Available online on www.ajper.com

Asian Journal of Pharmaceutical Education and Research

Vol -4, Issue-1, January-March 2015

ISSN: 2278-7496

REVIEW ARTICLE

A WAR AGAINST INFLUENZA VIRUS - TAMIFLU

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Article Received on 15 November 2014

Accepted on 22 December 2014

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Abstract:

Tamiflu or oseltamivir is one of the blockbuster drugs used for prophylaxis and treatment of flu caused by influenza virus Type A (H1N1) and B. Oseltamivir was invented and patented by Californian company Gilead Sciences in 1996. A Swiss pharmaceutical company Hoffmann-La Roche (Roche)then purchased the rights of it and marketedthis drug worldwide under the trade name 'Tamiflu'. Roche Company had got approval for Tamiflu by US Food and Drug Administration (FDA)& Europe for prophylaxis in children and adults. The drug is now available in about 80 countries globally, including the US, EU countries, Latin America, Canada, Japan, Australia and Switzerland. This review overlooks on History, mechanism of action, dose, side effects, manufacturing processes, synthetic pathways, Clinical Efficacy and Claims of Tamiflu in treatment of Influenza.

KeyWords: Tamiflu, History, Marketing commentary,Clinical Efficacy and Claims, Influenza.

Introduction:

The emergence of the extremely aggressive avian H5N1 influenza virus, in particular in Asia, has made the likelihood of a human influenza pandemic and the possible socioeconomic impact a major worldwide concern. During seasonal influenza epidemics in the United States, it is estimated up to 431,000 patients are hospitalized and nearly 51,000 deaths can be attributed to influenza per annual epidemic. Influenza-related complications requiring hospitalization can result from direct effects of the disease or from complications associated with age, pregnancy, or underlying chronic conditions. An influenza infection can cause severe disease in patients of all ages but rates of infection tend to be highest among children and persons aged ≥65 years. Estimated rates of pulmonary or cardiac deaths related to an influenza infection per 100,000 persons are 0.4 to 0.6 in patients aged ≤49 years, 7.5 in patients aged 50-64 years, and 98.3 in patients aged ≥65 years. The appearance of H5N1, and the human fatalities it has already caused, has heightened the awareness of both the general population and governments to the threat of influenza virus to the extent that many governments have implemented preparedness plans, and available anti-influenza drugs are being stockpiled.

There has been considerable effort worldwide to discover novel therapeutic agents against all types of influenza, and several valuable reviews concerned with aspects of influenza virus have been published. Of the available drugs, Osmeltavir acts as blockbuster drug for the treatment of Influenza. This article reviews some background on the influenza virus and its key surface glycoprotein's and an overview on Osmeltavir.

The virus: The influenza virus belongs to the family of RNA viruses known as the orthomyxoviridae family. The influenza virus is divided into three serologic types (A, B, or C) and classified based on the type of surface glycoprotein present (hemagglutinin or sialidase). Only influenza viruses A and B appear to cause significant disease in humans and influenza a virus have been associated with higher mortality [1].

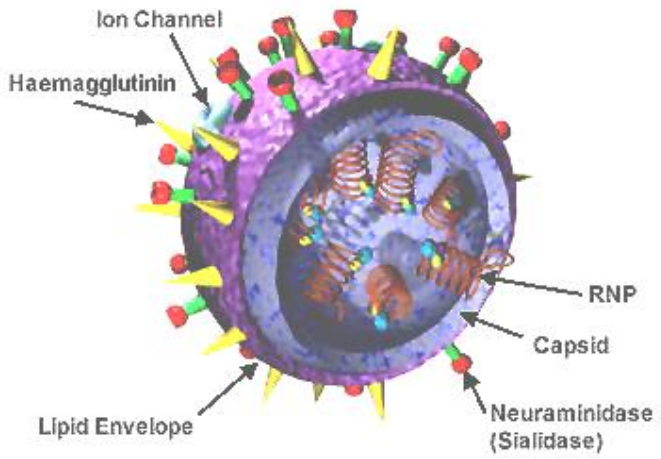


Figure 1: Structure of the influenza virus

Further classification of influenza virus is based on the antigenic properties of its surface glycoproteins haemagglutinin and sialidase (FIG. 1), both of which are essential for infection to proceed (FIG. 2). These surface glycoproteins are carbohydrate-recognizing proteins and in humans are known to recognize the sialic acid *N*‑acetylneuraminic acid.

