



Action Plan for Catalonia against a possible Influenza Pandemic

Protocol for the Use of Antiviral Drugs

Version: May 2008

Introduction

Although vaccination is the main flu prevention strategy it is likely that, at least in the early phases of the pandemic period, there may not be a vaccine available.

Two families of antiviral drugs are currently on sale: M2 protein inhibitors and neuraminidase inhibitors. Annex 1 shows the characteristics, doses, adverse reactions and contraindications they may have.

Antiviral drugs may be used to prevent and treat flu and also to reduce morbidity and mortality. Gani *et al.* have estimated that the reduction in mortality in cases when antiviral drugs are administered early (during the first 36 or 48 hours of clinical manifestations) can be 50%. However, their preventive effects are limited to the period when the drug is being taken, so the prophylactic indications have to be precisely established. In addition, the use of antiviral drugs involves the risk of creating resistance when they are used incorrectly or on a large scale. In current conditions, therefore, these drugs must be used in accordance with the objectives of the Directorate-General for Public Health for each phase of the pandemic. For this reason, rational use must be made of the antiviral drugs available, in accordance with the scientific knowledge we have of them.

PANDEMIC ALERT PHASE 3

The aim of the Directorate-General for Public Health for this phase, the most important characteristic of which is that there is no inter-human transmission, is to ensure the early detection and notification of cases.

The indications for using antiviral drugs are as follows:

1. Suspected case

- If a suspected case of infection with the H5N1 virus is discovered, in accordance with the definitions established in the protocol for action in a suspected case, the corresponding epidemic alert unit must be contacted and treatment must be begun as early as possible.
- Treatment details will be noted on the epidemiology form for the case (see the protocol for the detection of a possible human case). The first-choice drug is Oseltamivir.

2. Prophylactic treatment for a co-exposed person

- It must be investigated whether another person has been exposed (co-exposed) to the infection source (contact with infected animals).
- If it is considered that exposure is significant (intensive or prolonged contact with infected birds), contact must be made with the corresponding epidemic alert unit to begin prophylactic treatment as early as possible. The first-choice drug is Oseltamivir.
- The details of the co-exposed person will be collected on the prophylactic antiviral indication form (see Annex 2).

As there is no inter-human transmission, none of the contacts with the patient or contacts with co-exposed people will need to receive an antiviral prophylactic.

3. Contact with birds

Concerning prophylactic treatment of people who may be exposed to contagion from potentially infected wild or domestic birds (or other animals), the following circumstances will be considered:

3.1. Wild birds*

3.1.1. A person who has had physical contact with a healthy wild bird in an area where it has been shown or is suspected that there are infected birds

- There is no experience of cases occurring in these circumstances and, therefore, there is no need to administer prophylactic treatment.

3.1.2. A person who has had physical contact with a sick or dead wild bird in an area where it has not been shown that there is infection with H5N1 in birds

- There is no experience of cases occurring in these circumstances and, therefore, there is no need to administer prophylactic treatment. It must quickly be investigated whether the birds are infected.

3.1.3. Physical contact with a sick or dead wild bird in an area where it has been shown or is suspected that there is H5N1 infection in birds

- There is no experience of cases occurring in these circumstances and, therefore, there is no need to administer prophylactic treatment.
- It must quickly be investigated whether the birds are infected.

3.1.4. Physical contact with a sick or dead wild bird which it has subsequently been confirmed was infected with H5N1

- If the person who has had the contact was properly protected (see the infection prevention protocol for personnel exposed to infected birds) there is no need for post-exposure prophylactic treatment.
- If by mistake or accident the person was not properly protected, the use of post-exposure prophylactic treatment must be evaluated. The first-choice drug is Oseltamivir. Contact with the corresponding epidemiology alert unit is necessary.

* If a mammal is involved, the same criteria must be followed.

3.2. Domestic birds

3.2.1. A person who has had contact with healthy domestic birds in an area where it has been shown or is suspected that there is infection with H5N1 in domestic birds

- The use of post-exposure prophylactic treatment must be considered only when the exposure has been very intensive, as in the case of people who slaughter birds and, above all, when the birds have been exposed to the H5N1 virus. Contact with the corresponding epidemiology alert unit is necessary. The first-choice drug is Oseltamivir.

