive, i.e. that the benefits of the product outweigh the risks associated with the product; consequently, Tamiflu continues to be authorised as a medicine at EU level.

Medicines Unit & Health Protection Unit

25 July 2013