

Guidelines for the establishment and use of the Stockpile of Oseltamivir



Contents

1. Background
2. Pandemic preparedness strategies and role of antivirals
3. Why oseltamivir stockpiling is needed?
4. Establishing and managing stockpile
5. Locations of stockpile
6. Period of stockpiling and fate of unused drugs
7. Guiding principles for use of stockpile
8. Epidemiological and operational criteria
9. Release and shipment
10. Use of oseltamivir
11. Replenishment of stockpile
12. Reporting and monitoring
13. Possible roles of partner organizations

1. BACKGROUND

1.1 Influenza virus A H5N1 has been causing outbreaks of highly pathogenic avian influenza in poultry in Asia since late 2003. Occurrence of outbreaks in 17 countries including Viet Nam, Indonesia, Thailand, China, Cambodia and Laos and lately in such far areas as Russia, Croatia, Turkey, Ukraine, Romania, Mongolia, and Kazakhstan is historically unprecedented. The fear is mounting regarding the emergence of the next pandemic. Human cases have been reported in Cambodia, China, Indonesia, Thailand, Turkey and Viet Nam. The continued occurrence of avian influenza in birds and continuous human exposure has greatly increased the chances of emergence of a novel virus through re-assortment.

1.2 Although no one can predict with certainty when and where the next pandemic of influenza will start and how severe it will be, the experts warn that it is imminent. There is a great possibility that it would begin from Asia and could be very severe. The pandemic may lead to massive social, political and economic disruption. Experts estimate that the pandemic may cause more than 1 billion cases and 2-7 million deaths. With up to 28 million likely to be hospitalized, this would severely strain the health services as well as other essential services like public transport, police, fire brigade, air traffic control, water and electric supply etc.

1.3 There is also evidence to suggest that it would be possible through early and strategic use of antiviral medicines to pre-empt the pandemic at the source and to limit its adverse impact to the minimum.

2. PANDEMIC PREPAREDNESS STRATEGIES AND ROLE OF ANTIVIRALS

2.1 Key strategies for pandemic preparedness and response include (i) planning, partnership and coordination, (ii) risk reduction for human infection including poultry management, food safety and infection control, (iii) surveillance, early warning and response in both animal and human health sectors, (iv) risk communication, and (v) public health measures including antiviral, vaccine, quarantine, social distancing etc.

2.2 To **pre-empt** the pandemic, it is necessary that (i) the surveillance system for animal health should be able to detect infection in poultry quickly, followed by rapid and safe culling of infected and exposed poultry and proper disposal of carcasses, and (ii) that the surveillance system for human health should be able to detect first human cases quickly followed by rapid containment measures particularly early and strategic use of antiviral medicines and social distancing.

2.3 Presently, only oseltamivir is considered effective against all subtypes of influenza A virus and is recommended for stockpiling and use during the outbreak and to pre-empt the pandemic. However, as of 6 January 2006, oseltamivir is manufactured only by one company. The manufacturing capacity, although being augmented remains limited compared to the world demand. It is believed that currently there is a lag period of more than one year between ordering oseltamivir and its supply. Some of pharmaceutical manufacturing companies from India, Thailand and Indonesia have shown interest in manufacturing the drug but, it is unlikely to alter present situation at least up to middle of 2006.

3. WHY OSELTAMIVIR STOCKPILING IS NEEDED?

3.1 The early and strategic use of oseltamivir is a potential intervention to pre-empt the pandemic by containing any outbreak at its source. However, in order for the drug to be effective, it must be taken within 48 hours of onset of illness. Experts believe that stockpiling of 1-3 million treatment courses would be enough to pre-empt the pandemic if used early and in targeted manner.

Currently, several developed countries are aggressively engaged in stockpiling this drug. The demand for the drug has exceeded the production capacity of the manufacturer.

3.2 A need for stockpiling of antiviral at multiple sites and locations near the countries in Asia, which is likely to be the epicenter of the next pandemic is felt to be necessary so that the medicine can be rushed to the site to meet the immediate needs of the countries and to preempt the outbreak at its source.

3.3 In a WHO meeting in Bangkok in August 2005, the need for stockpiling of oseltamivir at various levels was articulated. The meeting of the ASEAN Health ministers requested WHO to assist in operationalizing the regional/sub-regional stockpile.

In response to that request and based on somewhat limited experience in the Region, these draft guidelines have been developed. The objective is to provide guiding principles and mechanism for management of a stockpile of oseltamivir. The purpose of the stockpile is to enhance the ability to release the antiviral medicines and to ship quickly to areas and countries in the event of an avian influenza outbreak in human with the explicit objective of containing the outbreak through prompt response and thereby pre-empting the pandemic.

