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Oseltamivir

Anne Bardsley-Elliot and *Stuart Noble*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Oseltamivir is the oral prodrug of GS4071, a selective inhibitor of influenza A and B viral neuraminidase. After absorption from the gastrointestinal tract oseltamivir is efficiently converted to GS4071, which is maintained at high and sustained concentrations in plasma.

▲ Based on studies in rats and ferrets, GS4071 appears to be effectively distributed to all tissues, including major sites of infection in the upper and lower respiratory tracts.

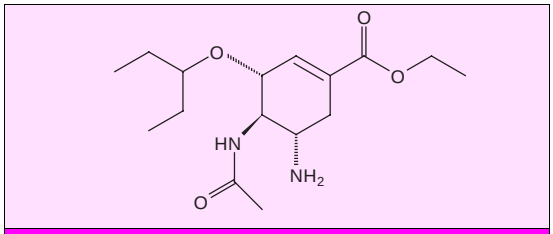
▲ Oral oseltamivir was an effective treatment in naturally occurring influenza when administered within 36 hours of symptom onset, reducing both the duration and severity of symptoms and the incidence of secondary complications in influenza-infected patients enrolled in 2 large placebo-controlled, double-blind trials.

▲ Prophylactic oral administration of oseltamivir was effective in reducing the incidence of influenza illness according to pooled data from 2 large placebo-controlled, double-blind trials of healthy nonimmunised volunteers during periods of seasonal influenza activity.

▲ The reported incidence of viral resistance to GS4071 was low in clinical isolates from oseltamivir treatment studies. All known GS4071 resistant genotypes are growth disadvantaged and display significantly reduced infectivity in animals.

▲ Oseltamivir was well tolerated in human volunteers and patients in clinical trials. Treatment-related adverse events (primarily gastrointestinal) were mild and transient in nature.

Features and properties of oseltamivir (GS4104, RO 64-0796)	
Indications	
Influenza A and B infection (treatment and prevention)	
Mechanism of action	
Antiviral	Neuraminidase inhibitor
Dosage and administration	
Usual dosage in clinical trials	Treatment: 75 or 150mg twice daily × 5 days Prophylaxis: 75mg once or twice daily × 6 weeks
Route of administration	Oral
Pharmacokinetic profile (of GS4071 after oral oseltamivir 100mg single dose in healthy volunteers)	
Peak plasma concentration	250 μg/L
Time to peak plasma concentration	2-3h
Area under the concentration-time curve (0-∞)	2.7 mg/L • h
Elimination half-life	8.2h
Adverse events	
Most frequent	Mild and transient nausea
Serious events	None



Oseltamivir

Influenza virus continues to exert an enormous toll on society in terms of illness, loss of productivity, medical consultations, hospitalisation and death. Mortality due to influenza infection is estimated at 20 000 per year in the US alone, and the disease affects all age groups.[1] Death rates have not changed in the last 60 years despite use of vaccines, and continuing pandemics of influenza infection are likely.[2] Recently, neuraminidase (sialadase) inhibitors have been developed for prophylactic and therapeutic use against influenza, specifically targeting the highly conserved active site of the viral enzyme. The first such compound to reach clinical trials was zanamivir, which is not orally active and thus is administered by dry powder inhalation to the lungs. Oseltamivir has been specifically designed as an orally active prodrug that is easier to administer than an inhaled drug. After oral administration, the active drug is able to reach all sites of influenza virus infection.

1. Pharmacodynamic Profile

Mechanism of Action

• Oseltamivir is the ethyl ester prodrug of GS4071, a highly selective inhibitor of influenza virus-encoded neuraminidase. It is enzymatically converted to active GS4071 after oral administration (see section 2). The lipophilic side chain on GS4071, a modification from other sialic acid mimics such as zanamivir, exploits a hydrophobic pocket at the active site of the virus enzyme. Binding of the drug blocks the enzyme's ability to cleave sialic acid residues on the surface of the infected cell, thereby inhibiting release of progeny virions from infected cells.

Antiviral Activity

In Vitro

Oseltamivir is converted *in vivo* to GS4071, which inhibits influenza neuraminidase and is active in antiviral assays. GS4071 was used in the *in vitro* experiments described below.