Haemagglutinin is made up of three identical subunits (FIG. 1a) and is anchored to the lipid membrane of the virus. This glycoprotein seems to have two significant roles. The first is to provide an initial point of contact for the virus to the target host cell-surface glycoconjugates by α‑ketosidically linked terminal NeuAc residues1. The second is to trigger the internalization process of the virus through fusion of the viral envelope with the host cell.[2]

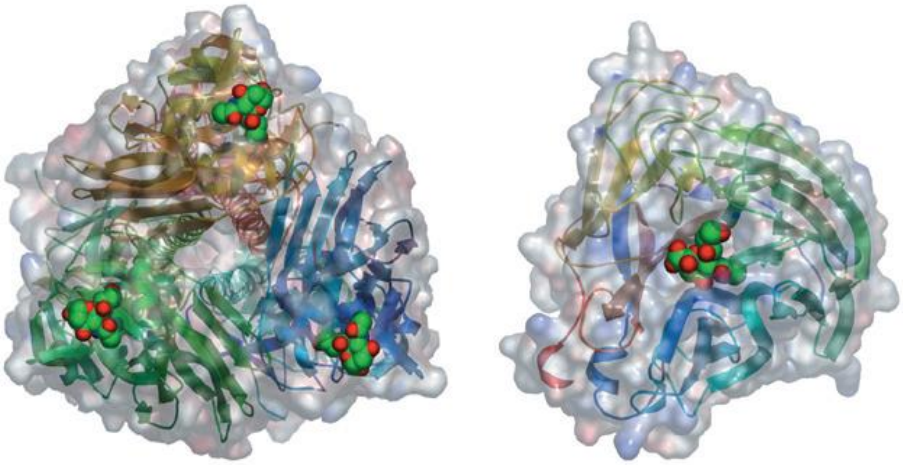


Figure 2:**Influenza virus surface glycoproteins.**

a- A view of the influenza virus haemagglutinintrimer complexed with *N*-acetylneuraminic acid (Neu5Ac; in CPK form).

b- A monomeric subunit of influenza A virus sialidase complexed with Neu5Ac (in CPK form). The catalytic site is located near the pseudo-symmetry axis).

Life cycle of the influenza virus and targets for therapeutic intervention:

The surface of influenza virus A is decorated with three proteins: an M2 ion channel protein, the lectinhaemagglutinin and the enzyme sialidase. Typically, the influenza virus adheres to the target host cell by using its surface glycoprotein haemagglutinin to recognize glycoconjugates such as GD1a that display terminal α‑linked *N*‑acetylneuraminicacid residues. The virus is then endocytosed, fusion occurs and the host-cell machinery is engaged to produce the necessary viral components. Subsequent viral protein synthesis and particle assembly in the host cell prepares the virion progeny for the budding process to exit the host cell. The enzyme sialidase cleaves the terminal α‑Neu5Ac residues from both the newly synthesized virion progeny glycoproteins as well as from the host-cell surface. The action of sialidase enables the host-cell-surface aggregated virion progeny to elute away from the infected cell and seek new host cells to infect. Both haemagglutinin and sialidase have been proposed as potential anti-influenza drug discovery targets. zanamivir and oseltamivir efficiently block the action of sialidase and significantly inhibit the release mechanism. The M2 ion channel protein of influenza virus A has also been targeted by a class of drugs referred to as the adamantanes, which include amantadine and rimantadine. Last, ribavirin has also been demonstrated to inhibit virus replication by acting on the RNA polymerase function.[3]

