The Pharmacist Activist

Volume 4, No. 10 • October 2009

Editorial

The Influenza Follies

On October 24 President Obama declared H^1N^1 (swine) influenza a national emergency, thereby reflecting the level of concern that exists regarding this threat. However, prior to this action, some of the efforts to address an anticipated influenza epidemic could almost be considered comical if the situation was not so serious. Numerous initiatives have been poorly planned and implemented, and important questions exist.

What did we learn from last year's experience?

The answer is very clear – not nearly enough! Yes, influenza viruses are a moving target and it takes many months to develop vaccines against them. However, the threat presented by H^1N^1 influenza was recognized last year and predicted to be a much greater problem this year. Although the communication and planning involving government agencies and pharmaceutical companies were more extensive than typical as the current flu season approached, problems have been experienced that could have been avoided.

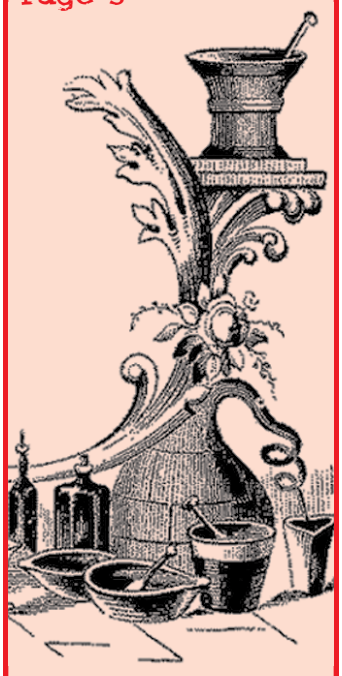
When there is a serious and imminent threat to the public health, as H^1N^1 influenza has been identified to be, the resources that are needed to control the risk to the fullest extent possible must be committed. It is likely that those resources will largely be my and your tax dollars but is there any better use for our tax dollars than programs that will protect and restore our health? I would much prefer that my tax dollars be used for this purpose than to bail out organizations with serious financial problems, many of which have self-destructed as a consequence of failed leadership.

Where is the vaccine?

Over a period of many years pharmaceutical companies have acquired extensive expertise and experience in producing seasonal influenza vaccine. However, at the present time, there is a significant shortage of this vaccine. Many pharmacists and physicians who anticipated their needs and submitted their vaccine orders many months ago have received only a fraction of the supply of vaccine that they ordered. They are informed that there is a shortage but provided with little or no information as to whether or when the shortage will be resolved, and when they can expect to receive additional supplies.

Some federal officials have tried to assure the public that eventually there will be

Contents



enough seasonal influenza vaccine and H^1N^1 influenza vaccine for every American who wants to be immunized. However, "eventually" is not defined and concern is already being voiced that most of the supply of vaccine may not become available until after the disease has taken a large toll.

Numerous questions continue to exist. Why is it that one large chain pharmacy reports that its supply of seasonal influenza vaccine is fine, but another large chain pharmacy, as well as many other pharmacies and physician practices have received only a small fraction of the supplies of vaccine they ordered? Why is it that, as recently as a month ago, the public was informed that supplies of the H^1N^1 influenza vaccine would be available even sooner than anticipated but now we are informed that the supplies of this vaccine are much smaller than anticipated and that there will be significant delays in obtaining the anticipated supplies?

There have been many explanations offered for the vaccine shortages, and some of these explanations have some validity. However, overall, the explanations are thinly-disguised excuses for poor planning.

Pharmacist administration of H^1N^1 influenza vaccine

The laws/regulations that provide the authorization for pharmacists to participate in immunization programs vary from state to state. Although many pharmacists currently are involved in the administration of seasonal influenza vaccine, questions exist as to whether supplies of the H^1N^1 influenza vaccine will be made available to these pharmacists, and the extent to which these pharmacists will be able to participate in immunization programs in which this vaccine is to be administered. These questions must be resolved immediately to enable the fullest extent of pharmacist participation possible. Perhaps this can be done under the provisions of the national emergency that has been declared so that it will not be necessary for every state to address this situation on an individual basis. There has already been a significant delay in the production and distribution of H^1N^1 influenza vaccine. There is an urgent need to immunize millions of individuals as quickly as possible once supplies become available. There can be no excuse for not including pharmacists who are prepared and available to participate in these immunization programs. To not do so will contribute to a further delay for many to receive immunizations, with a potential for deadly consequences for some.

Dosing errors with Tamiflu for suspension

Oseltamivir (Tamiflu) is supplied in capsules in 30 mg, 45 mg, and 75 mg potencies, and as a powder for oral suspension which, when constituted according to instructions, provides the drug in a concentration of 12 mg/mL. An oral dosing dispenser with calibrations for doses of 30 mg, 45 mg, and 60 mg is provided with the oral suspension. Because prescribers often write prescriptions for liquid formulations with instructions to administer one teaspoonful (or a fraction of a teaspoonful), or a designated number of milliliters (mL), dosage errors have occurred since the dosage instructions do not correspond to the markings (in milligrams) on the dosing dispenser. In late September the Food and Drug Administration (FDA) issued an alert regarding this situation, in which it noted that pharmacists should ensure that the units of measure on the prescription instructions match the dosing device provided with the drug. More specifically, it is noted that, "If prescription instructions specify administration using mL, the dosing device accompanying the product should be replaced with a measuring device (e.g., a syringe) calibrated in mL." The question remains as to why the FDA has apparently not directed Roche, the manufacturer of Tamiflu, to change/clarify the dosing instructions and dispenser which are the source of the confusion that has resulted in the errors.

