THE ROYAL SOCIETY

The Academy of Medical Sciences

Summary of oral evidence: John Harrison, Roche Products UK (with additional evidence provided by Dr James Smith)

27 April 2006

Mr John Harrison, Influenza Therapy Manager, Roche Products UK gave evidence to the group. Roche Products UK is the UK affiliated company.

Dr James Smith is International Medical Leader: Tamiflu, F. Hoffmann-La Roche Ltd, the international parent company based in Basel, Switzerland. Dr Smith provided written answers to questions raised by the working group during the evidence session.

Members of the working group present were: Sir John Skehel, Professor Glynis Breakwell, Professor Neil Ferguson, Professor Barry Furr, Dr John McCauley, Professor Andrew McMichael, Professor Karl Nicholson, Dr Geoffrey Schild (in part) and Richard Stubbins.

Key points

Use of oseltamivir

Oseltamivir (Tamiflu) was launched in the UK in 1999. Mr Harrison told the working group that Roche have been in discussion with the Department of Health (DH) and Health Protection Agency (HPA) since 2000 on the use of oseltamivir in seasonal influenza. Discussions between Roche, DH and HPA have increased since the H5N1 outbreak and focussed on efficacy data, licence indications and resistance.

Oseltamivir is licensed in 75mg capsules in packs of 10 to be taken within 48 hours of symptoms for the treatment of influenza in adults and in children one year and above. Roche are preparing a development plan to potentially extend to children under one year. Oseltamivir is licensed for use as both seasonal prophylaxis and post exposure prophylaxis to influenza (one 75mg capsule daily for 10 days). The antiviral has been shown to be protective in 89% of individuals and 85% of family members in clinical trials. For seasonal prophylaxis, oseltamivir is licensed over a six week course, based on the normal time course of seasonal influenza, but beyond six weeks doctors can only prescribe the drug off-licence. Roche are preparing clinical trials to determine the efficacy and safety data for prophylaxis over longer time periods.

Synthesis and formulation of oseltamivir

The synthesis of the oseltamivir is a complicated ten stage process which takes nine months. The raw ingredient is shikimic acid which is isolated from Chinese star anise. Roche has developed an alternative method to derive shikimic acid by the fermentation route, which will account for two thirds of the total supply of shikimic acid. Roche has sixteen contract partners involved with the synthesis of oseltamivir, specifically the epoxide to azide step which is explosive. Three companies are also licensed to manufacture oseltamivir: Shanghai Pharmaceuticals (China), Hetero Pharmaceuticals (India) and HEC Pharmaceuticals (China). Roche began investing in the manufacture of oseltamivir before the current H5N1 outbreak. Manufacture capability was increased eight fold in 2004 and there are currently four factories manufacturing and two factories which capsulate and pack the drug, but this will be increased to four by the end of 2006.

Roche does not have any ongoing research activities examining new antivirals against influenza. Dr Smith told the working group that Roche remains vigilant to third party research and is interested in the

commercialisation of new antivirals, as with other therapeutic areas. However, research is being conducted to looking at alternative formulations of oseltamivir.

Supply of oseltamivir

Following advice by WHO, governments around the world are developing pandemic plans and subsequently talking to Roche about supply of oseltamivir. To date, 75 governments worldwide have asked Roche to provide Tamiflu for pandemic use. Some governments have not officially ordered their Tamiflu stockpile, however a number of these governments have initiated discussions with Roche on stockpiling. Roche's agreements with governments preclude the release of information on the status of their plans. The absolute demand for oseltamivir is determined by governments indicating the percentage of their population they wish to buy the drug for. By the end of 2006 Roche will have the capacity to produce 400 million treatment courses worldwide, well in excess of the 200 million treatment courses received in orders from governments to data.

Roche contacted WHO about a stockpile and have provided three million packs to deliver to countries as needed as a rapid response stockpile. They are able to provide two million packs within 24 hours and another million packs within 48 hours. Roche has also donated two million packs to the WHO to be held as regional stockpiles.