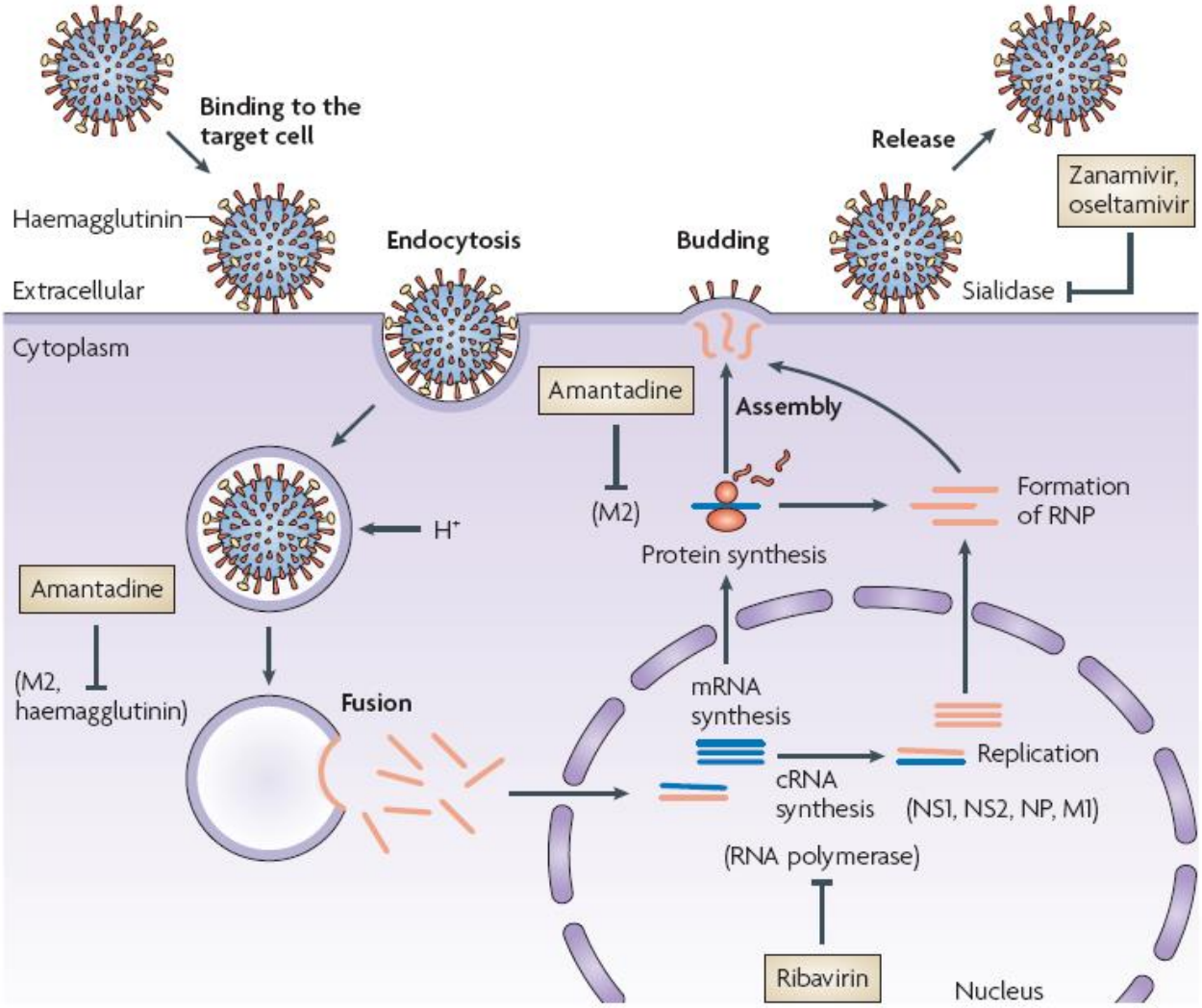


Figure 3: Life cycle of the influenza virus

Marketed Available Drug: Osmeltamivir

Oseltamivir, marketed under the trade name Tamiflu, is an antiviral licensed to prevent or slow the spread of influenza A and influenza B (flu) virus.

Chemically it is ethyl (3R, 4R, 5S)-5-amino-4-acetamido-3-(pentan-3-yloxy)-cyclohex-1-ene-1-carboxylate.

Oseltamivir is a prodrug, a (relatively) inactive chemical, which is converted into its active form by metabolic process after it is taken into the body. It was the first orally active neuraminidase inhibitor commercially available. Neuraminidaseenables the virus to continue to

infect host cells. The neuraminidase inhibitors prevent the influenza virus enzyme known to cleave the budding viral progeny from its cellular envelope attachment point just prior to release. This is thought to alter virus particle aggregation and replication. 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[4].

History of Osmeltamivir-Tamiflu

- ✓ Around 40 Hoffman-LaRoche sponsored randomised clinical trials -around the end of the nineties.
- ✓ In October 1999 and November 2000 FDA approved oseltamivir for treatment and prophylaxis of influenza.
- ✓ In June 2002 EMA approved oseltamivir for prophylaxis and treatment of influenza.
- ✓ In 2003 the Kaiser pooled analysis of 10 randomized clinical trials concluded that oseltamivir reduced the risk of lower respiratory tract infections resulting in antibiotic use and hospital admissions in adults.
- ✓ From 2004 governments around the world begun stockpiling oseltamivir by fears of avian influenza H5N1.
- ✓ In January 2006 a Cochrane review concluded that oseltamivir reduced complications such as pneumonia.
- ✓ The Kaiser 2003 paper drove the result in the meta-analysis.
- ✓ In 2009 a new A/H1N1 influenza virus was discovered to be spreading in North America.