3.2.2. A person who has had physical contact without protective barriers with sick domestic birds in which H5N1 infection is confirmed or strongly suspected

- In these circumstances, experience says that cases can occur in humans. Prophylactic treatment must therefore be administered immediately to people who have had contact with these birds without wearing protective equipment. The first-choice drug is Oseltamivir.
- The vet must notify the exposure of these people to the corresponding epidemic alert unit so it can co-ordinate actions aimed at applying the prophylactic treatment. The antiviral prophylactic indication form must be filled in.

4. Laboratory staff who have analysed samples from suspected or confirmed cases of H5N1

- These staff must be properly protected. Post-exposure prophylactic treatment needs to be administered only if good practice rules have not been followed or if there has been an accident. The drug of choice is Zanamivir or Oseltamivir, depending on the exposure route.
- The corresponding epidemic alert unit will authorise the use of prophylactic treatment and will fill in the prophylactic antiviral indication form.

5. Staff who work to slaughter birds to contain an outbreak of H5N1 flu

- These staff must be properly protected. They must be given post-exposure prophylactic treatment if there is an error or accident affecting protective barriers. The appropriateness of administering prophylactics can also be evaluated if the exposure is likely to be prolonged and very intensive. The drug of choice is Oseltamivir.
- The corresponding epidemic alert unit will authorise the use of prophylactic treatment and will fill in the prophylactic antiviral indication form.

6. Veterinary staff exposed to birds infected with H5N1

- These staff must be properly protected. Post-exposure prophylactic treatment needs to be administered only if there has been an error or an accident.

PANDEMIC ALERT PHASES 4 AND 5

The most important characteristic of these phases is that inter-human transmission has been detected.

The aim of the Directorate-General for Public Health is to contain transmission of the new virus in localised focuses and to delay the spread of the pandemic virus.

Although the strain of the pandemic is not known, transmission by droplets or contact, as happens with the epidemic flu virus, must be prevented and, therefore, exposed contacts will be those who have been affected by droplets from a patient during the transmission period.

In relation to seasonal or epidemic flu

It must be remembered that:

- The incubation period (time when a person is infected but has not developed the symptoms of epidemic flu) is normally between 1 and 4 days.
- Adults are potentially infectious (they can be contagious) 24-48 hours before they develop symptoms until 4-5 days after they start.
- Small children are potentially contagious for a longer period of time (7 days or more). The transmission period can be extended still further in the case of immunodepressed children or adults or if they have an underlying disease.
- The basic reproduction number (R_0) is normally between 1.8 and 2.0. This figure indicates the average number of people likely to be infected (if there is no prior immunity in the population) when they come into contact with a person ill with flu.
- The generation time is the average time between the beginning of the clinical picture of a case and the onset of the clinical presentation of a case secondary to it. It makes it possible to measure the explosiveness of the epidemic or the speed of propagation of an epidemic. In flu, this period is usually 3 days (shorter than the incubation time). So, flu epidemics spread very quickly.

The main flu transmission mechanisms

Droplet transmission

- Flu viruses are transmitted largely by large droplets ($> 5 \mu\text{m}$).

- Large droplets are expelled when coughing, talking and sneezing and do not travel more than a metre in the air.
- To be transmitted, these droplets require proximity between the source person and the possible recipient. They do not remain suspended in the air; they have to come into direct contact with the oral, nasal or conjunctival mucosa.

Direct transmission by contact

- The proportion of transmission of flu virus by direct contact is unknown, but this transmission route is clearly possible.
- Direct contact involves skin contact, such as with the hands, between an infected person and a susceptible one.
- The flu virus can survive 24-48 hours on non-porous surrounding surfaces, up to 8-12 hours on clothes or paper and up to 5 minutes on the hands. The most usual transmission depends on hand contact with these surfaces and subsequent contact between the contaminated hands and the nasal, oral or conjunctival mucosa.

Aerial transmission

- Some studies have suggested the aerial transmission of the flu virus (via droplet nuclei of less than 5 μm in diameter, which remain suspended in the air and which can travel several metres). This transmission route has been described in experiments carried out on animals, but in humans the evidence supporting aerial transmission is limited and concerns closed spaces with little ventilation in which there could also have been transmission by contact or droplets.
- There is no evidence that droplet nuclei with the flu virus move long distances in ventilation systems, as can happen in the case of other viruses or the tuberculosis bacillus.

Use of antiviral drugs

They are used in the following situations:

1. Treatment

The drug of choice is Oseltamivir.

2. Prophylactic treatment for health staff who have had unprotected contact with cases

When the WHO has declared the beginning of phase 4, all health staff and related services must adopt precautionary measures to prevent contact and droplet transmission (see the protocol for the prevention of hospital-acquired infections).

