Uncertainty still surrounds oseltamivir after 13 year old dies

Jane Parry Hong Kong

Not enough studies have yet been done to determine the most effective way of using the antiviral drug oseltamivir (Tamiflu) and other antivirals against the H5N1 strain of avian influenza, a leading expert has warned. "In terms of dose, time, or strategy, all the studies have so far been done on H3N1 and H1N1 flu," said Professor Robert Webster, of the division of virology at St Jude Children's Research Hospital, Memphis, Tennessee, and visiting professor at the University of Hong Kong's department of virology. "It is inevitable that we will get resistance, but we also need to learn how best to use these drugs against H5N1 avian flu. So far, animal studies suggest that they are useful, but we are still on a learning curve."

Roche, the manufacturer of oseltamivir, says that the drug may need to be used in combination with other antivirals and in larger doses than first thought to combat H5N1 avian influenza. "Roche agrees that other treatment regimens for the H5N1 virus need to be explored, including higher dose and/or longer duration of treatment with Tamiflu, or a combination of antiviral agents," a statement from the company said.

The statement was in response to a paper published in the *New England Journal of Medicine* on 22 December that described resistance to oseltamivir in two fatal cases of H5N1 avian flu in Vietnam (2005;353:2667-72). In the first case, a 13 year old girl began

treatment with oseltamivir and remained stable for three days, but, on the fourth day, she became increasingly dependent on oxygen, white cell and platelet counts fell, and she developed hepatitis. "At the time of her death, the viral load in her throat had increased. These observations suggest that the development of drug resistance contributed to the failure of therapy and, ultimately, the death of this patient," the authors wrote.

In the second patient, the viral load declined during treatment but was still detectable. "Although a direct relationship between the emergence of resistance and this patient's death was less clear, the presence of replicating virus after 14 days of illness suggests an

effect on outcome," the paper's authors wrote.

Tamiflu remains the best available treatment for H5N1 avian influenza, however, and signs of resistance are not necessarily cause for alarm, said the World Health Organization. "Whenever you use any kind of drugs, antivirals or antibiotics, you expect to see resistance develop in organisms. Finding some resistance of itself is not surprising and is not necessarily alarming," said Keiji Fukuda, an expert in WHO's global influenza programme, in an interview with Reuters. "It just points out the need for more information... what is really critical in understanding whether the way we are using the drugs contributes to that (resistance)," he said. □

Indian firm to produce oseltamivir for developing countries

Ganapati Mudur New Delhi

Roche has granted India's Hetero Drugs a sublicense for the production of the antiviral drug oseltamivir (Tamiflu) to accelerate the international stockpiling of the drug as part of influenza pandemic preparedness.

It said that the agreement would enhance supply of oseltamivir to developing countries "earlier than anticipated" and create capacity for future orders. Hetero, which is based in Hyderabad, will be able to sell oseltamivir in India and export it to almost 100 countries across Asia, Africa, and Latin America.

Hetero officials said that the company had shown the technical ability and capacity to deliver the product in the first half of 2006. "We will have 40 million capsules of oseltamivir ready for delivery by March 2006," Male

Srinivas Reddy, the marketing director at Hetero told the *BMJ*.

Another Indian drug company, Ranbaxy Laboratories, announced in early December that it was "well prepared" to produce 300 million capsules of oseltamivir within six months and 1.3 billion within a year. Ranbaxy officials had said that the company was exploring a partnership with Roche.

More than 50 countries have placed orders for oseltamivir from Roche. Oseltamivir is one of two antiviral drugs, both neuraminidase inhibitors, considered most likely to be effective against ordinary influenza and bird flu. The other drug is zanamivir, an inhaled drug from GlaxoSmithKline.

The raw material used to produce oseltamivir is shikimic

Oseltamivir is being produced in China by Shanghai Pharmaceutical under an agreement with Roche

acid, a compound extracted from the pods of the star anise plant, which is grown mainly in China. Industry analysts have said that although the demand for oseltamivir has grown steeply in recent months, the supply of shikimic acid has been limited.

"We expect the sublicensing agreement to make more medi-

cine available at lower cost," said Jai Narain, director of communicable diseases at the South East Asia regional office of the World Health Organization in New Delhi.

"Stockpiling of the antiviral drug is a key component of comprehensive influenza pandemic preparedness," Dr Narain added. □