

4. TAMIFLU[®] (*oseltamivir phosphate*) Background

What role could TAMIFLU play in a pandemic?

TAMIFLU to play dual role: prevention and treatment

The antiviral TAMIFLU could play two principal roles in the management of seasonal flu: prophylaxis, aimed at decreasing the likelihood of developing flu, and treatment, aimed at reducing the duration of flu by 1.3 days. Research has demonstrated the effectiveness of antivirals when used for both purposes. When used for treatment purposes, these drugs need to be administered within 48 hours after the onset of symptoms.²²

Experts recommend TAMIFLU for pandemic flu management³⁰

1. The Centers for Disease Control and Prevention (CDC) provides interim guidelines that identify TAMIFLU, in the absence of sensitivity testing, as the “first choice” for protection of workers involved in activities to control and eradicate outbreaks of influenza among poultry in the United States. For more information, visit <http://www.cdc.gov/flu/avian/index.htm>.³⁰
2. The WHO recommends TAMIFLU for the prevention of pandemic influenza disease in household contacts. This recommendation is based on the effectiveness of TAMIFLU in preventing ordinary influenza in healthy and elderly patients and children ages 1 year and older.³¹
3. Recent studies, based on mathematical modeling, suggest that antivirals like TAMIFLU could be used prophylactically near the start of a pandemic to reduce the risk that a fully transmissible virus will emerge—or at least to delay its spread internationally—thus gaining time to augment vaccine supplies. The success of this strategy, which has never been tested, depends on several assumptions about the early behavior of a pandemic virus, which cannot be known in advance. Success also depends on excellent

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What role could TAMIFLU play in a pandemic? (cont'd)

Experts recommend TAMIFLU for pandemic flu management³⁰ (cont'd)

surveillance and logistics capacity in the initially affected areas, combined with an ability to enforce movement restrictions in and out of the affected area. To increase the likelihood that early intervention using the WHO rapid-intervention stockpile of antiviral drugs will be successful, surveillance in affected countries needs to improve, particularly concerning the capacity to detect clusters of cases closely related in time and place.³²

TAMIFLU: one of two antivirals for pandemic flu

Both TAMIFLU and Relenza® (zanamivir)* are currently being stockpiled as part of the federal government's pandemic preparedness plan.²² TAMIFLU is available in capsule and suspension form, while Relenza is available in dry powder form via an inhaled delivery system. Both drugs are indicated for the prevention and treatment of influenza in adults and children (TAMIFLU ≥1 year; Relenza ≥7 years for treatment, ≥5 years for prevention).

It should be noted that TAMIFLU, based on number of prescriptions, is the flu antiviral of choice by physicians.³³

*Relenza is a registered trademark of GlaxoSmithKline.



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What role could TAMIFLU play in a pandemic? (cont'd)

Experts look to neuraminidase inhibitors for pandemic flu

- TAMIFLU and Relenza® (zanamivir) are antivirals that belong to a drug class known as neuraminidase inhibitors. In laboratory studies, the neuraminidase inhibitors have been shown to reduce the duration of illness caused by seasonal influenza.³⁴ The efficacy of the neuraminidase inhibitors depends on their administration within 48 hours after symptom onset. Studies are currently underway to examine the efficacy of TAMIFLU against potential pandemic strains of influenza.³²
- Another class of antiviral drugs, the M2 inhibitors amantadine and rimantadine, could potentially be used against pandemic influenza, but resistance to these drugs may develop.³⁵

—HHS Pandemic Plan

For more information about TAMIFLU resistance, please see page 41, “What is the resistance profile of TAMIFLU?”



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4. TAMIFLU® (oseltamivir phosphate) Background

What is TAMIFLU?

TAMIFLU is the only prescription antiviral pill indicated to prevent and treat type A and type B influenza in patients one year and older³⁶

- TAMIFLU was approved by the US Food and Drug Administration (FDA) in October 1999 for the treatment of uncomplicated acute illness due to influenza infection in adults
- TAMIFLU was granted FDA approval in November 2000 for the prevention of influenza in adults and adolescents 13 years and older
- TAMIFLU oral suspension was approved in December 2000 for use in the treatment of influenza types A and B in children 1 year and older. TAMIFLU oral suspension can also be used in adult patients who cannot swallow a capsule
- In December 2005, the FDA approved the extension of the indication of TAMIFLU to include the prevention of influenza types A and B in children aged 1 through 12 years following close contact with an infected individual

About 40 million people worldwide have been treated with TAMIFLU*

- TAMIFLU is approved in more than 80 countries,³⁷ including the United States, Japan, Canada, the United Kingdom, South Africa and Australia, as well as many countries in Europe, the Far East and Latin America

*As of May 2006.