In August 2005 the UK Government asked Roche to supply 14.6 million courses of oseltamivir, to cover 25% of the UK population. This order will be completed by September 2006. Roche were not involved in the discussions to reach the figure of 25% population coverage, which was made by the DH and the HPA.

The majority (14 million) of the doses will be supplied as capsules (75mg) in packs of ten. The remaining 0.6 million doses will be available as the active pharmaceutical ingredient (API), supplied in drums, to be reconstituted with benzoic acid and water. Roche have provided 72 drums with 7000 courses per drum. This oral suspension will be reconstituted for children under five years who are too young to take the drug in capsule form, at a dose based on weight. The drug has a bitter taste and Roche have spoken to DH on how to mask the taste. Mr Harrison was asked about the reconstitution and supply of the drug. Roche have produced a manual and an instruction video on how to reconstitute the API, but Mr Harrison stressed that the logistics of how to reconstitute the drug and its supply to the population are the responsibly of the Government through the DH, and not that of Roche.

Oseltamivir is made to order with a maximum shelf life of five years. Roche guarantee that it is supplied with an expiry date of at least four and a half years on delivery. After this time DH can test the drug to extend the shelf life, but this is outside the control of Roche and their licence for the drug.

Drug resistance

Roche and other pharmaceutical companies support the Neuraminidase Inhibitor Susceptibility network (NISN) which carries out resistance surveillance during seasonal influenza epidemics. The NISN report continued low levels of resistance in the community to both registered neuraminidase inhibitors, oseltamivir and zanamivir. Roche has recently examined 4000 influenza isolates for resistance to oseltamivir. Resistance to oseltamivir has been shown in 0.4% of adults and 4% of children which in contrast to the high resistance levels seen with amantadine is still very low. NISN continue to monitor drug resistance and Roche have been involved with organising and attending international meetings on resistance to antivirals.

Use of Oseltamivir in a pandemic

Oseltamivir is licensed in adults and children (one year and above) for the treatment of influenza within 48 hours of the development of symptoms and also prevention. Mr Harrison was asked about the timeline it is

effective in humans. He stressed that the drug has only been tested in seasonal flu within 48 hours of symptoms and there is no controlled clinical trial data available on avian influenza. However, it was designed to be effective against all strains of influenza. Dr Smith told the group that some recent evidence from Professor McGeer (University of Toronto) would indicate that oseltamivir can still be of benefit in reducing secondary complications of influenza when the drug is administered after 48 hours. Roche are planning to perform additional clinical trials using prophylaxis beyond six weeks. Additionally, a long term prophylaxis study up to 20 weeks is in an early planning stage.

Mr Harrison was asked about the issues of how Roche will react if there is a scarcity of the drug in a pandemic and if there is a strategy within Roche incase it proves ineffective in a pandemic. These issues have been highlighted within Roche but the virus is currently avian. Roche has examined efficacy in mice and ferrets with the H5N1 virus. Oseltamivir at a dose of 5mg/kg twice daily when given early prevents death in ferrets and mice in a model of infection where there was 100% mortality in control untreated animals. It is unclear if delayed treatment may require a higher dose or prolonged treatment durations.

Dr Smith told the group that because the pandemic strain must differ from existing H5N1 strains of the virus, Roche is working with external groups to develop predictive models using existing clinical and laboratory data regarding the pathogenicity of different influenza strains and the activity and efficacy of oseltamivir against such strains. Such predictive models would then be used in conjunction with rapid laboratory assays to predict the characteristics of a newly emerging pandemic strain and the activity of oseltamivir against the novel pandemic strain at different doses and durations of therapy. Roche has also developed a pharmacovigilance plan outlining how the company will address safety reporting during a pandemic. This plan is currently under discussion with the regulatory authorities.

Dr Smith told the group that there are no clinical data within the Roche database on the bioavailability of oseltamivir in sick people with diarrhoea.

Communication

Roche have an internal communication plan on the use of the drug and a joint communication plan with DH They have also had input into the advice given to GPs and participated in DH's practice simulation response model.