From 2010 to 2012 Cochrane in vain requested the full clinical study reports of their trials to Roche, but in 2011 a freedom of information request to the European Medicines Agency provided them with the clinical study reports from Roche oseltamivir trials.[5][6]

Drug Profile [7]:

Name	**Oseltamivir**
Description	An acetamido cyclohexene that is a structural homolog of sialic acid and inhibits neuraminidase.
Salts	Oseltamivir phosphate
Categories	Antiviral Agents , Enzyme Inhibitors
Weight	Average: 312.4045
Chemical Formula	$C_{16}H_{28}N_2O_4$
IUPAC Name	ethyl (3R,4R,5S)-5-amino-4-acetamido-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate

Pharmacology:

Oseltamivir (Tamiflu) is for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who has been symptomatic for no more than 2 days. It is also used for the prophylaxis of influenza in adult patients and adolescents 13 years and older.[8]

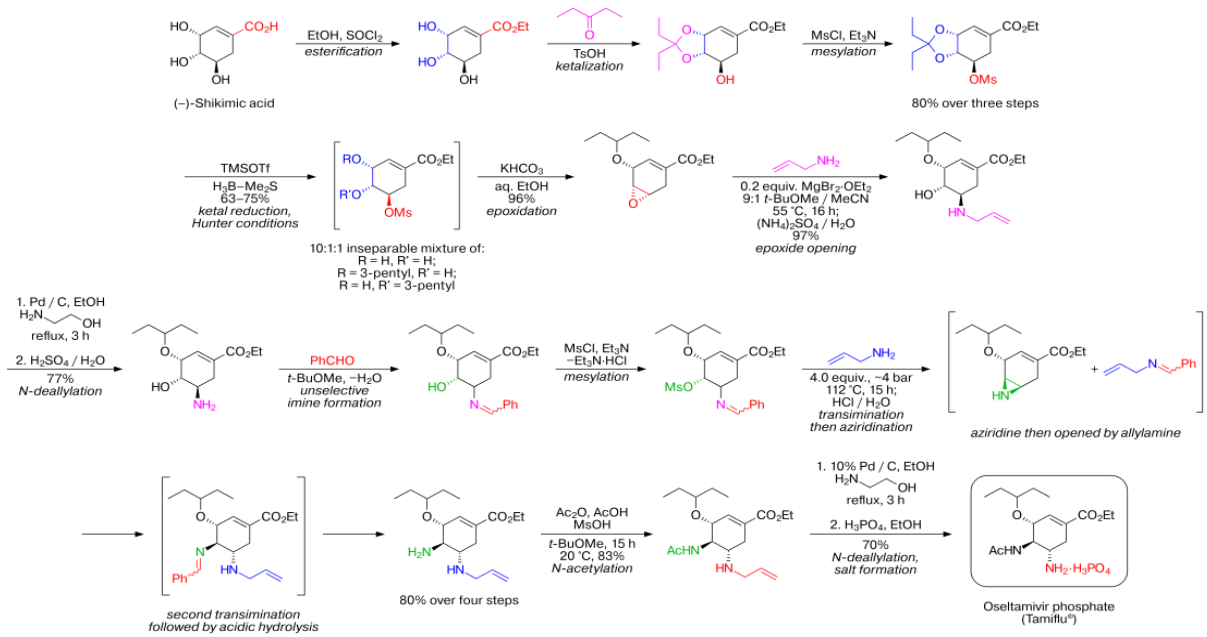
Pharmacokinetics:

- **Absorption**: Readily absorbed from the gastrointestinal tract after oral administration with a bioavailability of 75%.
- **Volume of distribution**: 23 to 26 L
- **Protein binding**: Oseltamivir carboxylate: low (3%), Oseltamivir free base: 42%.
- **Metabolism**: Extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate.
- **Route of elimination**: Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir carboxylate. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion.
- **Half life**: 1 to 3 hours in most subjects after oral administration.

