

# Factsheet Tamiflu

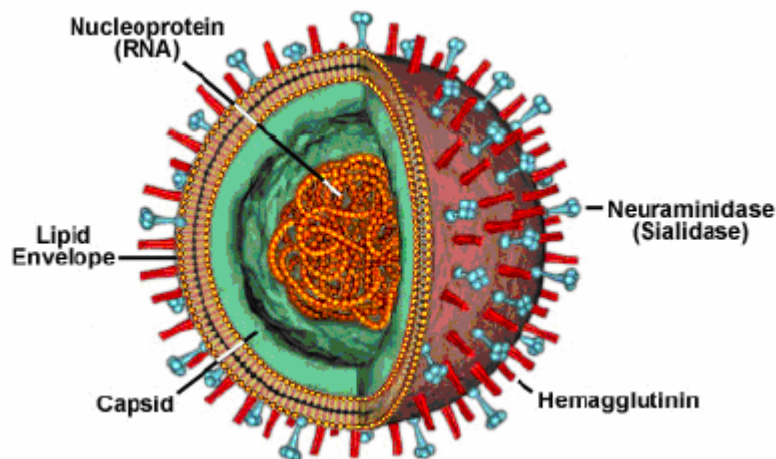


17 November 2006

For residents of the US please go to [www.tamiflu.com](http://www.tamiflu.com) for further information.

## Tamiflu in brief

- Tamiflu (oseltamivir), a prescription drug, 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.
- Neuraminidase enables the virus to continue to infect host cells. When neuraminidase is inhibited, the virus is unable to exit the host cell and dies. Therefore the virus is not able to spread to and infect other cells in the body. In contrast to the older antivirals, the M2 inhibitors, NAIs are effective against both influenza A and B viruses.



- Tamiflu is proven to be effective in the treatment and for the prevention of influenza in adults and in children 1 year and older.
- Tamiflu is given orally, as a convenient capsule (75 mg) and is systemically absorbed, meaning that it can reach 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 in adults the dosage is one 75 mg capsule daily for 10 days and for seasonal prophylaxis the dose 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, Foster City, California.

- Tamiflu was launched in North America (US and Canada) and Switzerland during 1999/2000. It was launched in all key European markets by 2002/2003.
- Around 42 million patients have been treated to date 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**

- When administered according to its approved dosage (75 mg twice daily for 5 days), there is a reduction in the duration of influenza illness. Tamiflu also reduces the severity of symptoms and lower respiratory tracts infections, such as bronchitis, in otherwise healthy individuals.
- In children Tamiflu reduces the duration of influenza illness and the severity of symptoms. There is also a reduction in incidence of associated otitis media as compared to standard care.
- In adults Tamiflu is effective in protecting individual persons against influenza illness and is effective in preventing outbreaks in households. In children Tamiflu is effective in reducing the likelihood of febrile influenza in households with a positive index case. Tamiflu reduces the overall amount of virus and significantly reduces the amount of viral shedding in the body

### **Tamiflu safety data**

- Tamiflu has been used by about 42 million people worldwide since launch and has been found to have a favourable safety profile and is well tolerated. The majority of adverse events are gastrointestinal and self limiting and seldom lead to treatment discontinuation.
- In Japan, where 11.6 million children (24.5 million patients in total, adults and children) have taken Tamiflu since 2001, there have been 16 deaths of children from 1 to 16 years of age (data as of 05 June 2006). According to the FDA who conducted a thorough review of 12 of these cases in November 2005, there is no causal relationship with 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 oedema, myocarditis, and pancreatitis.

### **Tamiflu resistance data**

- Data collected from around 4000 people treated with Tamiflu demonstrate that resistance is very infrequent. The overall incidence of resistant virus of 0.32% in adults and 4.1% in children aged one to 12. This resistant virus was found to be less virulent than the wild type virus and did not affect the course of the illness.