The guiding principles shall address following issues pertaining to stockpile:

- Establishment
- Use
- Replenishment of drug

4. ESTABLISHING AND MANAGING STOCKPILE

4.1 Presently only one manufacturer (Roche) is producing this drug and supply is rather limited as many countries in the west are stockpiling in large numbers.

4.2 WHO will maintain its own stockpile of 3 million treatment doses provided on donation by Roche as announced on 26th August 2005.

4.3 Since the regional / subregional stockpile is meant only for pre-empting the pandemic which is relevant and crucial for the global security, support for this type of stockpile is for everyone's welfare. For example, the Health ministers of ASEAN countries pledged to contribute to a regional/sub-regional stockpile out of their own country stockpiles.

4.4 Following three essential prerequisites need to be identified for managing a stockpile

- a. A group of countries (or Regional Association of countries) who would be responsible to guide, manage and fund the stockpiling. This group can be an existing Regional Association (viz SAARC, ASEAN) or an international organization (WHO, UNICEF). The countries will enter into an agreement. The important tasks of the group shall be:
 - To enter into an agreement for mutual cooperation in creating and modalities of using the stockpile
 - To ensure fast track approach to licensing, deployment and use of oseltamivir
 - To identify of site(s) for stockpiling and refurbishing these
 - To provide funds and implement mechanism for appropriate audits
- b. Review Committee (**RC**) to assess the need and advice on the distribution of oseltamivir on the basis of assessed need (referred to as RC in this document). RC may comprise of eminent public health professionals and managers from the Member State, Regional Associations or technical organizations such as WHO and UNICEF. Following tasks shall be delegated to the RC
 - To make a decision on assessment of request from the country and the number of doses required.
 - To decide whether partial release will be appropriate to meet the emergent needs
 - In case of multiple requests, to decide about the quantum of drug for every request with the objective of containing outbreak at source and preventive pandemic.
 - To advise on the optimal level of stockpile
- c. Secretariat which would be responsible for procurement, storage, inventory management and logistics to make the drug available in shortest possible time (referred to as **Manager** in this document). Managers would be needed in each location where the stockpile is maintained and shall perform following duties
 - Provides managerial and logistic support through liaison with RC and recipient country.
 - Submits financial and inventory reports to Group of countries/Regional Association on regular basis. Ensures that a minimum level of stockpile is always maintained.

The stockpile will function on a revolving mechanism. This means that the doses released should be later replenished so that the stockpile can be maintained at original levels.

Oseltamivir does not appear to be registered in most SEAR countries. Therefore, if an emergency stock is released for use in a country, there could be problems at customs/ imports unless procedures have been put in place beforehand.

There could be no possibility of submitting registration dossiers. Oseltamivir will therefore have to be imported under a "Public Health Need" clause; such clauses are commonly a part of national regulations on medicines. The Drug Regulatory Authority of the country should be apprised by the Ministry of Health and ideally there should be a document specifying that oseltamivir could be imported into the country during an emergency. Alternatively the Ministry of Health should examine the provision for emergency import of drugs and be ready to issue an import authorization.

It is important to provide information to the doctors who will be using this drug during the emergency. Therefore it is suggested that the countries at risk prepare an information sheet on the use of oseltamivir in influenza. This datasheet would include a brief description of the drug, the dosage, possible side effects, contra-indications and how to monitor the treatment.

5. LOCATIONS OF STOCKPILE

5.1 Locations and criteria (concept of 'virtual global stockpile') – A sub-regional stockpile of substantive amount should be established in a location where rapid delivery to the affected countries within 24 hours or less is practicable. For example, at least 500,000 capsules which are enough for prophylactic treatment of 50,000 people for ten days may be placed in one of the capital cities where daily flights to all or most other capital cities in the region are available.

5.2 The stockpile can be done at one or multiple strategic places – This is to ensure that the drug supplies can be rushed to the affected area(s) in the shortest possible time may be within 24 hours.

6. PERIOD OF STOCKPILING AND FATE OF UNUSED DRUG

6.1 The stockpile will be maintained with a revolving mechanism for an initial period of 2 years or till such time the need is there. After this period the stockpile mechanism will be evaluated by the RC and decision will be made on its possible continuation or to stop it.

6.2 Should it be decided not to re-conduct the stockpile of oseltamivir, the remaining stock of drug will be divided according to the agreement between the countries

7. GUIDING PRINCIPLES FOR USE OF THE STOCKPILE

7.1 Guiding Principles

Early and strategic use could be helpful for pre-empting the pandemic if following guiding principles are adhered to:

- the human, animal, and virological surveillance is established and country is willing to share the lab samples and information on the outbreak;
- oseltamivir is used only for the express purpose of pre-empting the pandemic, not for the purpose of enhancing its national stockpile;
- use of osetamivir is part of the national pandemic preparedness plan;
- oseltamivir is considered as an adjunct measure and is implemented along with social distancing.