• GS4071 acts as a competitive inhibitor of both influenza A and B neuraminidase *in vitro*. When tested against a variety of influenza A and B subtypes, GS4071 showed inhibitory activity against all strains in low nanomolar concentrations [kinetic inhibition constant (K_i) = 0.5 to 1.2 nmol/L]. GS4071 inhibitory activity against neuraminidases from other sources, including parainfluenza virus and Newcastle disease virus, was at least 10^6-fold lower ($K_i \geq 360$ μmol/L).[3]

• GS4071 was approximately 3 to 6 times more potent than zanamivir in inhibition of N2 neuraminidase activity [concentration required to inhibit enzyme activity by 50% (IC_{50}) 0.3 to 0.8 *vs* 1.1 to 4.6 nmol/L].[3] Similarly, the concentration of GS4071 required to produce 50% inhibition of viral plaque formation (EC_{50}) in Madin Darby canine kidney (MDCK) cells was consistently lower than that of zanamivir for influenza A N2 laboratory strains (EC_{50} 0.6 to 0.8 *vs* 3.1 to 3.5 nmol/L).[3] Similar results were observed using an assay for inhibition of viral cytopathic effect.[3,4]

• The antiviral and antineuraminidase potency of GS4071 and zanamivir were similar for other laboratory strains and recent clinical isolates, aside from 1 influenza B isolate (B/Harbin/07/94) for which the EC_{50} value of zanamivir was 3-fold lower than that of GS4071 (IC_{50} values for enzyme inhibition were comparable). GS4071 inhibited replication of all influenza viruses tested, with EC_{50} values varying from 0.6 nmol/L for influenza A/Victoria/3/75 (H3N2) to 155 nmol/L for influenza B/Hong Kong/5/72.[3]

• GS4071 exhibited antiviral activity against a laboratory strain of influenza A/Texas/91 (H1N1)

in a transformed human bronchial epithelial cell line (BEAS-2B) with an EC_{90} value (90% effective concentration; ≥1 log_{10} reduced virus yield at 48 hours) 10-fold lower than that of zanamivir (0.02 *vs* 0.2 μg/ml for zanamivir; published as an abstract).[5]

In Animal Models

• In mice, oseltamivir provided dose-dependent protection against a 90% lethal dose of influenza virus when administered by oral gavage 4 hours prior to inoculation and continued twice daily for 5 days. Survival rates were assessed at 21 days post infection. Complete protection against influenza A/NWS/33 (H1N1) and A/Victoria/3/75 (H3N2) and nearly complete protection against influenza B/Hong Kong/5/72 was achieved with oseltamivir 10 mg/kg/day, whereas survival among control mice was low. Oseltamivir was also protective at 1 mg/kg/day against A/NWS/33, and at 3.2 mg/kg/day against B/Hong Kong/5/72 ($p < 0.01$ *vs* untreated controls).[3]

• Oseltamivir significantly increased survival of influenza A/NWS/33 (H1N1)-infected mice at a lower dosage (1 mg/kg/day) than either GS4071 or zanamivir when administered by oral gavage twice daily for 5 days (0.1 to 10 mg/kg/day) beginning 4 hours prior to virus exposure. Complete survival (8 of 8 animals) was achieved with the 10 mg/kg/day oseltamivir dose regimen, and nearly complete survival (7 of 8) was achieved with 1 mg/kg/day ($p < 0.01$ *vs* saline treated controls). Survival of mice receiving oral GS4071 or zanamivir 1 mg/kg/day was not significantly improved over that of saline-treated control mice (3 or 2 of 8).[4]

• Peak lung virus titres in influenza A/NW5/33 (H1N1)-infected mice were lowered to a greater extent with oral oseltamivir 10 mg/kg/day than with the same dose of zanamivir. Moreover, a low oral oseltamivir dosage (0.1 mg/kg/day) significantly increased the mean number of days to death (11.1 *vs* 9.6 for saline-treated controls; $p < 0.01$) and reduced pulmonary function decline (measured by decrease in arterial oxygen saturation; mean day-10 SaO_2 = 83 *vs* 77.8% for control mice; $p < 0.05$). Similar low dosages of oral GS4071 or zanamivir were not effective at improving these parameters relative to infected, saline-treated controls.[4]

• Oral oseltamivir was effective against moderate virus challenge in mice even when administration was delayed up to 60 hours after infection. At dosages of 10 mg/kg/day for 5 days, mice were fully protected against virus-induced SaO_2 decline and death. High virus challenge required administration of the same dosage within 24 to 36 hours of inoculation.[4]

