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## Tamiflu in brief

- Tamiflu (oseltamivir) is an oral antiviral treatment (not a vaccine!) for influenza, and belongs to a class of medicines called neuraminidase inhibitors (NAI). These medicines prevent the influenza virus from spreading inside the body and are designed to be active against all clinically relevant influenza virus strains. Tamiflu can be used both for prevention and treatment of influenza.
- Tamiflu is proven to be effective in the treatment of influenza in adults and in children 1 year and older and for the prevention of influenza in adults and adolescents 13 years of age or older.
- Tamiflu is given orally, as a convenient capsule (75 mg), enabling it to reach all key sites in the body where the virus multiplies. The dose for the adult treatment of influenza is a 75 mg capsule, taken twice daily for five days. One pack of Tamiflu contains a full treatment course of 10 capsules. Treatment must commence within 48 hours of the onset of symptoms for full efficacy. For post exposure prophylaxis the dosage is one 75 mg capsule daily for up to 6 weeks.
- In 1996 Roche acquired the worldwide rights to develop and market the drug from Gilead Sciences, South San Francisco.
- Tamiflu was launched in North America (US and Canada) and Switzerland during 1999/2000. In all key European markets, it was launched by 2002/2003.
- Over 33 million patients have been treated with Tamiflu in about 80 countries worldwide including United States, Japan, Canada, Australia, the EU, Switzerland and Latin America.
- Tamiflu is patent protected until 2016; the patent is owned by Gilead.

## Tamiflu efficacy data

- When administered according to its approved dosage (75 mg twice daily for 5 days), Tamiflu delivers a 38 per cent reduction in the severity of symptoms, a 67 per cent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals and a 37 per cent reduction in the duration of influenza illness. These data were derived from seasonal outbreaks of influenza.
- As with any antiviral, a theoretical potential exists for an influenza virus to emerge with decreased sensitivity to a drug. Data collected from around 4000 treated with Tamiflu demonstrate an overall incidence of resistant virus of 0.4% in adults and 4% in children aged one to 12. The greatest use of Tamiflu today is in Japan. To illustrate this, there were

an estimated 16 million influenza infections in Japan over the 2004/2005 influenza season; and Roche estimates that around 6 million of those individuals received Tamiflu. Even with this high degree of usage, resistance appears very infrequent. This is supported by recent data compiled by the neuraminidase inhibitor susceptibility network (NISN) which surveyed resistance amongst virus isolated from 1180 influenza patients in Japan. Only four of the 1180 isolates showed reduced susceptibility to Tamiflu, highlighting the low frequency of resistance to Tamiflu.

### **Tamiflu safety data**

- Mortality in patients taking Tamiflu, both in adults and children, is lower than in influenza patients who are not treated with Tamiflu. Based on independent studies, death rates in children treated with Tamiflu are reduced between 60 to 90 percent.
- There is no increase in neuropsychiatric events in patients on Tamiflu versus influenza patients in general. It is important to know that neuropsychiatric events can occur often with influenza patients and are often related with high fever. Beginning in the mid-1990s, there have been many reports in the pediatric scientific literature describing a syndrome of influenza-associated encephalitis (inflammation of the brain) or encephalopathy.
- In Japan, where 11.6 million children (24.5 million patients in total, adults and children) have taken Tamiflu since 2001, there have been 12 deaths of children from 1 to age 16. According to the FDA there is no causal relationship between these cases and the administration of Tamiflu. At least 8 of the children who died suffered from pre-existing diseases such as kidney impairment, congenital central nervous system disease and asthma, or major complications of influenza, including pneumonia, pulmonary edema, myocarditis, and pancreatitis.

### **Influenza pandemics**

- Influenza, commonly called – the ‘flu’- is a serious disease caused by influenza A and B viruses, which usually occurs seasonally in the autumn and winter months. According to the World Health Organisation (WHO) 3 to 5 million cases of seasonal influenza occur every year; around 250,000 to 500,000 people are dying from this disease.
- According to the WHO an influenza pandemic occurs when a new strain of influenza A virus appears, against which the human population has no immunity resulting in several, simultaneous epidemics worldwide with enormous numbers of deaths and illness. Influenza pandemics have occurred around 3 times in each century, when a new strain of the influenza virus caused simultaneous deaths worldwide.

*For further information concerning pandemics and avian influenza, such as how it is different to seasonal influenza, and how it is transmitted, please visit the following WHO website:*

[http://www.who.int/csr/disease/avian\\_influenza/avian\\_faqs/en/index.html](http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html)

### **Influenza pandemics and Tamiflu**

- Tamiflu is designed to be active against all clinically relevant influenza virus strains therefore should be effective against any pandemic strain.

- Key international research groups have evaluated the therapies available to fight the H5N1 avian and human virus strain using animal models of influenza demonstrating that Tamiflu is effective against these avian strains. Roche recommends that approved dose and duration of treatment/chemoprophylaxis represents the minimum required for the management of pandemic influenza. In the absence of a vaccination against this virus strain, Tamiflu will prove an important management option.
- Roche is funding additional animal studies to further evaluate the antiviral activity of Tamiflu against the H5N1 avian influenza virus. Roche is also in discussions with WHO on clinical studies which may provide additional clinical data.

