The Prudent Prescriber

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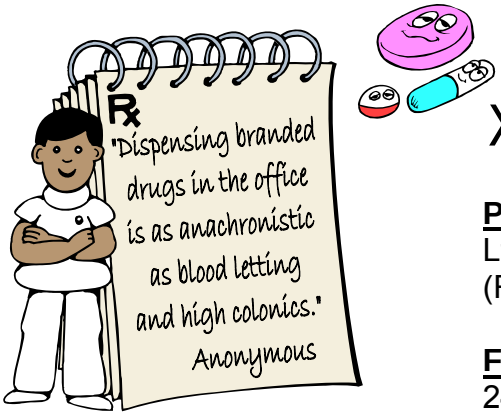


Xofluza (baloxavir marboxil)

Pharmaceutical company: Shionogi and Co. Ltd (created Crestor); marketed by Genetech (Roche) in the US.

FDA approved: via Priority Review, October 24, 2018. Approved in Japan, February 2018, for influenza types A and B in adults and pediatric patients

Priced: $150/tablet. Genetech indicates they will make Xofluza available for $30 with coupons for insured patients and $90 for uninsured.

Indication: for uncomplicated influenza in healthy persons, aged 12 to <65 years within 48 hours of onset of symptoms.

Dosing: single 40mg dose if weight >40kg (88lbs) but <80kg (176 lbs); single 80mg dose if weight >80kg (176 lbs).

Mechanism of Action: Baloxavir marboxil is a selective inhibitor of influenza cap-dependent endonuclease. This novel drug blocks the replication of endonuclease, an enzyme essential for viral replication. A long half-life of 49-91 hours makes a single dose feasible.

Side Effects: diarrhea (3%), bronchitis (2.6%), nausea (1.3%) and sinusitis (1.1%).

Pharm Reps ≠ Rational Prescribing
(PR) (RP)

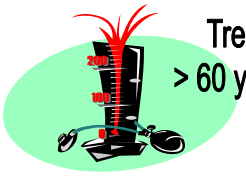
Antibiotics do NOT help acute bronchitis

CHF?
Think:
Ace
Aldactone
B-blocker
Dig
Diuretic

Avoid these expensive "me-too" drugs:
Intermezzo
Vimovo
Livalo
Gralise
Viibyrd
Edarbi
Daliresp

ß-blockers in post-MI save lives

Pill splitters save BIG



Treat patients > 60 years to 150/90

NOW AVAILABLE ON THE GENERIC MARQUEE

Viagra→sildenafil
Effient→prasugel
Strattera→atomoxetine
Asacol HD→mesalamine DR
Pristiq→desvenlafaxine

Clinical trials: The phase 2 trial was a double-blind, placebo-controlled, dose-ranging, randomized trial (randomization ratio, 1:1:1:1) of single doses of baloxavir (10, 20, or 40mg) or placebo. The trial enrolled Japanese adults 20 to 64 years of age with acute influenza from December 2015 through March 2016.

The phase 3 trial (CAPSTONE-1) was a double-blind, randomized, placebo-controlled and active comparator with oseltamivir (generic for Tamiflu) trial that enrolled outpatients 12 to 64 years of age with influenza-like illness in the United States and Japan from December 2016 through March 2017. Patients 20 to 64 years of age were randomly assigned, in a 2:2:1 ratio, to receive a single oral dose of baloxavir (40mg for patients weighing <80kg or 80mg for those weighing ≥80kg), oseltamivir at a dose of 75mg twice daily for 5 days, or matching placebos.

Patients: Patients who were enrolled had fever (axillary temperature, ≥38.0°C), at least one systemic symptom and at least one respiratory symptom of at least moderate severity, and a symptom duration of no more than 48 hours.

The trials excluded patients with underlying comorbidities, including pregnant women, those weighing less than 40kg, and those with illness resulting in hospitalization.

Methods: Patients self-assessed the severity of seven influenza-associated symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) on a 4-point scale (with 0 indicating no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms) twice daily from enrollment day 1 to day 9 and once daily on days 10 through 14. Body temperature was measured four times daily through day 3 and twice daily through day 14. In addition, patients assessed their overall health status on a scale of 0 (worst possible) to 10 (normal) each evening through day 14.

The primary endpoint: The median time from the intake of medication to the alleviation of symptoms.

Results:
Phase 2 Trial: Of the 400 patients who underwent randomization, 389 completed the trial. A majority of the patients who underwent randomization were infected with the influenza A (H1N1) virus. The median time to alleviation of symptoms in each of the baloxavir dose groups (54.2 hours in the 10mg group, 51.0 hours in the 20mg group, and 49.5 hours in the 40mg group) was significantly shorter than in the placebo group (77.7 hours). All three baloxavir dose groups had significantly greater reductions in influenza virus titers on days 2 and 3 than the placebo group.

Phase 3 Trial: Overall, 1436 patients underwent randomization, of which 1366 completed the trial and 1064 were included in the intention-to-treat infected population. The median time to alleviation of symptoms was shorter in the baloxavir group than in the placebo group (53.7 hours vs. 80.2 hours) a median difference of 26.5 hours. A shorter time to alleviation of symptoms with baloxavir than with placebo was observed in both adolescents (median difference, 38.6 hours) and adults (median difference, 25.6 hours).

The difference in the time to alleviation of symptoms between the baloxavir group and the placebo group was greater in patients who initiated the trial regimen within 24 hours after symptom onset (median difference, 32.8 hours) than in those who initiated it later (median difference, 13.2 hours). The median time to the resolution of fever was shorter with baloxavir than with placebo (24.5 hours vs. 42.0 hours). The median time to a return to usual health was 129.2 hours in the baloxavir group and 168.8 hours in the placebo group; the difference was not significant (P = 0.06). The time to alleviation of symptoms was similar with baloxavir and oseltamivir.

Baloxavir was associated with greater reductions in viral load one day after initiation of the regimen than placebo or oseltamivir. The median duration of infectious virus detection was shorter in the baloxavir group (24.0 hours) than in the oseltamivir group (72.0 hours, and the placebo group (96.0 hours).

Pros:

- A once a day alternative to neuramidase inhibitors for treatment of influenza.
- Innocuous side effect profile, to date, but small to modest "N".
- Potentially less spread of the influenza virus than with oseltamivir.

Cons:

- Only modest benefit in shortening the course of the illness (~1 day) and only 13 hours shorter if you delay more than 24 hours in taking the drug. Not superior to oseltamivir.
- Pricey ($150 vs $47.50 for 10 caps of generic Tamiflu)
- Evidence of rapid development of influenza resistance to baloxovir (as with other flu anti-virals)
- Logistically the problem of taking Xofluza within 48 hours of the onset of the illness.

My Take:

- 80,000 Americans died last flu season. We need better prevention and treatments.
- My anger persists toward the previous perfidious behavior of Roché in concealing the studies that showed how lousy their drug Tamiflu really is, was, always will be. Will Roché (Genetech/Shionogi) play by the rules this time?
- The results from the, as yet, unpublished phase 3 CAPSTONE-2 study in patients at high risk of complications from the flu showed "superior efficacy of Xofluza in the primary outcome of time to improvement of influenza symptoms versus placebo." We will skeptically await the details.