- **Affected organisms**: Influenza Virus.[7]

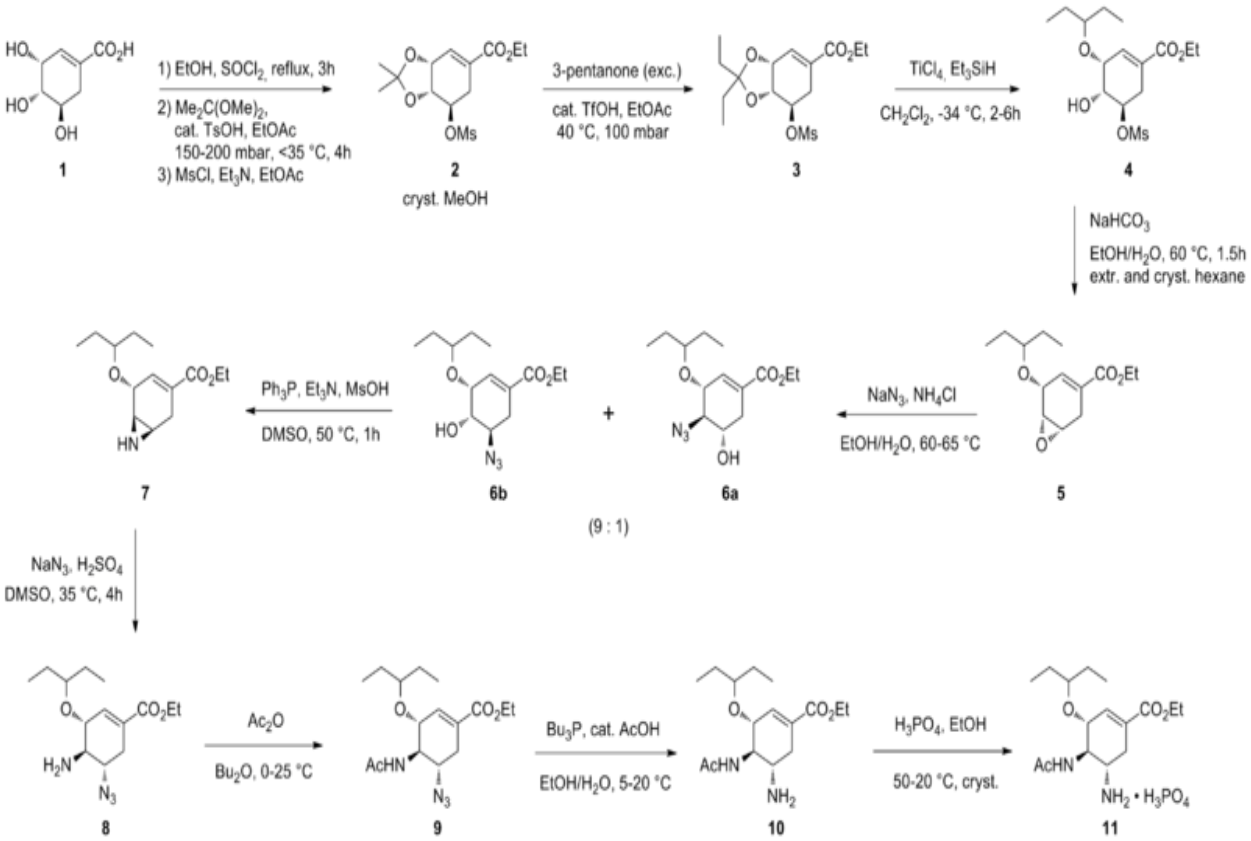
Chemical synthesis:

Aqueous solubility of oseltamivir in form of phosphate salt is 588 mg/ml at 25 °C (77 °F) [9]. The currentproduction method features a number of reaction steps, two of which involving potentially hazardous azides. A reported azide-free Roche synthesis of the drug is summarized graphically below.[10]



Manufacturing:

Oseltamivir is marketed by **Genentech** under the trade name Tamiflu, as capsules (containing oseltamivir phosphate 98.5 mg equivalent to oseltamivir 75 mg) and as a powder for oral suspension (oseltamivir phosphate equivalent to oseltamivir 6 mg/ml)[11]



Marketed formulations of Tamiflu: [7]

Form	**Route**	**Strength**
Capsule	Oral	
Capsule	Oral	75 mg
Powder, for suspension	Oral	
Powder, for suspension	Oral	12 mg/ml

Mechanism of action:

The prodrug oseltamivir is itself not virally effective; however, once in the liver it is hydrolysed to its active metabolite - the free oseltamivir carboxylate.[12]

Oseltamivir is a neuraminidase inhibitor, serving as a competitive inhibitor of the activity of the viral neuraminidase (NA) enzyme upon sialic acid, found on glycoproteins on the surface of normal host cells. By blocking the activity of the enzyme, oseltamivir prevents new viral particles from being released through the cleaving of terminal sialic acid on glycosylated hemagglutinin and thus fail to facilitate virus release[13].