Therefore, the option of post-exposure prophylactic treatment must be evaluated only in situations when the corresponding precautions have not been adopted and there has been exposure to risk: resuscitation manoeuvres, intubation, nasopharyngeal aspiration, bronchoscopy, nebulisation, sputum induction, thoracic physiotherapy, tracheotomy treatment, necropsy of the pulmonary tissue or any other aerosol-generating manoeuvre.

Contact must be made with the corresponding epidemic alert unit to determine the people who must follow prophylactic treatment.

Under these circumstances, the drug of choice is Zanamivir. If it is not available, Oseltamivir will be used. The prophylactic indication form must be filled in in phases 4 and 5 (see Annex 3).

3. Prophylactic treatment of close contacts of cases

A close contact of a probable or confirmed case is considered as:

3.1. Anyone who has been living in the same dwelling as a person recorded as a case during the disease transmission period, running from 2 days before to 5 days after the onset of symptoms in adults and up to 7 days after in children.

3.2. Anyone who has been in direct, close and prolonged contact with the person (case), during the disease transmission period.

In these situations, the recommended drug is Oseltamivir. Contact must be made with the corresponding epidemic alert unit to determine the people who must follow prophylactic treatment. The prophylactic indication form must be filled in in phases 4 and 5 (see Annex 3).

Once the case has been diagnosed as probable or confirmed, new close contacts must be informed of the protection measures they must adopt, and it is not then necessary for them to receive prophylactic treatment.

4. Post-exposure prophylactic treatment when 2 or more cases are detected in geriatric homes, social services/health centres or closed institutions with people for whom flu could have serious consequences

The first-choice drug is Oseltamivir. Contact must be made with the corresponding epidemic alert unit to determine the people who must follow prophylactic treatment. The prophylactic indication form must be filled in in phases 4 and 5 (see Annex 3).

5. Use of prophylactic treatment in the community sphere

The purpose of this form of prophylactic treatment is to contain the first outbreaks of virus with inter-human transmission. Its application will be limited to geographical areas where the first groups in which there is inter-human transmission are detected and always according to the recommendations established by the WHO. In fact, the mathematical models published recently show that the mass application of prophylactic antiviral drugs in the community would not significantly reduce the number of cases. Instead these would occur later and be caused by resistant strains.

PANDEMIC PHASE 6

The most important characteristic of this phase is that there is a high and sustained level of transmission of the pandemic virus in the general population.

The aim of the Directorate-General for Public Health is to reduce the impact of the pandemic as much as possible.

Although it can be expected that, some months after the beginning of this phase, a vaccine will be available, it must be assumed that none will be available for the first wave.

In this phase, the available antiviral drugs will preferably be used for the early treatment (during the first 48 hours after the beginning of symptoms) and the treatment of hospitalised patients will be prioritised, together with health staff and other workers in essential services.

For non-hospitalised patients, account must be taken of the number of treatments available and the priorities determined, according to the information on groups in which the virus is causing most mortality and the largest number of complications.

Currently, the first-choice drug is Oseltamivir.

In this phase, the use of antiviral drugs as a prophylactic measure (post-exposure prophylactic treatment) is only planned for health staff in a position of unprotected exposure and for the control of outbreaks in closed institutions where there are particularly vulnerable people for whom flu could have serious consequences.

All care service staff who come into contact with patients must follow standard precautions and those intended to prevent droplet transmission. Post-exposure prophylactic treatment for health staff will only be applied in the case of a clear error or accident in staff who have had risk exposure without adequate protection (see phases 4 and 5). The first-choice drug is Zanamivir. In these circumstances contact must be made with the corresponding regional epidemiologist, who will be the person to authorise prophylactic treatment. The same prophylactic antiviral drug indication form as for phases 4 and 5 must be filled in (Annex 3).