### **Manufacturing of Tamiflu**

- The manufacturing of Tamiflu is complex and involves 10 main steps, some of which have been identified as complicated (e.g. azide chemistry). Manufacturing takes approximately 6-8 months once all the raw materials have been sourced however, Roche's assumption is that for any party starting from scratch it would take 2 to 3 years to produce Tamiflu.
- The starting material of the Tamiflu production process, shikimic acid, is extracted from the pods (the part which wraps the seeds, in the form of an octagon) of the star anise. This process is handled by a Roche supplier. Roche uses a specific type of anise grown in four mountain provinces in the south west of China (Guanxi, Sichuan, Yunnan und Guizhou) which provides a much higher purity and yield than the one grown elsewhere. The crop requires specific agro climatic conditions (humid, hot weather and high altitude) available only in the mountainous traditional growing area. 30 kg of anise yields 1 kg of Shikimic Acid.
- Today, the larger part of the shikimic acid is gained from star anise. However, Roche and its partners are substantially increasing their fermentation capacities over the course of the next years and the ratio will change over time. For the fermentation process, Roche uses a special e-coli bacteria which, when overfed glucose, produces shikimic acid. The bacteria need to be multiplied and grown, and are transferred from small to large and larger fermenters.

### **Roche's action to respond to heightened demand for Tamiflu**

- Roche believes that it is not the patent that is the concern but the production capacities. Roche is working with a collaborative production network to expand those and is open to negotiate with any partner about granting a license under these patents at equitable conditions.
- More than a dozen manufacturing facilities worldwide network for Tamiflu production, more than half of which are with third party manufacturers. The different raw materials and excipients needed for the manufacture of Tamiflu are provided by about 50 external suppliers today.
- Roche will have increased its own production capacity by the end of 2006. It will then be in a position to potentially produce 300 million treatments of Tamiflu annually. The expansion will be achieved by a further stepwise scale-up of Roche's production network. It means a

ten fold increase over the capacity in 2004 when the decision was taken to increase production, without any firm pandemic orders in place, in order to meet government's needs for pandemic planning.

- In less than two months, Roche has completed the evaluation of around 200 third parties interested in getting involved in the manufacturing of Tamiflu. After systematic screening, Roche production experts started detailed negotiations with twelve companies that met the defined criteria in terms of quality, technical ability, capacity and the speed of bringing that capacity on stream. These companies include major pharmaceutical companies, large generic manufacturers and specialty chemical producers. Roche is now actively engaged in further discussions about technology transfers and commercial terms with this shortlist of companies.
- Roche is aware that the heightened interest in avian influenza in the last few weeks has resulted in increased demand for Tamiflu, particularly by individuals and institutions. Roche's priority is to ensure Tamiflu will be available for seasonal use to patients and to fulfil government pandemic orders. Based on their assessments of the local situation, some Roche affiliates have temporarily limited or stopped deliveries of Tamiflu to wholesalers, as it is important to note that there is no influenza currently circulating and the threat of the pandemic has not been realized. Roche is asking people to act responsibly so that Tamiflu is available to patients who need it once the influenza season starts.

### **Tamiflu pandemic orders**

- Roche has agreed quantities and delivery schedules with around 50 countries to date for stockpiling of Tamiflu.
- Because of the high demand and long manufacturing lead times for Tamiflu Roche has made clear that it is highly unlikely to fulfill large Tamiflu orders at short notice. This is why Roche has been encouraging governments over the last three years to stockpile in advance.
- The API (Active pharmaceutical ingredient) is available at a significantly reduced price (developed world: € 7.70 per 1 treatment course; developing world: € 7.00 per 1 treatment course) and Tamiflu capsules purchased by governments for pandemic use are at a significant discount (developed world: € 15.00 per 1 treatment course; developing world: € 12.00 per 1 treatment course) compared to the seasonal price (seasonal ex-factory price ranges between € 20 and € 51 in Europe).
- Status in selected countries:
  - China: Roche and Shanghai Pharmaceutical Group have signed the first sub-licensing agreement for the overall production of oseltamivir for pandemic use in China.
  - Taiwan: Roche will be in a position to deliver requested quantities during 2006.
  - Vietnam: Roche will be providing capsules or active pharmaceutical ingredient for third parties to encapsulate locally.
  - Korea and Malaysia: Roche is providing capsules.
  - India: Roche will be delivering 100,000 treatment courses of Tamiflu ordered by the Indian Government and is in negotiations about a local sub-license are ongoing with local manufacturers.

In some countries, e.g. Thailand, Philippines and Indonesia, Tamiflu is not patent protected. These governments are therefore free to purchase or manufacture oseltamivir at their

discretion. Roche remains willing to discuss supplying governments' orders and the quality requirements of supply.

### **Tamiflu donations for rapid deployment**

- The co-ordination of pandemic plans for third world countries is the responsibility of the WHO. Roche is working with the WHO to develop a central stockpile of Tamiflu for distribution at the discretion of the WHO to countries in need, and initially donated 125,000 packs of Tamiflu to the stockpile last year. In August 2005, Roche announced the donation of another 3 million treatment courses of Tamiflu to the WHO for rapid deployment at the epicentre of the pandemic. 3 million treatment courses is the quantity indicated by modelling (Science, Nature) that will reduce morbidity and mortality and help delay its spread in an affected nation. This stockpile is not a substitute for national preparedness and stockpiling by individual markets.
- In October 2005 Roche donated 5000 packs to Turkey and 2400 packs to Romania following the emergence of the H5N1 avian influenza virus in birds in these countries. These donations were made to protect highly exposed emergency workers collecting birds in farms close to location of the outbreak.

### **Counterfeit Tamiflu**

- Tamiflu is a prescription medicine and as with any prescription medicine, Roche does not advocate the purchase of Tamiflu via the internet. Patients should always gain a diagnosis from a healthcare professional before buying Tamiflu and ensure they obtain it from a reliable source.

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