- Roche has both internal and external programmes in place to monitor for emerging reports of resistance and has been rigorous in its efforts to evaluate the emergence of viral resistance to Tamiflu.
- Roche continues to support the independent Neuraminidase Inhibitor Susceptibility Network (NISN), which works in collaboration with World Health Organization (WHO) in monitoring sensitivity of the virus. The NISN published their findings on resistance in 2005 and concluded that concerns about viral resistance, particularly neuraminidase inhibitors (NAIs) such as Tamiflu, should not dissuade countries from developing adequate antiviral stockpiles for a pandemic response
- 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; 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 (0.34%) showed reduced susceptibility to Tamiflu, highlighting the low frequency of resistance to Tamiflu.
- To date, three cases of reduced susceptibility of H5N1 to Tamiflu oseltamivir have been reported. In one case, the preventative dose rather than the treatment dose was given to a patient already exhibiting clinical symptoms. In the other two cases, the recommended dose and duration were followed. However, while one patient received treatment on the second day of illness, the other patient did not begin treatment until the sixth day. Analysis has revealed the presence of a mutation associated with the rare cases of reduced susceptibility to Tamiflu reported from clinical trials and post marketing surveillance.

### **Influenza pandemics**

- Influenza, commonly called – the ‘flu’- is 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 widespread morbidity and mortality. 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 A & B viruses, which includes the H5N1 virus, and has been shown to be active against the H5N1 virus in the

laboratory, in animals infected with the H5N1 strain taken from humans (Ives, J. et al. The H274Y mutation in the influenza A/H1N1 neuraminidase active site following oseltamivir phosphate treatment leave virus severely compromised both in vitro and in vivo. *Antiviral Research* 2002: 55; 307-317).

- Due to the fact that human infection with the current H5N1 strains is rare and geographically dispersed, there are no controlled clinical studies evaluating the clinical efficacy of Tamiflu in people infected with H5N1.
- The available evidence on the clinical effectiveness of Tamiflu against avian influenza consists largely of anecdotal case reports involving small groups of patients. Unfortunately, in the majority of cases, the administration of Tamiflu to people infected with H5N1 has been associated with significant delays, and not within the 48 hours recommended for start of Tamiflu treatment. However, case reports indicate that when given early after the onset of symptoms, Tamiflu has provided benefit to people infected with H5N1 avian influenza.
- The WHO currently advises that in suspected cases of human infection with H5N1 influenza, Tamiflu should be prescribed as soon as possible (ideally, within 48 hours following symptom onset) to maximise its therapeutic benefits. However, given the significant mortality currently associated with H5N1 infection and evidence of prolonged viral replication in this disease, administration of the drug should also be still considered in patients presenting later in the course of illness (WHO. World Health Organization. Avian influenza ("bird flu") - Fact sheet: World Health Organization, 2006).
- Tamiflu is being used as prophylaxis to protect individuals involved in the culling of animals infected by H5N1 influenza and for healthcare workers involved in the management of people infected by the virus.
- Roche is funding additional 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 on a large scale.
- The starting material of the Tamiflu production process, shikimic acid, is either gained via a fermentation process or extracted from the pods (the part which wraps the seeds, in the form of an octagon) of the star anise.
  - For the fermentation process, a special e-coli bacteria is used 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. Today the majority of shikimic acid is derived from the fermentation process.
  - 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.

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

- Roche's global network for the manufacture of Tamiflu includes several Roche sites and more than 15 external contractors located in 10 different countries around the world. These production partners have been selected primarily on the basis of their ability to produce substantial quantities of intermediates and finished materials in accordance with Roche's quality standards in a relatively short time frame. Ampac Fine Chemicals LLC, API Corporation, Clariant, DSM, FIS, Martek, Novasep/Dynamit Nobel, PHT International, PPG Industries, Sanofi-Aventis, Shaanxi Jiahe Phytochem Co and Siegfried Ltd are amongst these production partners.
- Roche will have increased its production capacity by the end of 2006 and will then have the capacity to produce up to 400 million treatments of Tamiflu annually, significantly exceeding government orders of 200 million treatments received to date.
- The expansion will be achieved by a further stepwise scale-up of Roche's production network, both internally and together with third parties. 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.

### **Tamiflu pandemic orders**

- Roche has agreed quantities and delivery schedules with more than 75 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 has granted sub-licenses to Shanghai Pharmaceutical Group and to HEC Group 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 has offered to provide either capsules or active pharmaceutical ingredient for third parties to encapsulate locally.
  - Korea and Malaysia: Roche is providing capsules.
  - India: Roche has granted a sub-license to India's Hetero Drugs to make oseltamivir for India and developing countries.

- Africa: Agreement reached with Aspen on providing oseltamivir for pandemic use to further help to address the needs of governments and other not for profit organisations in the African sub- continent.