Bibliography

- Anonymous. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) (ERRATUM) (ART 541855). MMWR 2005;54:1-41.
- Anonymous. N Engl J Med 2008;358:261-73.
- Aoki FY, Boivin G, Roberts N. Influenza virus susceptibility and resistance to Oseltamivir. Antivir Ther 2007;12:603-16.
- Aristegui J, Fargas P, Domínguez A, Pérez Breña P, Portela A, Salmerón F, *et al.* Conferencia de consenso sobre la gripe. Madrid: Asociación Española de Vacunología, 2005.
- Bardsley-Elliot A, Noble S. Oseltamivir. Drugs 1999;58:851-60.
- Centers for Disease Control and Prevention. Prevention and control of Influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2004;53:1-40.
- Canadian Pandemic Influenza Plan for the Health Sector. Planning recommendations for the use of anti-influenza (antiviral) drugs in Canada during a Pandemic, October 2006.
- Cher SM, Wagstaff AJ. Zanamavi. An update of its use in Influenza. Drugs 2002;62:71-106.
- Consejo General de Colegios Oficiales de Farmacéuticos. Base de Datos del Medicamento 2005.
- Drugdex®. Editorial Staff. Drugdex® Information System. Micromedex Inc. Denver, Colorado (edition expires 2006). Drug Evaluation Monograph.
- Gani RD, Hughes H, Fleming D *et al.* Potential Impact of Antiviral Drug Use during Influenza Pandemic. Emerg Infect Dis 2005;11:1280-2.
- Goodman C, Mukherjee D, Faulkner E. How effective would antiviral vaccination and antiviral drug prevention and treatment strategies be for reducing the impact of next Influenza pandemic? Copenhagen: WHO Regional Office for Europe, 2006.
- Guay DRP. Amantadine and Rimantadine prophylaxis of Influenza A in nursing homes: a tolerability. Drugs Aging 1994;5:8-19.

- Gubareva LV, Kaiser L, Hayden KJ. Influenza virus neuramidase inhibitors. *Lancet* 2000;355:827-35.
- Hayden FG, Gubareva LV, Monto AS et al. Inhaled Zanamivir for the prevention of influenza in families: Zanamivir Family Study Group. *New Eng J Med* 2000;343:1282-9.
- Hayden FG, Hay AJ. Emergence and transmission of Influenza A viruses resistant to Amantadine. *Curr Top Microbiol Immunol* 1992;176:119-30.
- Heyman DL, editor. *Control of Communicable Diseases Manual*. 18th ed. Washington: American Public Health Association, 2004.
- Jefferson T, Demicheli V, Rivetti D, Jones M, Pietrantoni CD, Rivetti A. Antivirals for influenza in healthy adults: systematic review. *Lancet* 2006;367:303-13.
- Kawai N, Ikematsu H, Iwaki N, Maeda T, Kanazawa H, Kawashima T, et al. A comparison of the effectiveness of Zanamivir and Oseltamivir for the treatment of Influenza A and B. *J Infect* 2008;56:51-7.
- Lipsitch M, Cohen T, Murray M, Levin BR. Antiviral resistance and the control of pandemic influenza. *PLoS Med* 2007;111-21.
- Moghadas SM, Bowman CS, Röst G, Wu J. Population-wide emergence of antiviral resistance during pandemic influenza. *PLoS ONE* 2008; 3:e1839.1-8).
- Monto AS, Robinson DP, Herlocher LM, Hinson JM, Elliot MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999;282:31-5.
- Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005; 353:1363-73.
- Murphy KB, Eivindson A, Pauksens K, et al. Efficacy and safety of inhaled Zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: a double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Investig* 2000;20:337-49.
- Nicholson KG, Wiselka MJ. Amantadine for Influenza A. *BMJ* 1991;302:425-6.
- Potter CW. Influenza. A: Zuckerman AJ et al, editors. *Principles and Practice of Clinical Virology*. 5th ed. Chichester: John Wiley & Sons, 2004:271-97.

- Rubin MS, Nivin B, Ackelsberg J. Effect of timing of Amantadine chemoprophylaxis on severity of outbreaks of Influenza A in adult long-term care facilities. *Clin Infect Dis* 2008;47:47-52.
- Stockley IH, editor. *Drug Interactions*. 7th Ed. Pharmaceutical Press 2006.
- Suzuki H, Saito R, Oshitani H. Excess Amantadine use and resistant viruses. *Lancet* 2001;358:1910.
- Tominack RL, Hayden FG. Rimantadine hydrochloride and Amantadine hydrochloride use in Influenza A virus infections. *Infect Dis Clin North Am* 1987;1:459-78.
- Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005;55(Suppl 1):15-21.
- Weinstock DM, Zuccotti G. Adamantane Resistance in Influenza A. *JAMA* 2006; Published online February 2, 2006.
- Whitley RJ, Monto AS. Prevention and treatment of Influenza in High-Risk groups: children, pregnant women, immunocompromised hosts, and nursing home residents. *Clin Infect Dis* 2006;194:S133-8.
- WHO pandemic influenza draft protocol for rapid response and containment. World Health Organization, March 2006.
- Wintermeyer SM, Nahata MC. Rimantadine: a clinical perspective. *Ann Pharmacother* 1995;29:299-310.
- Wong SSY, Yuen K. Avian influenza virus infections in humans. *CHEST* 2006;129:156-79.
- Zambon M, Hayden FG. Position statement: global neuramidase inhibitor susceptibility network. *Antiviral Res* 2001;49:147-56.