Emergency compounding of Tamiflu oral suspension

There is a shortage of the commercially-marketed Tamiflu for Oral Suspension formulation. In the labeling for Tamiflu, there is a section that addresses "Emergency Compounding of an Oral Suspension from Tamiflu Capsules." With its paranoia regarding pharmacist compounding, the FDA wants it to be clear that pharmacists should only compound a Tamiflu prescription when an emergency exists. Very specific instructions are provided for pharmacists to compound a Tamiflu suspension. However, the final concentration of this suspension contains the drug in a concentration of 15 mg/mL that is different from the 12 mg/mL concentration of the product supplied by the company (when it is available). This situation is ludicrous and the FDA and Roche are responsible for creating another situation that results in confusion and error! Pharmacists are perfectly capable of compounding a formulation that provides the drug in the same 12 mg/mL concentration contained in the product supplied by Roche. The FDA and Roche appear

(Continued on Page 4)

New Drug Review

Saxagliptin hydrochloride
(Onglyza – Bristol-Myers Squibb; AstraZeneca)

Antidiabetic Agent

New Drug Comparison Rating (NDCR) = 3

(no or minor advantages/ disadvantages)

in a scale of 1 to 5, with 5 being the highest rating

Indication:

As monotherapy or in combination regimens as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Comparable drug:

Sitagliptin (Januvia).

Advantages:

- May be less likely to cause hypersensitivity reactions.

Disadvantages:

- Has not been directly compared with sitagliptin in clinical studies;
- Is more likely to interact with CYP3A4/5 inhibitors;
- May be more likely to decrease absolute lymphocyte counts (clinical significance has not been determined);
- Not available in combination formulations with metformin.

Most important risks/adverse events:

Risk of hypoglycemia when used in combination with a sulfonylurea or other insulin secretagogues (a lower dosage of the sulfonylurea may be required); action may be increased by the concurrent use of a strong CYP3A4/5 inhibitor (e.g., clarithromycin [e.g., Biaxin]); is primarily eliminated in the urine and the dosage should be reduced in patients with moderate or severe renal impairment.

Most common adverse events:

Upper respiratory tract infection (8%), urinary tract infection (7%), headache (7%).

Usual dosage:

5 mg once a day; a dosage of 2.5 mg once a day is recommended in patients also being treated with a strong CYP3A4/5 inhibitor, and in patients with moderate or severe renal impairment or end-stage renal disease requiring hemodialysis; is removed by hemodialysis and should be administered following hemodialysis.

Products:

Tablets – 2.5 mg, 5 mg.

Comments:

Incretins are naturally occurring hormones that increase insulin secretion in the presence of elevated glucose concentrations (e.g., following meals). They are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Sitagliptin and saxagliptin are DPP-4 inhibitors that slow the inactivation of incretins, thereby increasing and prolonging their action. Saxagliptin is primarily metabolized via the CYP3A4/5 pathways to an active metabolite, 5-hydroxy saxagliptin, that is also a DPP-4 inhibitor with approximately one-half the potency of the parent compound.

When used as monotherapy, saxagliptin reduced glycosylated hemoglobin (A1C) by approximately 0.6% compared with placebo and, when used with metformin, a thiazolidinedione (pioglitazone [Actos], rosiglitazone [Avandia]), or glyburide, reduced A1C by approximately this same percentage compared with placebo plus the other drug.

Saxagliptin is well tolerated and the incidence of adverse events reported in the clinical studies was generally similar to that with placebo. When used in combination with a thiazolidinedione, peripheral edema was experienced more frequently (8%) than in the patients receiving placebo instead of the new drug (4%). The DPP-4 inhibitors do not cause hypoglycemia; however, their concurrent use with an agent known to cause hypoglycemia (e.g., a sulfonylurea) should be closely monitored. There have been infrequent reposts of serious hypersensitivity reactions in the postmarketing experience with sitagliptin, and saxagliptin may be less likely to cause such events. Although weight gain is sometimes associated with certain antidiabetic agents, significant changes in weight have not been experienced with saxagliptin. The new drug is more likely than sitagliptin to interact with strong CYP3A4/5 inhibitors.

Daniel A. Hussar

more concerned about limiting pharmacist compounding than preventing dosage errors for patients by resolving the underlying sources for confusion for which they are responsible.

Authorization of use of expired Tamiflu for oral suspension

The FDA has recently announced it is authorizing the use of certain lots of expired Tamiflu for Oral Suspension that are part of the Strategic National Stockpile and have been tested through the federal government's Shelf-Life Extension Program (SLEP). In my opinion, there are many medications that retain full potency well beyond the expiration dates designated on their packages, and the SLEP initiative has excellent potential. However, in the context of multiple sources of potential confusion and error with Tamiflu as discussed above, I feel that this initiative is highly problematic and recommend that pharmacists only use these government-approved lots of expired Tamiflu as a last resort. If they do this, they should be certain that they record and retain all pertinent information, including the authorization.

A broader question

Health care reform ranks second only to the economy as a topic for debate and legislative action. President Obama is very actively recruiting legislative and consumer support for his proposals. If the federal government is not successful in containing, preventing, and treating influenza, is there any reason to think that it will be successful in addressing the much more comprehensive and complex challenges of health care reform? At this time I can not give the government a passing grade in dealing with the issues regarding influenza!

Daniel A. Hussar

Author/Editor
Daniel A. Hussar, Ph.D.
Philadelphia College of Pharmacy
University of the Sciences in Philadelphia
Publishers
Christopher J. Polli • G. Patrick Polli II
Assistant Editor - John Buck
Publications Director - Jeff Zajac
Graphic Artist/Designer - Joe Monte

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The Pharmacist Activist
661 Moore Rd., Ste. 100, King of Prussia, PA 19406
610-337-1050 • Fax: 610-337-1049
E-mail: pharmacistactivist@news-line.com

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