Oseltamivir might induce a low immune response with low levels of pro-inflammatory cytokines. This may reduce symptoms of influenza, but is not related to inhibition of virus replication. There is also a potential temperature lowering effect that can contribute to symptom reduction. The influenza virus specific mechanism of action proposed by the producers does not fit the clinical evidence. Evidence rather suggests a multi-system and central action [14].

Dosage Forms along with dose and Price:

Unit description	**Cost**	**Unit**
Tamiflu 75 mg gel capsule	9.76USD	gel capsule
Tamiflu 45 mg gel capsule	9.76USD	gel capsule
Tamiflu 30 mg gel capsule	9.76USD	gel capsule
Tamiflu 12 mg/ml Suspension	51.0USD	bottle
Tamiflu 10 75 mg capsule Disp Pack	101.54USD	disp
Tamiflu 10 45 mg capsule Box	101.54USD	box
Tamiflu 10 30 mg capsule Box	101.54USD	box

Marketing commentary of tamiflu -

The patent for oseltamivir is held by Gilead Sciences and is valid at least until 2016. Gilead licensed the exclusive rights to Roche in 1996. The drug does not enjoy patent protection in Thailand, the Philippines, Indonesia, and several other countries[15].

In late October 2005, Roche announced it was suspending shipments to pharmacies in the United States and Canada until the North American seasonal flu outbreak began, to address concerns about private stockpiling and to preserve supplies for seasonal influenza.[36] Sales were suspended in Hong Kong as well, and on November 8, 2005, also in China. Roche said it would instead send all supplies to China's health ministry[17].

On November 9, 2005, Vietnam became the first country to be granted permission by Roche to produce a generic version of oseltamivir. The week before, Thai authorities said they would begin producing generic oseltamivir, claiming that Roche had not patented Tamiflu in Thailand.[18] The first Thai generic oseltamivir was produced in February 2006, and was to have been available to the public in July 2006.

In November 2005, U.S. President George W. Bush requested that Congress fund US$1 billion for the production and stockpile of oseltamivir, after Congress had already approved $1.8 billion for military use of the drug. Defense Secretary Rumsfeld recused himself from all government decisions regarding the drug.[19]

In December 2005, Roche signed a sublicense for complete oseltamivir production with China's Shanghai Pharmaceuticals, and by March 2006, a sublicense had also been granted to India's Hetero [20, 21].

In May 2006, the WHO asked Roche to be ready to ship an emergency stockpile of oseltamivir to Indonesia if needed. The alert was in response to suspected human-to-human transmission within a family, and was planned to last for two weeks [22].

In December 2008, the Indian drug company, Ciplawon its case in India's court system allowing it to manufacture a cheaper generic version of Tamiflu, called Antiflu. In May 2009,

Cipla won approval from the WHO certifying that its drug Antiflu was as effective as Tamiflu, and Antiflu is included in the WHO list of prequalified medicinal products [23].

Tamiflu has been found to be active against the new swine flu virus A (H1N1) discovered in 2009, according to the reports from the WHO, the US Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC). In April 2009 the CDC even came out with a guidance that has recommended the use of Tamiflu or Relenza (zanamivir) for the prophylaxis and treatment of swine flu.

Clinical Efficacy:

Clinical evidence evaluating the risk of influenza-related complications and hospitalization suggests improved outcomes with oseltamivir therapy compared to another antiviral therapy. A second trial found reduced risk of influenza-related complications and healthcare costs when oseltamivir was prescribed immediately upon presentation of influenza. In addition, when oseltamivir was used as post-exposure prophylaxis, improvements were seen in rates of morbidity and mortality associated with influenza infection.38 overall, current evidence suggests oseltamivir and zanamivir are effective options for treatment of influenza A or B [24].

Side Effects and Safety for Adults:

- ✓ Safety and tolerability have been established since 1999.
- ✓ Over 30 million Tamiflu prescriptions have been dispensed in the US over the past 12 years.
- ✓ Tamiflu has a demonstrated safety profile in children (>1 year of age), adults, and the elderly (>65 years of age).
- ✓ In vitro studies showed no interference with the cytochrome P450 pathway.
- ✓ No pharmacokinetic interactions have been observed when co-administering oseltamivir with amoxicillin, acetaminophen, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), or warfarin.

Side Effects and Safety for Childrens aged 1-12 years:

- ✓ Approximately 27.8 million Tamiflu prescriptions have been dispensed in the U.S. over the past 11 years.