ANNEX 1

M2 protein inhibitors

M2 protein inhibitors or adamantanes (Amantadine and Rimantadine), developed in the '60s, are primary tricyclic amines which inhibit viral decapsidation, because they neutralise the action of the M2 ionic channel while acidifying the inside of the virus particle. Rimantadine is not sold in Spain. These drugs have been shown to be active against subtypes H1N1, H2N2 and H3N2 of the group A human flu virus, and also against avian subtypes, which suggests the possible susceptibility of future pandemic strains. Despite this, the available studies indicate that the subtype A (H5N1) strains circulating in South East Asia are resistant to this family of anti-flu drugs. These drugs are administered orally and have proved effective in treating acute infection by the Influenza A virus when they are administered during the first 24 hours from the onset of the clinical presentation, as they reduce symptoms in 1-2 days. In therapeutic doses, they do not affect Influenza B virus or any other respiratory virus. Amantadine is absorbed well and reaches concentrations in the nasal mucosa of approximately half those in plasma. Of the total administered, 90% of the Amantadine is excreted unchanged in urine, by glomerular filtration and tubular secretion. The concentrations of Rimantadine in the nasal mucosa are greater (150%) than in plasma. Of the total administered, 75% of the drug is metabolised in the liver and various studies have shown that it is tolerated better than Amantadine in equivalent doses. Amantadine and Rimantadine can cause slight secondary effects on the gastrointestinal and central nervous systems (CNS), which cease after the drug is withdrawn. Serious secondary effects on the CNS (behavioural changes, delirium, hallucinations, convulsions, etc.) have been described associated with high concentrations of Amantadine in plasma in patients with renal insufficiency, damage to the CNS or in elderly patients. Because of this, in these situations it must be administered with caution and the dose adjusted. Because of the anticholinergic activity of Amantadine, it must not be administered with antihistamines or anticholinergics, as this would increase the incidence of secondary effects on the CNS.

Amantadine and Rimantadine have shown practically 90% effectiveness in preventing infection with the Influenza A virus. When used as chemoprophylactics they prevent the disease but do not prevent subclinical infection and the consequent development of the protective immune response against the circulating virus. Amantadine and Rimantadine do not interfere with the humoral immune response to vaccination. Various studies have proved the effectiveness of M2 protein inhibitors in controlling flu outbreaks in closed communities, geriatric homes and within families. It is very important that prophylactic treatment begin as early as possible. In a study recently published by Rubin *et al.* it

was observed that the beginning of chemoprophylactic treatment with Amantadine in long-stay centres more than 5 days after the beginning of the outbreak is related to a significant prolongation of the outbreak, an increase in rates of incidence and greater lethality.

One of the main disadvantages of treatment with Amantadine and Rimantadine is the rapid selection of strains with cross-resistance to the two drugs 2-3 days after the beginning of treatment in approximately one third of patients. The resistant variants do not show a reduction in their biological effects and can particularly be transmitted in outbreaks in closed communities, which leads to the failure of chemoprophylactic treatment in these situations. However, the screening for epidemic strains of flu virus has only sporadically detected strains resistant to adamantanes, even in countries that regularly use Amantadine in flu treatment, as is the case with Japan, since 1998.

Neuraminidase inhibitors

Neuraminidase is a glycoprotein present in the envelope of the flu virus which takes part, thanks to its sialidase activity, in liberating new virus particles from the target cell. Specifically, it impedes the aggregation of these particles to the sialic acid receptors on the cell surface as well as facilitating the spreading of virions via the mucin of the respiratory epithelial tissue. There are currently two neuraminidase inhibiting drugs approved for clinical use: Zanamivir and Oseltamivir. Both have been shown to be effective against all known neuraminidases of Influenza A virus and against Influenza B virus. These drugs are effective in treating acute infection with Influenza A and B viruses when administered during the first 24-48 hours from the beginning of the clinical picture, and they reduce symptoms in approximately 2 days. The study by Kawai *et al.* showed that Zanamivir is more effective against Influenza B than Oseltamivir in patients with Influenza A and B, although the differences were marginal.