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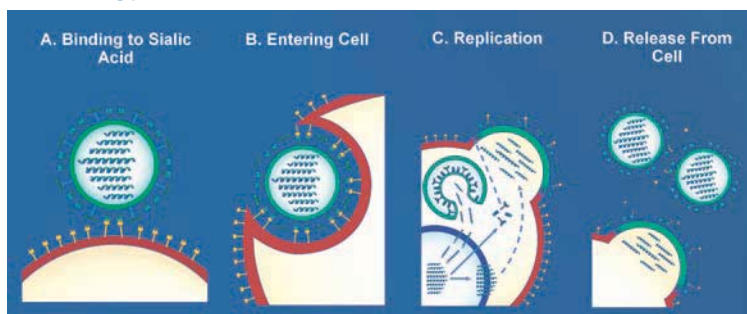
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How does TAMIFLU work?

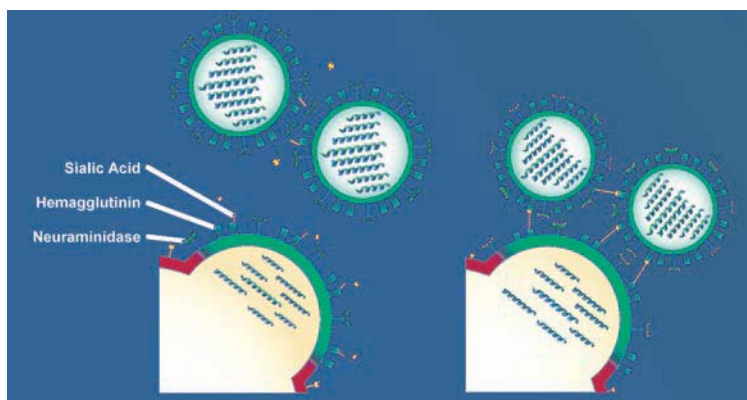
- Neuraminidase is a critical protein on the surface membrane of the influenza virus³⁸
- Enables the replicated influenza virus to bud from host cell³⁸
- Helps the virus to pass through mucous between cells in the entire respiratory tract³⁸
- Common to both influenza type A and type B
- In in vitro studies, inhibition of viral neuraminidase is shown to prevent newly formed influenza virus from escaping infected cells, therefore interrupting the spread of infection between cells^{38,39}
 - The relationship between the in vitro antiviral in cell culture and the inhibition of influenza virus replication in humans has not been established

The concept of neuraminidase inhibition

Pathology of influenza infection



Selective neuraminidase inhibition



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4. TAMIFLU® (oseltamivir phosphate) Background

What is the efficacy and safety profile of TAMIFLU?

Proven efficacy in clinical trials*

Treatment³⁴

In clinical trials for seasonal flu, adult patients who took TAMIFLU start to feel better sooner (30%, or 1.3 days faster) compared with patients who did not take TAMIFLU. Patients took TAMIFLU 75 mg twice daily for 5 days. Similar results were seen in children.

For more information, visit

http://www.tamiflu.com/hcp/treatment/treat_index.asp

Prevention

The results of a clinical study showed that TAMIFLU was effective for postexposure prophylaxis in adolescents and adults when taken once daily for 7 days.⁴⁰ In this study, 24 of 200 contacts in the placebo group developed clinical influenza compared with 2 of 205 patients taking TAMIFLU. The protective efficacy of TAMIFLU in this group was 92%.⁴⁰ Similar results were seen in children.

For more information, visit

http://www.tamiflu.com/hcp/prophylaxis/prophy_index.asp

Safety and tolerability

Prior to its launch, TAMIFLU was studied in more than 4,000 patients in clinical trial settings. In adult prevention trials, some patients were on TAMIFLU for up to 6 weeks.

TAMIFLU is generally well tolerated. In treatment studies in adult patients, the most frequently reported adverse events were mild to moderate transient nausea or vomiting. Other events reported more frequently than with placebo were bronchitis, insomnia and vertigo. Premature discontinuation of TAMIFLU use in clinical trials due to nausea or vomiting occurred in less than 1% of patients.