• Ferrets infected with influenza virus exhibit symptoms similar to those observed in humans. Administration of oral oseltamivir 5 or 25 mg/kg twice daily to ferrets, initiated 2 hours prior to virus exposure and continued twice daily for 3 days, reduced peak virus titres in nasal washings 2- or 8-fold, respectively ($p < 0.01$ *vs* untreated control for the 8-fold decrease). In animals receiving oseltamivir 25 mg/kg/day, the peak number of inflammatory cells present in nasal washings was 10% that for untreated infected controls.[3] Similar treatment was also shown to reduce inflammatory cell counts in bronchial alveolar lavage compared with vehicle treatment (1.5×10^6 *vs* 7.1×10^6 cells/ml).[6]

• In ferrets inoculated with influenza B/Argentina/97 virus, oral oseltamivir (5 mg/kg initiated 2 hours prior to viral challenge and continued twice daily for 6 days) reduced viral titres in nasal washes (≈0.3 *vs* 4.0 log_{10} 50% tissue culture infective doses [$TCID_{50}$] on day 2; $p = 0.004$) compared with animals receiving vehicle alone.[6,7]

In Humans with Experimental Influenza

• When given as an early treatment in experimental influenza in humans, oseltamivir significantly reduced the amount of virus shed, the duration of viral shedding, and the duration of symptoms compared with placebo. In a randomised, double-blind trial, 80 susceptible adults were inoculated intranasally with ~10^6 $TCID_{50}$ of influenza A/Texas/91 (H1N1) and given twice-daily oral oseltamivir 20, 100 or 200mg or placebo, or once-daily oseltamivir 200mg (n = 16 per group), starting 28 hours

after inoculation and continuing for 5 days.[8] In individuals with confirmed influenza infection, viral load was reduced 100-fold at 24 hours and 1000-fold at 36 hours in the combined oseltamivir groups compared with the placebo group ($p \leq 0.05$). The duration of viral shedding was significantly reduced with oseltamivir (combined groups; $p \leq 0.01$) compared with placebo, as was the median time to resolution of illness ($p = 0.03$) [fig. 1].

• In the above study, local production of pro-inflammatory cytokines IL-6, TNFα and IFNγ was reduced in nasal washings of influenza-infected volunteers receiving oseltamivir 20 to 200mg compared with those receiving placebo. Production of these cytokines increased 4-, 2- and 3-fold above baseline, respectively, in placebo recipients after experimental infection with influenza A/Texas/91 (H1N1), significantly correlating with viral titre ($p \leq 0.01$). No increases from baseline were observed in oseltamivir recipients.[8,9]

• The efficacy of oseltamivir against influenza B was evaluated in a randomised, double-blind, placebo-controlled trial in 60 healthy volunteers

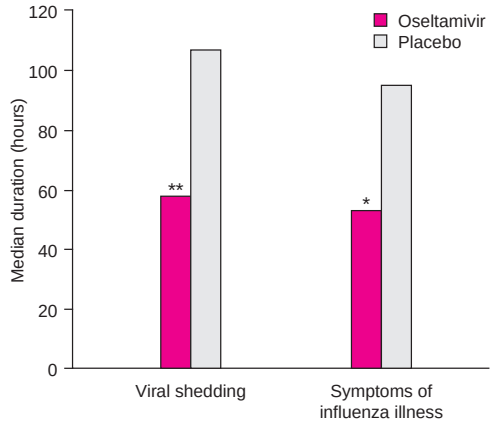


Fig. 1. Effect of oral oseltamivir on duration of viral shedding and symptoms of influenza illness in experimentally infected volunteers. Eighty susceptible adults were intranasally inoculated with influenza A/Texas/91 (H1N1) in a randomized, double-blind, placebo-controlled trial.[8] Oseltamivir data were pooled from groups receiving 20 to 200mg twice daily or 200mg once daily for 5 days, beginning 28 hours after inoculation. * $p = 0.03$, ** $p \leq 0.01$ *vs* placebo.

intranasally inoculated with 10^7 $TCID_{50}$ of influenza B Yamagata/16/88 virus.[10] Treatment with oseltamivir 75 or 150mg twice daily or placebo was initiated 24 hours after viral inoculation, although the number of individuals with confirmed infection was low. The median viral titre AUC decreased by >95% in the combined oseltamivir groups compared with the placebo group (5.9 *vs* 149.7 $\log_{10}$ $TCID_{50}$/ml · h, not significant), and the duration of viral shedding was correspondingly reduced (95.7 *vs* 17.7 hours; $p = 0.042$). There was a trend toward reduction of peak viral titre and duration and severity of symptoms among oseltamivir recipients compared with placebo recipients, but these end-points did not reach statistical significance because of small sample size.