Zanamivir is a well-tolerated drug administered by oral inhalation. About 10-20% of the powder inhaled is deposited in the bronchial tubes and lungs and the remaining 78% in the oropharynx. It has low bio-availability - only 4-17% is systematically absorbed, with an average life of 2-5 hours, and it is excreted unchanged in the urine. The unabsorbed drug is eliminated in excrement. Cases have been described of a reduction in respiratory function and bronchospasms in patients with asthma or chronic pulmonary obstruction disease after the administration of Zanamivir. Treatment is not currently recommended in patients with respiratory disease. In healthy adults, the main secondary effects are: diarrhoea, nausea, sinusitis, nasal problems, bronchitis, coughing and cephalgia. These have been detected in less than 5% of subjects included in clinical trials. It has also been suggested as an option for treating

pregnant and breastfeeding women, as the exposure of the foetus or newborn baby to the drug would be minimised due to its limited distribution in the body. However, evidence in this population is very limited and we should act with caution. Oseltamivir is administered orally as a prodrug and 80% of it is systematically absorbed. The hepatic esterases metabolise it to oseltamivir carboxylate, its active form (average life 6-10 hours) and it is eliminated in the urine. In patients with creatinine clarification of 10-30ml/min, the treatment and prophylactic treatment doses must be reduced (75mg once a day) and (75mg every two days). There is no data for patients on blood dialysis. The main secondary effects of Oseltamivir are nausea and vomiting which improve after ingestion and are not usually a reason for withdrawing the treatment.

Effectiveness data for neuraminidase inhibitors in preventing serious flu complications or for high-risk subjects is very limited.

There is little data on possible secondary effects during pregnancy. Aftersales monitoring on the use of Oseltamivir in 61 pregnant women was related to good results, while the cases of toxicity could not be attributed to the drug.

The studies carried out on healthy adults indicate that both Oseltamivir and Zanamivir are effective in preventing flu syndrome with laboratory confirmation (Zanamivir 84%, Oseltamivir 82%). Neither of the two neuraminidase inhibitors on the market has been shown to be effective in the chemoprophylactic treatment of flu in patients with serious immunodepression.

The selection of strains resistant to Zanamivir and Oseltamivir has been demonstrated in vitro and in a limited number of isolations in humans. It is estimated that the incidence of resistance to Oseltamivir in adults is 0.32% and 4.1% in children. Resistant mutations are generated in highly preserved regions of neuraminidase and cause a considerable reduction in viral biological effectiveness. However, current experience continues to be very limited.

DOSE	ADULTS AND TEENAGERS (aged 13-64)	PEDIATRICS (aged 1-12)	GERIATRICS (≥65 and over)	RENAL INSUFFICIENCY	HEPATIC INSUFFICIENCY
AMANTADINE	Treatment* and prophylactic treatment 100 mg/12 h oral	Treatment and prophylactic treatment <ul style="list-style-type: none"> aged 10-12*: adult dose aged 1-9: 4.4-8.8 mg/kg** (max. 150 mg/24 h) in 2 doses Not approved in children < 1 year 	Treatment and prophylactic treatment ≤ 100 mg/day (depending on renal clarification)	Ccr 30-50 ml/min (100 mg/day) Ccr 15-30 ml/min (100 mg/alternate days) Ccr < 15 ml/min (200 mg/week) Not eliminated by HD	No change in doses
RIMANTADINE Foreign drug FDA indications: Prophylactic treatment and treatment, Influenza A virus	Treatment and prophylactic treatment 100 mg/12 h oral	Prophylactic treatment only <ul style="list-style-type: none"> aged 10-12: adult dose aged 1-9: 5 mg/kg** (max. 150 mg/24 h) in 2 doses Not approved in children < 1 year 	Treatment and prophylactic treatment 100 mg/day	Adjustment of dose in patients with Ccr ≤ 10 ml/min (100 mg/day) Not eliminated by HD	Patients with serious hepatic insufficiency: 100mg/day
ZANAMIVIR	Treatment and prophylactic treatment## 10 mg (= 2 inh.)/12 h (5 days)	Treatment and prophylactic treatment <ul style="list-style-type: none"> Children > 7 years: adult dose Not approved in children < 7 years 	No dose modification	No dose modification****	Not evaluated
OSELTAMIVIR FDA indications: Influenza A and B virus prophylactic treatment and treatment	Treatment Minor and averagely serious cases: 75 mg/12 h oral (5 days) Serious cases: 150 mg/12h oral (7-10 days) Prophylactic treatment###: 75 mg/24 h oral (7-10 days)	Treatment only <ul style="list-style-type: none"> Dose depending on body weight*** (5 days) Not approved in children < 1 year 	No dose modification	Adjusted dose in Ccr ≤ 30 ml/min (75 mg/day) No study available on HD	Not evaluated

* Dosing according to weight is recommended when less than 40 kg.