7.2 Processing of Requests

Requests from countries or international agencies for the release of oseltamivir from this stockpile may be submitted to the RC through the relevant designated national programme manager for influenza pandemic.

- The requests will be made on prescribed proforma giving adequate epidemiological details of the event and the response initiated by the local health authorities. A detailed plan for the use of drug requested should also be submitted;
- A meeting of RC will be convened immediately failing which a teleconference of communications through e-mail shall be resorted to review the request;
- Each member of the RC will assess or review the request and inform the Manager of their decision within one working day after reception of the request;
- The RC will review requests for oseltamivir on the basis of specific information provided by the requesting country or group of countries/Regional Association, and take a consensual decision based on the epidemiological and operational criteria as outlined above;
- A non-response of a member of RC, within the specified time limit (one working day) will be assumed by the RC as indicating concurrence with the group's decision. After reviewing the request, the RC can take action as follows:
 - a) The request meets the criteria: partial or complete release of the drug is granted.
 - b) the request does not meet the criteria and no drug would be released from the emergency stockpile, in which case the RC will send to the requesting instance a written answer explaining why the criteria was not met and propose potential alternatives.
 - c) The information provided is incomplete and the members of the RC can not conclude, in which case the RC will send to the requesting instance a written answer specifying what the missing information is required.

The Manager will immediately communicate the decision of the RC positive (full or partial release), negative or need for additional information) to the requesting instance. The answer from the RC should be communicated within a range of one working day after reception of the request.

8. EPIDEMIOLOGICAL AND OPERATIONAL CRITERIA

8.1 Requests from the countries to the RC should fulfil the following criteria and provide information:

- Evidence of an on-going outbreak and information on population at risk
- No. of cases and deaths
- Geographical distribution of cases
- Details of the clinical samples collected and detail of the laboratory confirmation of the causative strain, if available
- Ongoing containment action including the plan of action.
- Standard storage conditions & resources available
- A plan for the use of oseltamivir that has been requested

8.2 The request should also clearly indicate the exact amount of oseltamivir stocks, already available in the country.

8.3 The stockpile of drugs will be use only for the purpose of pre-empting the pandemic and should be used to initiate treatment of avian influenza cases within 48 hours of date of onset of symptoms and for prophylaxis of the close contacts.

9. RELEASE & SHIPMENT

- The release of oseltamivir from the emergency stockpile requires a consensual approval of the RC.
- The RC will decide on case by case bases from which sub-stock the drug will be released taking into account the requesting instance, and the expiration dates of the doses in the stockpile.
- The release of the drug for an area should be on the basis of needs and objective of pre-empting the pandemic
- Once the RC approves a request from the emergency stock, the Manager will immediately make arrangements to ship the drug to destination with advance information to the consignee

10. USE OF OSELTAMIVIR

The countries shall use oseltamivir strictly in accordance with WHO Guidelines and for the explicit purpose of containing the outbreak. The recipient should provide detailed report of the use of drug including the no. of persons administered the drug, purpose of administration (treatment or chemoprophylaxis), doses administered, impact of administration of drug etc.

Oseltamivir is recommended for treatment of cases and close contacts and from public health point of view to pre-empt the pandemic. The dose for adult patients is 75 mg twice daily for 5 days (one cap twice a day for 5 days) and for close contacts at least 7 days. Oseltamivir is indicated for treatment in patients 1 year and above and who have been symptomatic for no more than 2 days. Efficacy in cases where treatment is commenced after 40 hours of symptoms has not been established. Drug is indicated for chemoprophylaxis of close contacts including family members 13 years and above.

11. REPLENISHMENT OF STOCKPILE

11.1 Maintaining adequate levels of drug for rapid release for outbreak response, requires that all doses released from the stockpile are subsequently replenished thus ensuring the continuity of the revolving stock.

11.2 The costs of packaging, freight and insurance of the drug will be assumed by the requesting country.

12. REPORTING AND MONITORING

12.1 The Manager should report regularly (at each meeting/teleconference) to the RC on the use of the stockpile, and provide details including status of the stockpile and number of doses released by destination/country

12.2 The Manager will prepare an annual report on the status of the stockpile that will be submitted to the group of countries/Regional Association .

12.3 Annual review by RC would also be useful.

13. POSSIBLE ROLES OF PARTNER ORGANIZATIONS

World Health Organization

- Develop detailed guidelines for management of the stockpiles
- Working with interested partners in organizing national stockpiles in high-risk countries where emergence of pandemic strain might occur
- Provide an oversight to the management of sub-regional stockpiles in harmony with other levels of stockpiles through WHO system.
- Assess global anti-viral drug supply and production capacity and make recommendations as appropriate to increase production to parties concerned.

Unicef

- Procurement of drug
- Support in logistics and storage etc
- Technical support

Other agencies/organizations can be included as appropriate to meet the objectives of stockpiling.