• Oseltamivir was also effective in prevention of experimental influenza in humans. In a randomised, placebo-controlled double-blind trial, healthy adult volunteers received once- or twice-daily doses of oseltamivir 100mg or placebo beginning 26 hours prior to viral inoculation [~10^6 50% $TCID_{50}$ of influenza A/Texas/91 (H1N1)] and continuing for 5 days.[8,11] Challenge virus was recovered from 6 of 12 placebo recipients, but from none of the 21 oseltamivir recipients ($p = 0.0008$). More placebo recipients (8 of 12) than oseltamivir recipients (4 of 11 in the once-daily group and 4 of 10 in the twice-daily group) exhibited serological evidence of infection, and significantly more placebo recipients developed infection–associated upper-respiratory illness (4/12 for placebo *vs* 0/21 for oseltamivir combined groups; $p = 0.01$).

Cytotoxicity and Other Effects

• Oseltamivir and GS4071 have not been associated with secondary or toxic effects either *in vitro* or in animal and human *in vivo* studies.[3,4,12,13] No cytotoxic effects were observed in cell culture with GS4071 concentrations up to 1 mmol/L.[3]

• No signs of toxicity were found in rats following administration of oral oseltamivir 40 to 800 mg/kg/day for 14 days. Oseltamivir had no effects on body and organ weight, organ histopathology or haema-

tology parameters at doses at least 50-fold higher than those required to protect mice against the lethal effects of influenza virus infection.[3]

• Oseltamivir did not inhibit the primary immune response to influenza A (H1N1) virus infection in mice. Spleens from influenza virus-infected mice administered twice daily with oral oseltamivir at dosages of 100 mg/kg/day for 5 days (beginning 4 hours prior to virus exposure) were examined for immunological effects of therapy. Cytotoxic T lymphocyte activity and macrophage, T, T-helper, T-suppressor and B cell populations were similar to those of untreated infected animals, which exhibited an active primary immune response relative to uninfected controls.[14]

Viral Resistance

The substrate binding pocket of influenza neuraminidase is highly conserved because of its crucial role in enzyme function and viral replication. Because sialic acid mimics such as GS4071 act by binding to this site, development of resistant virus may be suppressed, as changes to the active site would be expected to reduce viability of the virus.[15]

• Resistance to GS4071 in clinical isolates from oseltamivir treatment studies was reported to be low (<1%).[16]

• Although influenza neuraminidase variants with reduced sensitivity to GS4071 have been generated *in vitro* after repeated passaging of influenza A viruses [A/Victoria/3/75 (H3N2) and A/turkey/Minnesota/833/80 (H4N2)] with GS4071 or zanamivir, these strains exhibited reduced neuraminidase activity and were at least 400-fold less infectious than wild-type virus *in vivo*.[17,18]

2. Pharmacokinetic Profile

Absorption

• The prodrug oseltamivir was developed to enhance the pharmacokinetic profile of its active parent compound GS4071, the oral bioavailability of which is low (5%) in animals, and similar to zanamivir (2%).[19,20] In a single-dose, randomised crossover study, 12 healthy male volunteers received 150mg of drug either as an intravenous infusion of GS4071 or an oral dose of oseltamivir under nonfasting conditions. Absolute bioavailability of GS4071 after administration of oral oseltamivir was approximately 80%, based on comparisons of the area under the plasma concentration-time curve (AUC) and urinary excretion.[21]