** The CDC recommends 5 mg/kg.

*** < 15 kg: 30 mg/12 h; 15-23 kg: 45 mg/12 h; > 23-40 kg: 60 mg/12 h; > 40 kg: 75 mg/12 h.

**** Limited studies.

Not considered a treatment of choice for avian flu due to the high resistance rate. Could only be used as a prophylactic or if infections by strains sensitive to this antiviral drug are detected.

The use of Zanamivir is recommended in prophylactic treatment for health staff, contacts of patients and as a treatment for less serious patients. More serious patients are treated with Oseltamivir because higher plasma concentrations are achieved (approx. 5 times greater than with Zanamivir).

It has been suggested that the prophylactic use of neuraminidase inhibitors in an epidemic or pandemic could increase vulnerability to infection and facilitate the selection of viruses resistant to these drugs.

HD: haemodialysis

	ADVERSE REACTIONS (> 1 %)	INTERACTIONS	COUNTER-INDICATIONS	PREGNANCY AND BREASTFEEDING
AMANTADINE	<ul style="list-style-type: none"> - Digestive (nausea, anorexia, dry mouth, constipation) - Cardiovascular (peripheral oedema, orthostatic hypotension) - CNS (nausea, cephalgia, ataxia, disorientation, insomnia, depression, anxiety, aggression, hallucinations) 	<ul style="list-style-type: none"> - Anticholinergics^a - Antihistamines^b - Bupropion^c - Hydrochlorothiazide/triamterene^d - Phenelzine^e; quinine, quinidine^f - Trimethoprim^g 	<ul style="list-style-type: none"> - Allergy to Amantadine - German measles - Epilepsy - Peptic ulcer 	<ul style="list-style-type: none"> - FDA category C* - Excreted in small quantities in human milk**
RIMANTADINE	Similar to Amantadine but a smaller proportion of adverse effects on the CNS	No important interaction reported	<ul style="list-style-type: none"> - HPS Rimantadine, Amantadine 	<ul style="list-style-type: none"> - FDA category C*
ZANAMIVIR	<ul style="list-style-type: none"> - Digestive (nausea, diarrhoea, vomiting) - CNS (nausea, cephalgia) - Respiratory: sinusitis, bronchitis, flu-like signs and symptoms - Allergic reactions - Asthmatic/COPD: bronchospasm**** 	Limited data, but it appears there are no clinical interactions	HPS to Zanamivir or some component in preparation	<ul style="list-style-type: none"> - FDA category C* - No information on secretion in human milk***
OSELTAMIVIR	<ul style="list-style-type: none"> - Digestive: nausea, vomiting - CNS: insomnia, vertigo 	<ul style="list-style-type: none"> - Limited studies - Probenecid***** 	<ul style="list-style-type: none"> - HPS to Oseltamivir 	<ul style="list-style-type: none"> - FDA category C* - No information on secretion in human milk***

^a Strengthened toxicity with the appearance of hallucinations or excited nervous states through the addition of its anticholinergic effects; ^b Possible strengthening of the toxicity of chlorphenamine. The mechanism is not known; ^c Possible addition or synergism of its neurotoxic effects; ^d Possible increase in plasma concentrations of Amantadine with possible strengthening of its toxicity due to the reduction in tubular secretion of Amantadine; ^e Possible increase in arterial pressure after administration. The mechanism is not known; ^f Possible strengthening of the toxicity of Amantadine through possible reduction in its renal elimination; ^g Possible strengthening of the toxicity of Amantadine and Trimethoprim through mutual reduction in their renal elimination.

*The studies on animals, using significantly higher doses than those used on humans, have shown embryotoxic and/or teratogenic effects. There is no adequate, properly controlled study on human beings. The use of this drug is only accepted in the absence of safer therapeutic alternatives.

** Although no adverse effects on breastfeeding babies have been recorded, there is a risk of urine retention, vomiting and reddening of the skin.

*** It must not be used during pregnancy unless it is considered that the expected benefit for the mother makes up for any possible risk to the foetus. The use of Zanamivir in breastfeeding mothers is not recommended.

**** No adverse pulmonary reactions have been described in patients with respiratory disease when Zanamivir is administered in the recommended doses.