*H5N1 was not circulating at the time of these studies.

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4. TAMIFLU® (oseltamivir phosphate) Background

What evidence supports TAMIFLU activity against avian flu?

Nonhuman data do not necessarily indicate clinical activity in humans. To date, results from clinical studies in humans are not available. Data from in vitro and animal studies that have been performed are summarized below.

In vitro activity (ie, outside an organism) against H5N1

–One study compared viral activity of novel neuraminidase inhibitors, zanamivir and oseltamivir, against various strains of influenza A and B viruses (including 2 strains of H5N1 avian virus).⁴¹ The analysis demonstrated a high level of viral inhibitory activity by all compounds against the specified H5N1 strains (A/duck/MN/1525/81 and A/gull/PA/4175/83) of avian influenza

In vivo activity (in animals) against H5N1 and H9N2

- One study in ferrets showed that TAMIFLU administered 4 hours after inoculation prevented viral replication in the upper respiratory tract and effectively treated all infected ferrets with no deaths.⁴² All ferrets in the control group died
- Another in vivo study in mice tested oseltamivir for protection against avian strains H5N1 and H9N2.⁴³ The results showed that oseltamivir provided complete protection against the H5N1 virus starting at a dose of 0.1 mg/kg/day and against the H9N2 virus starting at a dose of 1.0 mg/kg/day. Additionally, oseltamivir was tested as a treatment regimen for the H5N1 virus. The treatment was incrementally delayed from 24 to 60 hours, and oseltamivir was shown to significantly increase the survival rates of mice (65%-90%) compared with the untreated group (0% survival)

In vitro and animal data do not necessarily demonstrate clinical activity. To date, results from clinical studies are not available.

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4. TAMIFLU® (oseltamivir phosphate) Background

What is the resistance profile of TAMIFLU?

Roche has both internal and external programs in place to monitor for emerging reports of resistance to TAMIFLU and has been rigorous in its efforts to evaluate the emergence of viral resistance to TAMIFLU.

What is the potential for TAMIFLU resistance?

- As with any antiviral, a theoretical potential exists for an influenza virus to emerge with decreased sensitivity to a drug
- TAMIFLU is a highly specific antiviral agent that acts by specific inhibition of the influenza virus neuraminidase^{44,45}
- The probability of resistance can be minimized by taking the prescribed dose for the full treatment duration

What is the incidence of resistance with TAMIFLU?

- Data collected from thousands of patients worldwide who were treated with TAMIFLU for seasonal influenza indicated that the incidence of resistant virus is rare^{44,45}
- In clinical studies 1.3% (4/301) of adults and adolescents and 8.4% (9/105) of pediatric patients showed emergence of resistant virus
 - Other analyses collected from approximately 4000 patients treated with TAMIFLU demonstrate an overall incidence of resistant virus of 0.4% in adults and 4.1% in children aged 1 to 12 years. This resistant virus was found to be less virulent than the wild type virus and did not affect the course of the illness
- Resistance cannot develop unless there is influenza virus present, ie, resistance cannot develop if a person who has a common cold is prescribed TAMIFLU inadvertently

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How is TAMIFLU dosed for seasonal influenza?*

TAMIFLU is recommended for use for both treatment and prophylaxis of influenza. The currently recommended doses are:

For treatment of influenza:

TAMIFLU must be taken within 48 hours of symptom onset

Adults: 75 mg twice daily for five days

Children 1 year of age or older: weight-adjusted doses

30 mg twice daily for ≤ 33 lbs

45 mg twice daily for >33 lbs to 51 lbs

60 mg twice daily for >51 lbs to 88 lbs

75 mg twice daily for >88 lbs

For prevention of influenza:

Adults and teenagers 13 years of age or older: 75 mg once daily for at least 10 days[†]

Children from 1 year to 12 years of age:

30 mg once daily for ≤ 33 lbs

45 mg once daily for >33 lbs to 51 lbs

60 mg once daily for >51 lbs to 88 lbs

75 mg once daily for >88 lbs

Use in children up to 1 year of age is not recommended.

*For further information, please see a healthcare provider.

[†]In adults, the safety and efficacy of TAMIFLU have been demonstrated for up to 6 weeks.

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