• Pharmacokinetic properties of oseltamivir and the active metabolite GS4071 were monitored under fasting conditions in 48 healthy male volunteers. After administration of single oral doses of oseltamivir 20 to 1000mg, GS4071 reached a high and sustained plasma concentration, remaining at 35% of its peak level (C_{max}) 12 hours after administration. C_{max} for the 100mg dose was 250 μg/L; time to C_{max} (t_{max}) was 3.7 hours, and $AUC_{0-\infty}$ was 2.7 mg/L · h. The plasma concentration of oseltamivir peaked earlier and declined more rapidly than that of GS4071, reaching a C_{max} of 15 to 30% of the GS4071 C_{max}. The AUC for GS4071 increased dose proportionally over the 20 to 1000mg oseltamivir dose range. The AUC for oseltamivir was approximately 4% of that of GS4071, indicating efficient conversion of the prodrug to the active species.[12]

• Administration of oseltamivir with food in a randomised crossover study in 18 healthy volunteers did not significantly affect the C_{max} or overall systemic exposure to the active metabolite, although GS4071 t_{max} was delayed by approximately 1 hour following a high fat, high calorie breakfast.[22]

Distribution

• Influenza infection in ferrets is manifested primarily in the upper respiratory tract, where the virus replicates in nasal epithelial cells. Whole body autoradiography after oral administration of 5mg ^{14}C-labelled oseltamivir in ferrets demonstrated that GS4071 was distributed to all tissues, with good penetration to the middle ear, trachea lining and nasal mucosa. High concentrations were

observed in the lungs, where exposure (AUC_{0-6h}) was 5-fold higher than that found in blood.[23]

• The concentration-time profile of GS4071 in rat serum and bronchoalveolar lining fluid (BALF) was evaluated following oral administration of oseltamivir and intravenous injection of GS4071 (doses equivalent to 30 mg/kg GS4071).[24] The C_{max} value of GS4071 in BALF was similar to that in plasma, but the terminal half-life was approximately 4-fold longer in BALF.

• The tissue distribution of radiolabelled oseltamivir was examined in rats at 1, 6 and 24 hours after oral administration of a single 10 mg/kg dose. Lung concentrations at 6 hours post-administration were 2-fold higher than in serum, increasing to 30-fold higher at 24 hours. Highest concentrations of radioactivity were found in the gastrointestinal tract, liver and kidney.[25]

Metabolism and Elimination

• Oseltamivir is extensively converted to its active metabolite GS4071 by hepatic esterases. No other metabolites have been identified in humans.[26]

• The elimination half life ($t_{½}$) of GS4071 after administration of single oral doses of oseltamivir (20 to 1000mg) in healthy volunteers ranged from 6.7 to 8.2 hours.[27]

• Oseltamivir and GS4071 are primarily eliminated via the kidneys, through a combination of glomerular filtration and renal tubular excretion.[26] Approximately 5% of an oral oseltamivir dose is excreted unchanged in urine; 60 to 70% appears as GS4071. Less than 20% of an oral dose is excreted in faeces (50% as oseltamivir, 50% as GS4071).

Pharmacokinetics in Special Patient Groups

Elderly Individuals

• Comparison of C_{max} and $t_{½}$ values of GS4071 after oral administration of oseltamivir in 32 healthy young (aged 18 to 55 years) and 24 healthy elderly (aged ≥ 65 years) volunteers revealed similar pharmacokinetic profiles for the 2 groups, although the exposure to the active drug was moderately higher in the elderly group.[26,27] Based on comparative AUC values, a 7-day 150mg twice daily dosage regimen in healthy elderly individuals provided a GS4071 exposure profile comparable to a 200mg twice daily dosage regimen in healthy young individuals.[13] The difference in drug exposure between young and elderly individuals was not sufficient to warrant dose adjustments in the elderly.[27]

Individuals with Renal Impairment

• In groups of volunteers with normal or impaired renal function, [creatinine clearance (CL_{CR}) from >90 to <30 ml/min], elimination of oseltamivir and GS4071 decreased with increasing renal impairment, thereby increasing total drug exposure. This increase in exposure did not result in reduced tolerability of oseltamivir, although dose adjustments may be recommended in individuals with severe renal impairment (CL_{CR} <30 ml/min).[28]

Drug Interactions

• Unpublished *in vitro* data have indicated that neither oseltamivir nor GS4071 interact with human cytochrome P450 mixed-function oxidases or glucuronyl transferases, suggesting that drug interactions based on competition with P450 are unlikely.[7,26]