***** Reduction in the renal clearance rate for Zanamivir (approx. 50%) because they share the same elimination route.

FDA: Food and Drug Administration.

HPS: Hypersensitivity.

Prophylactic antiviral indication form in pandemic phase 3

Name: _____ Surnames: _____

Date of birth: ___/___/_____

Sex: Male Female

Normal address _____

Street: _____

Municipality: _____

Locality: _____

Telephone: _____

Exposure details: _____

1. Co-exposed
Name of case: _____ Place of exposure: _____

2. Unprotected contact with sick or dead wild bird infected with H5N1
Specify place of exposure: _____

3. Contact with domestic birds infected with H5N1 or strongly suspected of being infected
Specify place of exposure: _____

4. Bird slaughter personnel in outbreak of H5N1 flu
Specify place of exposure: _____

5. Professional not properly protected:
Laboratory Specify place of exposure _____
Veterinary Specify place of exposure _____

Day and time of exposure: ___/___/___ - ___:___

Day and time prophylactic treatment started: ___/___/___ - ___:___

Drug used: _____ Dose: _____

Has the person had prophylactic treatment in the last 3 months?: Yes No

Dates: ___/___/___ until: ___/___/___ Drug and dose: _____

Temperature $\geq 38^{\circ}\text{C}$ in the 10 days following exposure

Day 1 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 4 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 7 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 9 Yes <input type="checkbox"/>	No <input type="checkbox"/>
Day 2 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 5 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 8 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 10 Yes <input type="checkbox"/>	No <input type="checkbox"/>
Day 3 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 6 Yes <input type="checkbox"/>	No <input type="checkbox"/>				

Situation after 10 days from the start of prophylactic treatment: Healthy
Sick
Dead

Had prophylactic treatment been carried out correctly? Yes No

Declaring party: Doctor Vet Other (specify) _____
Name and surnames: _____ Contact number: _____

Person carrying out survey: _____ Alert unit: _____

Date of indication of antiviral prophylactic treatment in pandemic phases 4 and 5

Name: _____ Surnames: _____

Date of birth: ___/___/_____

Sex: Male Female

Normal address _____

Street: _____

Municipality: _____

Locality: _____

Telephone: _____

Exposure to risk*:

1. Living with case: Name of case: _____

2. Close contact of case: Relationship with case: _____
Name of case: _____

3. Health staff risk manoeuvre:
(specify) _____

4. Outbreak in closed institution:
Name of institution: _____

Day and time of exposure: ___/___/___ - ___:___

Day and time prophylactic treatment started: ___/___/___ - ___:___

Drug used: _____ Dose: _____

Has the person had prophylactic treatment in the last 3 months?: Yes No

Dates: ___/___/_____ until: ___/___/___ Drug and dose: _____

Temperature $\geq 38^{\circ}\text{C}$ in the 10 days following exposure**:

Day 1 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 4 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 7 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 9 Yes <input type="checkbox"/>	No <input type="checkbox"/>
Day 2 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 5 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 8 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 10 Yes <input type="checkbox"/>	No <input type="checkbox"/>
Day 3 Yes <input type="checkbox"/>	No <input type="checkbox"/>	Day 6 Yes <input type="checkbox"/>	No <input type="checkbox"/>				

Situation after 10 days from the start of prophylactic treatment: Healthy
Sick
Dead

Had prophylactic treatment been carried out correctly? Yes No

Declaring party: Doctor Vet Other (specify) _____

Name and surnames: _____ Contact number _____

Person carrying out survey: _____ Alert unit: _____

* It must be remembered that the transmission period is normally from 2 days before the start of symptoms to 5 days afterwards in adults and up to 7 days in children.

** The temperature must be taken twice a day (morning and evening).

This document has been drawn up by a working group made up of: Núria Casamitjana (Council of Professional Associations of Pharmacists of Catalonia), Salvador Cassany (Ministry of Health Pharmacy Service), Joan Caylà (Spanish Epidemiological Society), Àngela Domínguez (University of Barcelona), Santiago Grau (Catalan Clinical Pharmacy Society), Francesc Gudiol (Bellvitge Hospital Infectious Diseases Department, Catalan Health Institute), Tomàs Pumarola (Hospital Clinic Microbiology Department), Carlos Rodrigo (Catalan Pediatric Society), Antoni Trilla (Council of Professional Associations of Doctors of Catalonia) and Josep Vaqué (Preventive Medicine, Public Health and Hygiene Association) and has been approved by all members of the Scientific Advisory Council for the Influenza Pandemic Plan.