- ✓ Demonstrated safety profile in children (≥1 year of age), adults, and the elderly (>65 years of age).
- ✓ In vitro studies showed no interference with the cytochrome P450 pathway.
- ✓ Co-administration with amoxicillin does not alter plasma levels of either drug.

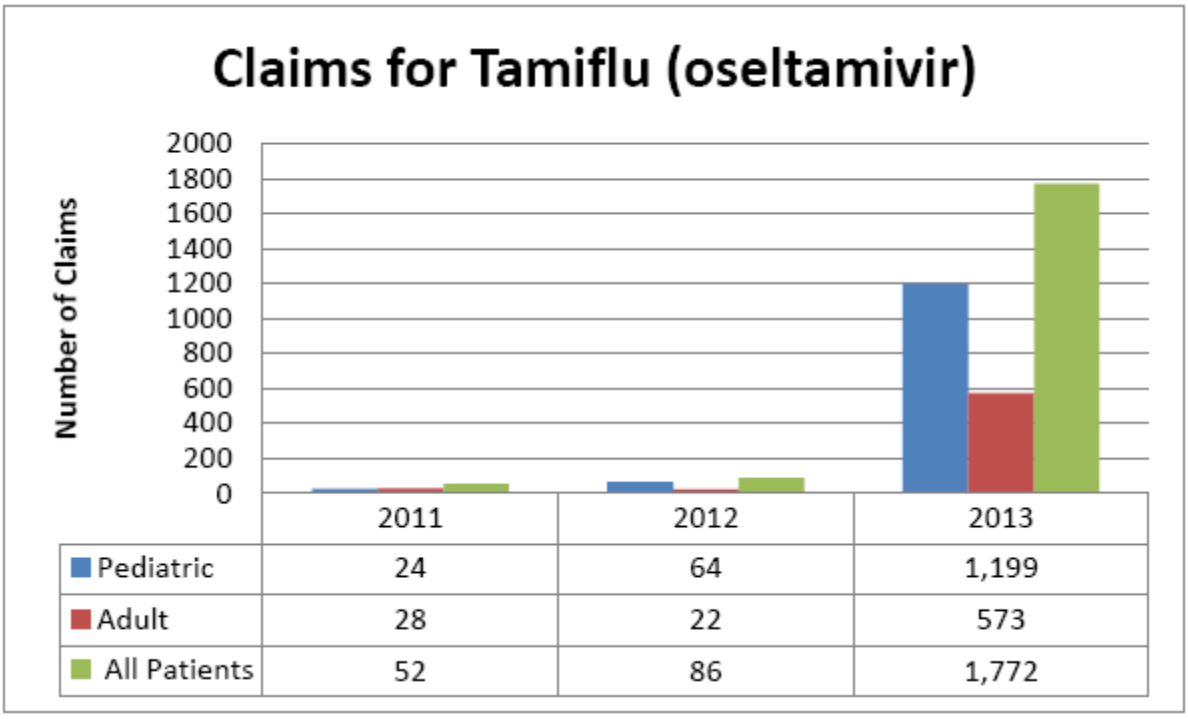
Safety comparison:

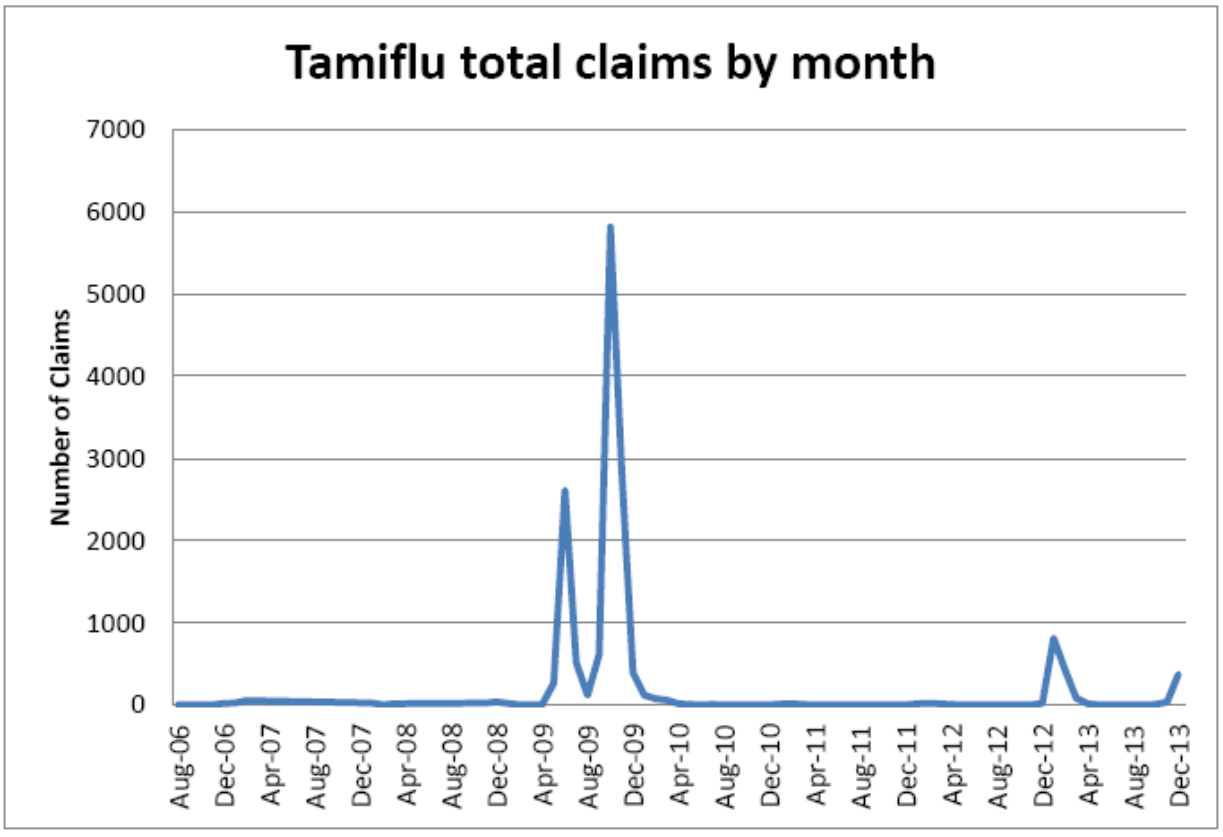
The neuraminidase inhibitors are well tolerated by patients with influenza infection. The most common drug-related adverse reactions to neuraminidase inhibitors include gastrointestinal adverse events (vomiting, nausea, abdominal pain, and diarrhea)[25].

Table 2. Adverse Reactions (%) to Anti-Influenza Agents Based on Package Inserts

	CNS adverse reactions	**Gastrointestinal adverse reactions**	**Orthostatic hypotension**	**Peripheral edema**	**Respiratory adverse reactions**	**Weakness**
Adamantanes						
Amantadine	1-10	1-10	1-10	1-10	1-10	<1
Rimantadine	Insomnia(2-3), Concentration impaired (≤2), Dizziness(1-2), Nervousness (1-2), Fatigue (1), Headache (1)	1-3	NR	<1	<1	1
Neuraminidase Inhibitors						
Oseltamivir	NR	Vomiting (2-15), Nausea (4-10), Abdominal pain (2-5), Diarrhea (1-3)	NR	NR	1-10	NR
Zanamivir	>10	>0	NR	NR	>10	1-10

Claims for Tamiflu[26]:





Detailed Utilization Data:

GENERIC	DESCRIPTION	2011				2012				2013			
		Claims	Pediatric	Adult	All Patients	Claims	Pediatric	Adult	All Patients	Claims	Pediatric	Adult	All Patients
Oseltamivir Phosphate	Tamiflu 30 mg Caps	1	1	0	1	0	0	0	0	60	0	55	55
Oseltamivir Phosphate	Tamiflu 45 mg Caps	0	0	0	0	0	0	0	0	62	0	59	59
Oseltamivir Phosphate	Tamiflu 75 mg Caps	31	4	26	30	22	2	19	21	788	223	549	772
Oseltamivir Phosphate	Tamiflu 6 mg/ml Susp	13	12	1	13	64	62	2	64	857	805	12	817
Oseltamivir Phosphate	Tamiflu 12 mg/ml Susp	7	7	0	7	0	0	0	0	5	4	1	5
		52	24	27	51	86	64	21	85	1,772	1,146	562	1708

Conclusion:

Currently, oseltamivir or Tamiflu are recommended for the treatment of confirmed or suspected cases of influenza. According to the most recent evidence, oseltamivir is effective options for treatment of influenza A or B. Some evidence suggests oseltamivir is less effective against Influenza B than Influenza A. With regard to safety, the neuraminidase inhibitors are generally well tolerated and the most common drug-related adverse reactions reported are gastrointestinal adverse events.

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