• The combination of oral oseltamivir 200mg (after 5 days of twice daily 200mg doses) and paracetamol 500mg resulted in moderate but non-statistically significant decreases in paracetamol AUC (13%) and C_{max} (9%) in a randomised crossover study in 6 healthy male volunteers. Concomitant administration of paracetamol and oseltamivir did not alter the pharmacokinetic profile of GS4071 compared with that in historical controls receiving oseltamivir alone.[29]

• In a randomised crossover study in healthy volunteers (n = 18), concurrent administration of oral oseltamivir 150mg with cimetidine (400mg 4 times daily) did not alter the pharmacokinetics of oseltamivir or GS4071. Coadministration of oseltamivir with probenecid (500mg 4 times daily), how-

ever, increased the overall exposure (AUC) to GS4071 2.5-fold due to a 50% reduction in renal clearance.[30] This change was not considered clinically relevant based on the wide safety margin of oseltamivir (see section 4).

3. Clinical Efficacy

Trials of oseltamivir for both treatment and prevention of influenza virus infection were conducted in otherwise healthy adult volunteers in the US, Canada, Europe and China during periods of seasonal influenza activity.

Treatment

• Orally administered oseltamivir was effective in decreasing both the duration and the severity of illness when evaluated as an early treatment for symptoms of naturally acquired influenza in 2 randomised, placebo-controlled, double-blind, multicentre trials.[31,32] A total of 1348 otherwise healthy, non-immunised adults with acute febrile respiratory illness received oseltamivir 75 or 150mg or placebo twice daily for 5 days, initiated within 36 hours of symptom onset. Compared with placebo treatment, both oseltamivir 75 and 150mg significantly reduced the time to alleviation of symptoms (≥25%, $p \leq 0.017$ and ≥30%, $p \leq 0.006$, respectively) in individuals who developed influenza infection (fig. 2). This effect was evident as early as 24 hours after initiation of treatment.

• Oseltamivir was particularly effective as an early intervention in alleviation of influenza symptoms. When treatment was initiated within 24 hours of symptom onset, oseltamivir reduced illness duration by up to 40% ($p \leq 0.02$ *vs* placebo) [fig. 2].[32]

• The effect of treatment on severity of illness was assessed by patients' scores of the presence and severity of influenza symptoms (cough, sore throat, fatigue, headache, myalgia and feverishness), and the area under the curve of symptom scores (symptom score AUC) was expressed as 'score-hours' (reported for only 1 of the 2 studies). By this measure, oseltamivir (either dosage) significantly reduced the severity of illness by >35% compared with placebo ($p \leq 0.0001$) [fig. 3].[31]

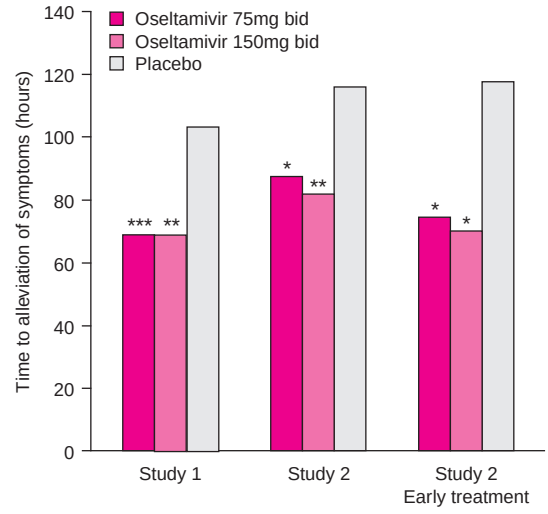


Fig. 2. Therapeutic efficacy of oral oseltamivir on duration of influenza illness in 2 separate placebo-controlled, double-blind trials.[31,32] A total of 1348 adults with acute respiratory illness were randomised to receive oral oseltamivir 75 or 150mg, or placebo twice daily (bid) for 5 days beginning within 36 hours symptom onset. In Study 2, a subset of patients received treatment within 24 hours (early treatment; patient numbers not reported). Patients with confirmed influenza infection were included in the analysis (Study 1,[31] n = 374; Study 2,[32] n = 475). * $p < 0.02$, ** $p \leq 0.007$, *** $p < 0.0001$ *vs* placebo.

• The effect of oseltamivir treatment on the incidence of secondary complications of influenza infection was assessed in 887 infected patients enrolled in 3 placebo-controlled, double-blind treatment studies.[33] Patients received oseltamivir 75 or 150 mg or placebo twice daily for 5 days, beginning within 36 hours of symptom onset. The proportion of patients treated with antibiotics for secondary illnesses including bronchitis, sinusitis, otitis media and pneumonia was reduced by 43 to 61% ($p = 0.03$) in the oseltamivir treatment groups compared with placebo.