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**

- In August 2005 Roche donated a rapid response stockpile of 3 million treatment courses of Tamiflu to be used to contain or slow the spread of a pandemic at its site of origin. This was in addition to 125,000 courses of therapy donated by Roche in 2004 which was used by the WHO in affected countries in Asia. In January 2006 Roche announced the donation of a further 2 million treatment courses, or 20 million doses, of Tamiflu to the WHO for the establishment of regional stockpiles for use in the management of the current avian influenza strain or in the event of a pandemic. These donations will result in a total of 5.125 million treatment courses being available to the WHO to help people affected by a potential pandemic.
- In 2005 and 2006 Roche donated 15,000 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 particularly made to protect highly exposed emergency workers collecting birds in farms close to location of the outbreak.

### **Counterfeit Tamiflu**

- Counterfeit drugs pose a number of risks to consumers, since they may not meet the strict quality standards imposed by regulatory authorities and legitimate manufacturers. Counterfeit drug products may be ineffective, contain harmful ingredients, or both.
- Nothing is more important to Roche than ensuring the health and safety of consumers who rely on our products. Roche has and will continue to do all it can to preserve the reliability of Tamiflu. Minimizing this threat requires the active cooperation of all parties involved – regulatory and law enforcement agencies, manufacturers, distributors, retailers and ultimately consumers.
- There are a number of steps consumers can take to protect themselves from the threats posed by counterfeit drug. Roche offers these practical guidelines for consumers to help ensure they receive only authentic Tamiflu antiviral medication.

#### **Obtain a diagnosis and prescription from a doctor**

- The patient is advised to see a doctor as soon as you feel symptoms suggestive of influenza such as sudden onset of fever, nausea, headache, congestion and cough.
- Prescription medications cannot be dispensed without a valid prescription.

#### **Only purchase from a credible pharmacy**

- The best way to avoid counterfeit medicine is to obtain prescription medicines from a reputable pharmacy.
- Roche advises patients against purchasing medicines via the internet.

### Inspect the Package

Check for altered containers, or changes in the packaging or label.

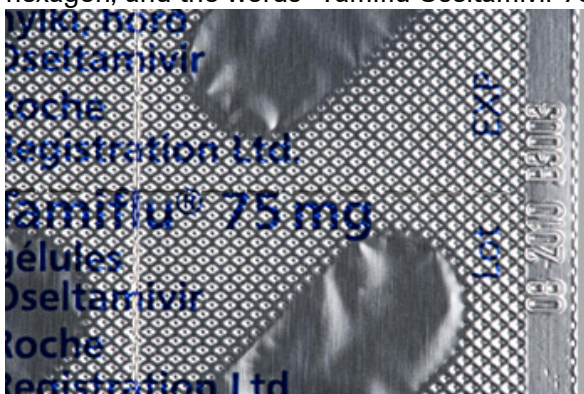
- Tamiflu comes in a white cardboard box with the wording “Tamiflu® Osetamivir 75mg” written clearly on the front with a green hexagon and the Roche logo. The right hand flap of the pack has an expiry date, batch number and, depending on the country, a manufactured date embossed into the pack. In addition the side of the pack has a distinctive logo.



- The US packaging is different please visit [www.tamiflu.com](http://www.tamiflu.com) for more details.
- The box contains a single blister package containing 10 Tamiflu capsules, which are a distinct yellow and light grey colour. Each blister contains one capsule which can be seen through the transparent outer layer:



- Each blister is printed on the aluminium foil of the reverse side with Roche and the Roche hexagon, and the words “Tamiflu Osetamivir 75mg”:



- The batch number and expiry date (in some countries also the manufacturing date) on the outside packaging should match the batch number and expiry date (and in some countries the manufacturing date) on the inner packaging:



- Each Tamiflu capsule is also printed with the words “Roche 75mg”.
- Tamiflu is also available as a suspension:



- If you have any doubts or suspicions about a product you have purchased, contact your pharmacist or physician immediately.

**What is Roche doing to improve the situation?**

- Roche continues to explore and implement new technological developments to deter counterfeiting.
- Roche is putting into place special packaging and printing techniques that make counterfeiting both more difficult to accomplish and easier to spot.
- Roche is also investigating state of the art technology (such as radio labeling) to deter counterfeiting.

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