Prophylaxis

• The overall protective efficacy of oseltamivir against naturally occurring influenza illness was

74% when compared with placebo in 2 randomised, double-blind, multicentre trials in healthy, nonimmunised adult volunteers (n = 1559 total).[34] During periods of local influenza activity, volunteers received oral oseltamivir 75mg once- or twice-daily or placebo for 6 weeks and were monitored for febrile (temperature ≥ 99°F), respiratory and systemic symptoms of influenza. Compared with placebo, oseltamivir reduced both incidence of illness (1.2 or 1.3% with once or twice daily *vs* 4.8% with placebo; $p \leq 0.001$) and laboratory evidence of infection (5.3% for all oseltamivir recipients *vs* 10.6% for placebo recipients; $p < 0.001$). Both once- and twice-daily administration of oseltamivir was considered protective against both infection and illness.

4. Tolerability

• Oseltamivir, administered either prophylactically or after onset of infuenza symptoms, was generally well tolerated with no serious drug-related adverse events reported in clinical trials.[31,32]

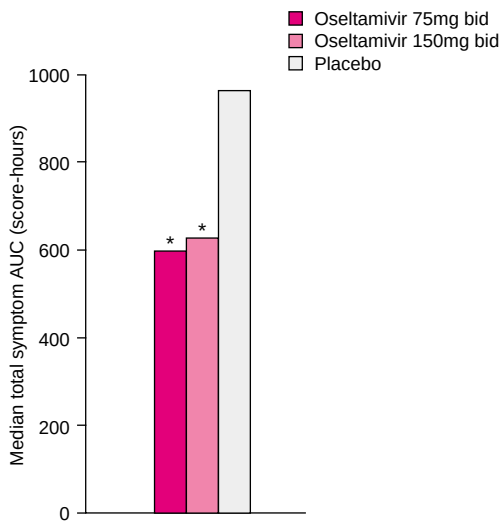


Fig. 3. Effect of oral oseltamivir on reducing the severity of influenza illness. Patients with confirmed influenza infection in a randomised, placebo-controlled, double-blind trial (n = 374) recorded the presence and scored the severity of influenza symptoms during and after treatment with oseltamivir 75 or 150mg or placebo (twice daily (bid) for 5 days initiated within 36 hours of symptom onset).[31] **AUC** = area under the curve of symptom scores. * $p < 0.0001$ *vs* placebo.

• In 2 placebo-controlled studies, mild and transient gastrointestinal effects were reported more frequently in the active treatment groups than in placebo groups (data not reported).[31,32] These events generally occurred on initiation of treatment and resolved within 2 days.[7] Dropout rates were low and similar between treatment and placebo groups.[31] A similar incidence of nausea and/or vomiting was reported in a 6-week study of oseltamivir prophylactic efficacy and tolerability; again most of the gastrointestinal disturbances occurred during the first 2 days of oseltamivir treatment and subsequently declined to levels similar to those in the placebo group.[34]

• In a study of experimental influenza infection, gastrointestinal disturbances occurred less often when oseltamivir was administered with food (2 of 28 volunteers) than in the fasted state (11 of 36).[8]

• When tested under fasting conditions in healthy adult volunteers, single oral doses of up to 1000mg were tolerated, producing no clinically relevant changes in vital signs, ECG readings or laboratory tests.[12,13]

• The combination of oseltamivir and paracetamol was well tolerated; no clinically relevant drug interaction was observed.[29] Coadministration of oseltamivir with drugs that compete for renal tubular clearance (such as cimetidine or probenecid) does not appear to cause clinically relevant changes in exposure to oseltamivir's active metabolite, GS4071.[30]

5. Oseltamivir: Current Status

Oseltamivir has shown efficacy in late phase clinical trials for the treatment and prevention of influenza illness, and was generally well tolerated. Phase II/III trials involving 1400 healthy adults found that treatment with twice daily oral oseltamivir 75mg significantly reduced illness duration and severity, and minimised disease complications. Further trials are ongoing in high-risk populations and children.

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Correspondence: *Anne Bardsley-Elliot*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz