Information for Pharmacists on Dispensing of Oseltamivir

This information article has been prepared to update pharmacists regarding recent changes to the SPC for Tamiflu and in particular the procedures outlined in the SPC for the extemporaneous dispensing of suspension(s) prepared from the contents of Tamiflu capsules for children and adults unable to swallow capsules, and for infants under the age of 12 months.

This article has been prepared under the auspices of a Pharmacy Pandemic Preparedness Group, chaired by the Chief Pharmacist at the Department of Health and Children. The group, which comprises pharmacists from the PSI, HSE, DoHC and IPU, is working on a number of pharmacy-related issues around the current pandemic. Much of the information contained in the article is derived directly from the updated SPC – pharmacists should, however, also consult the full SPC first for more detailed information. The SPC is available from the IMB website (www.imb.ie), the EMEA website (www.emea.europa.eu), or on www.medicines.ie

- Oseltamivir (Tamiflu) is being prescribed for treatment in this pandemic phase of the influenza virus Pandemic (H1N1) 2009. It may also be prescribed for post-exposure prevention of infection in individual cases, in exceptional circumstances where this is considered clinically appropriate, for example in certain residential settings.
- Prescriptions for oseltamivir should be prescribed and dispensed in accordance with the current treatment algorithms. Treatment with oseltamivir should commence as soon as possible after onset of symptoms and preferably within 48 hours. In accordance with the 29 July letter from the HSE, requests or pressure from the public to obtain antiviral drugs for people going on holidays or for those with minor illness should be resisted – antiviral drugs are a valuable resource and need to be used judiciously so as to avoid the development of resistance and to ensure that those who need them can avail of them.
- The shelf life of Tamiflu capsules was extended earlier this summer – the original expiry period of 5 years (after date of manufacture) was extended to 7 years. Further information on the identification of the relevant batches and any necessary action will shortly be issued by the IMB and HSE.
- The summary of product characteristics (SPC) for Tamiflu has been updated and includes important information on the following:
  - (a) the use of oseltamivir in infants under 12 months during a pandemic influenza outbreak
  - (b) the extemporaneous formulation of a suspension from Tamiflu capsule contents using water containing 0.1% w/v sodium benzoate added as a preservative –
  - (i) for adults and children over 1 year who cannot swallow capsules using a **15mg/ml** monograph*; and
  - (ii) infants under 12 months using a **10mg/ml** monograph

*(*Alternatively for adults and children over 1 year who are unable to swallow intact capsules, the capsules can be opened and contents mixed directly with a small amount of sweetened food product immediately before administration)*

Pharmacovigilance

- Patients should be advised of common side effects, which include nausea and headache in adults and children over 12 years, and nausea and vomiting in children under 12, including infants. Pharmacists should be familiar with the SPC for oseltamivir and the recently published IMB Drug Safety Newsletter on anti-virals. Suspected ADRs should be reported to the IMB, preferably online via the IMB website.

The following information is taken from the SPC for Tamiflu. The SPC should be consulted first for fuller information and is available from the EMEA website (www.emea.europa.eu), the IMB website (www.imb.ie), or on www.medicines.ie

Oseltamivir Doses

Treatment doses are given twice daily for 5 days.

(Post-exposure prophylaxis doses are given once daily for 10 days).

Doses mentioned in this article are for treatment, unless otherwise indicated.

It will be apparent from the information below that it is desirable for the pharmacist to be aware of the patient's weight, especially for children under 12 years of age.

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

For adults and children over 12 years: The recommended oral dose is 75mg oseltamivir twice daily for 5 days.

For children over 1 year: Tamiflu 30mg and 45mg capsules are available.

The following weight-adjusted dosing regimens are recommended for children 1 year of age and older:

Body Weight	Recommended dose for 5 days
≤ 15kg	30mg twice daily
> 15kg to 23kg	45mg twice daily
> 23kg to 40kg	60mg twice daily
> 40kg	75mg twice daily

For infants below 12 months of age: The recommended treatment dose for infants less than 12 months is between 2mg/kg twice daily and 3mg/kg twice daily during a pandemic influenza outbreak. This is based upon limited pharmacokinetic data indicating that these doses provide plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in older children and adults. The following weight-adjusted dosing regimens are recommended for treatment of infants below 1 year of age:

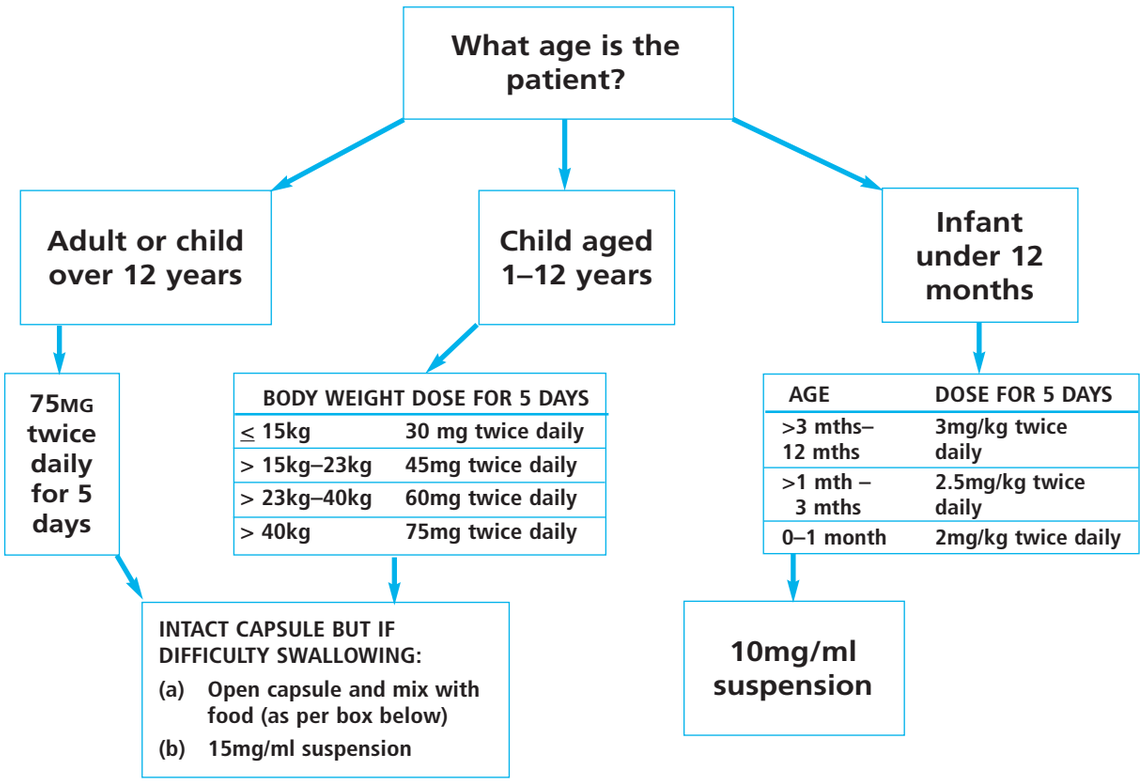
Age	Recommended dose for 5 days
> 3 months to 12 months	3mg/kg twice daily
> 1 month to 3 months	2.5mg/kg twice daily
0 to 1 month*	2mg/kg twice daily

** There is no data available regarding the administration of Tamiflu to infants less than one month of age.*

Administration of Tamiflu to infants less than one year of age should be based upon the judgment of the physician after considering the potential benefit of treatment versus any potential risk to the infant.

Dispensing/Extemporaneous Formulation of Oseltamivir

*Patient presenting prescription for **treatment** of influenza during pandemic outbreak*



(a) Open Capsules and Mix With Food

- For adults and children over 1 year who are unable to swallow intact capsules, the capsules can be opened and contents mixed directly with a small amount (max. 1 teaspoon) of sweetened food product by a parent or carer immediately before administration to mask the bitter taste.
- The mixture should be stirred and the entire contents given to the patient.
- The mixture must be swallowed immediately after its preparation.
- The parent/carer should be counselled to handle powder inside capsules carefully as it may cause irritation to skin and eyes.
- The decision on whether to use this method of administration or the 15mg/ml suspension for an individual patient should be made by the pharmacist using their professional judgement and in consultation with the patient or their parent/carer.

The following monographs describe the preparation of the **15mg/ml** and **10mg/ml** suspensions, prepared from Tamiflu capsules, as per the updated SPC.

- The vehicle for these suspensions is **water containing 0.1% w/v sodium benzoate added as a preservative**. Sodium benzoate and water containing sodium benzoate are commercially available in a number of forms (including a 10% w/v solution which would require a 1 in 100 dilution for the purposes described here).
- While the active drug oseltamivir phosphate readily dissolves in the vehicle and forms a uniform solution, undissolved residue, comprised of inert ingredients from the Tamiflu capsule contents, will be visible. Hence, the terms solution and suspension are used interchangeably in the SPC.
- The equipment required for compounding the suspension, from the SPC procedure, is:
  - ~ Mortar and pestle
  - ~ Funnel
  - ~ Amber glass or amber PET bottle with child-resistant cap
- As with all extemporaneous dispensing, all equipment used must be clean, regularly calibrated (where appropriate) and maintained in an hygienic and operable condition, and adequate records must be kept.

(b) 15mg/ml Suspension

Extemporaneous formulation

Pharmacy compounding

Adults and children greater than 1 year who are unable to swallow intact capsules

This procedure describes the preparation of a 15mg/ml solution that will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a suspension (15mg/ml) from Tamiflu 30mg, 45mg or 75mg capsules using water containing 0.1% w/v sodium benzoate added as a preservative.

- First, calculate the Total Volume needed to be compounded and dispensed to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The Total Volume required is determined by the weight of the patient according to the recommendation in the table below:

Volume of Compounded Suspension (15mg/ml) Prepared Based Upon the Patient's Weight (the recommended dose of oseltamivir is included in the left hand column for ease of reference)

Recommended oseltamivir dose for 5 days	Body Weight (kg)	Total Volume to Compound per Patient Weight (ml)
30mg twice daily	10 to 15kg	30ml
45mg twice daily	> 15 to 23kg	40ml
60mg twice daily	> 23 to 40kg	50ml
75mg twice daily	> 40kg	60ml

- Second, determine the number of capsules and the amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) that is needed to prepare the Total Volume (calculated from the table above: 30ml, 40ml, 50ml or 60ml) of compounded suspension (15mg/ml) as shown in the table below:

Number of Capsules and Amount of Vehicle Needed to Prepare the Total Volume of a Compounded Suspension (15mg/ml)

Total Volume of Suspension to be prepared	Required Number of Tamiflu Capsules (mg of oseltamivir)			Required Volume of Vehicle
	75mg	45mg	30mg	
30ml	6 capsules (450mg)	10 capsules (450mg)	15 capsules (450mg)	29ml
40ml	8 capsules (600mg)	Please use alternative capsule strength*	20 capsules (600mg)	38.5ml
50ml	10 capsules (750mg)	Please use alternative capsule strength*	25 capsules (750mg)	48ml
60ml	12 capsules (900mg)	20 capsules (900mg)	30 capsules (900mg)	57ml

** No integral number of capsules can be used to achieve the target concentration; therefore, please use either the 30mg or 75mg capsules.*

- Third, follow the procedure below for compounding the suspension (15mg/ml) from Tamiflu capsules:

Procedure for compounding the suspension:

1 Carefully separate the capsule body and cap and transfer the contents of the required number of Tamiflu capsules into a clean mortar.
2 Triturate the granules to a fine powder.
3 Add one-third (1/3) of the specified amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) and triturate the powder until a uniform suspension is achieved.
4 Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5 Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion and transfer the vehicle into the bottle.
6 Repeat the rinsing (Step 5) with the remainder of the vehicle.
7 Close the bottle using a child-resistant cap.
8 Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. *(Note: Undissolved residue may be visible but is comprised of inert ingredients of Tamiflu capsules, which are insoluble. However, the active drug, oseltamivir phosphate, readily dissolves in the specified vehicle and therefore forms a uniform solution.)*
9 Put an ancillary label on the bottle indicating 'Shake Gently Before Use'.
10 Instruct the parent or caregiver that after the patient has completed the full course of therapy any remaining solution must be discarded. It is recommended that this information be provided by affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
11 Place an appropriate expiration date label according to storage condition (see below).

Storage of the Pharmacy-compounded Suspension

Room temperature storage conditions: Stable for 3 weeks (21 days) when stored at room temperature. 'Do not store above 25°C'.

Refrigerated storage conditions: Stable for 6 weeks when stored at 2°C – 8°C.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, drug name.

Ensure that the units of measure on the label instructions for use are in the same dosing units as the measurement/dosing device dispensed with the solution.

Refer to the table below for the proper dosing instructions.

Dosing Chart for Pharmacy-Compounded Suspension from Tamiflu Capsules for Children One Year of Age or Older (15mg/ml suspension)

Body Weight (kg)	Dose (mg)	Volume per Dose 15mg/ml	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
10kg to 15kg	30mg	2ml	2ml twice daily	2ml once daily
> 15 to 23kg	45mg	3ml	3ml twice daily	3ml once daily
> 23 to 40kg	60mg	4ml	4ml twice daily	4ml once daily
> 40kg	75mg	5ml	5ml twice daily	5ml once daily

Note: This compounding procedure results in a 15mg/ml suspension, which is different from the commercially available Tamiflu powder for oral suspension.

Dispense the suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (2ml, 3ml, 4ml or 5ml) on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Patient Counselling

- Verbally advise to 'shake gently before use'.
- Advise that undissolved residue may be visible but reassure that the active drug is completely dissolved.
- Ensure that the patient understands the dosage instructions and the correct use of the measurement/dosing device. If dispensing different strength solution to different members of the same household, ensure these are clearly labelled and differentiated.
- Advise dose should be mixed with equal quantity of sweetened liquid to mask bitter taste
- Advise dose best taken with or after food to reduce chance of side effects such as nausea and/or vomiting
- Advise on storage requirements and stability periods.

(c) 10mg/ml Suspension

Extemporaneous formulation

Pharmacy compounding

Infants less than 1 year of age

This procedure describes the preparation of a 10mg/ml solution that will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a suspension (10mg/ml) from Tamiflu 30 mg, 45mg or 75mg capsules using water containing 0.1% w/v sodium benzoate added as a preservative.

- First, calculate the Total Volume needed to be compounded and dispensed for each patient. The Total Volume required is determined by the weight of the patient according to the recommendation in the table below:

Volume of Compounded Suspension (10mg/ml) Prepared, Based Upon the Patient's Weight

Body Weight	Total Volume to Compound per Patient Weight (ml)
Up to 7kg	30ml
7 to 12kg	45ml

- Second, determine the number of capsules and the amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) that is needed to prepare the Total Volume (calculated from the table above: 30ml, 45ml) of compounded suspension (10mg/ml) as shown in the table below:

Total Volume of Suspension to be prepared	Required Number of Tamiflu Capsules (mg of oseltamivir)			Required Volume of Vehicle
	75mg	45mg	30mg	
30ml	4 capsules (300mg)	Please use alternative capsule strength*	10 capsules (300mg)	29.5ml
45ml	6 capsules (450mg)	10 capsules (450mg)	15 capsules (450mg)	44ml

** No integral number of capsules can be used to achieve the target concentration; therefore, please use either the 30mg or 75mg capsules.*

- Third, follow the procedure below for compounding the suspension (10mg/ml) from Tamiflu capsules

Procedure for compounding the suspension:

1 Carefully separate the capsule body and cap and transfer the contents of the required number of Tamiflu capsules into a clean mortar.
2 Triturate the granules to a fine powder.
3 Add one-third (1/3) of the specified amount of vehicle and triturate the powder until a uniform suspension is achieved.
4 Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5 Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion and transfer the vehicle into the bottle.
6 Repeat the rinsing (step 5) with the remainder of the vehicle.
7 Close the bottle using a child-resistant cap.
8 Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. *Note: Undissolved residue may be visible but is comprised of inert ingredients of Tamiflu capsules, which are insoluble. However, the active drug, oseltamivir phosphate, readily dissolves in the specified vehicle and therefore forms a uniform solution.*
9 Put an ancillary label on the bottle indicating 'Shake Gently Before Use'.
10 Instruct the parent or caregiver that after the patient has completed the full course of therapy any remaining solution must be discarded. It is recommended that this information be provided by affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
11 Place an appropriate expiration date label according to storage condition (see below).

Storage of the Pharmacy-compounded Suspension (10mg/ml)

Room temperature storage conditions: Stable for 3 weeks (21 days) when stored at room temperature 'do not store above 25°C'.

Refrigerated storage conditions: Stable for 6 weeks when stored at 2°C–8°C.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, and drug name.

Ensure that the units of measure on the label instructions for use are in the same dosing units as the measurement/dosing device dispensed with the solution.

Refer to the table below for the proper dosing instructions.

Dosing Chart for Pharmacy-Compounded Suspension (10mg/ml) from Tamiflu Capsules for Infants Less Than One Month of Age

Body Weight (rounded to the nearest 0.5kg)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
3kg	0.60ml twice daily	0.60ml once daily
3.5kg	0.70ml twice daily	0.70ml once daily
4kg	0.80ml twice daily	0.80ml once daily
4.5kg	0.90ml twice daily	0.90ml once daily

Dosing Chart for Pharmacy-Compounded Suspension (10mg/ml) from Tamiflu Capsules for Infants One to Twelve Months of Age

Body Weight (rounded to the nearest 0.5kg)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
4kg	1.00ml twice daily	1.00ml once daily
4.5kg	1.10ml twice daily	1.10ml once daily
5kg	1.30ml twice daily	1.30ml once daily
5.5kg	1.40ml twice daily	1.40ml once daily
6kg	1.50ml twice daily	1.50ml once daily
7kg	2.10ml twice daily	2.10ml once daily
8kg	2.40ml twice daily	2.40ml once daily
9kg	2.70ml twice daily	2.70ml once daily
≥10kg	3.00ml twice daily	3.00ml once daily

This compounding procedure results in a 10mg/ml suspension, which is different from the commercially available Tamiflu powder for oral suspension.

Dispense the suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Patient Counselling

- Verbally advise to 'shake gently before use'.
- Advise that undissolved residue may be visible but reassure that the active drug is completely dissolved.
- Ensure that the patient understands the dosage instructions and the correct use of the measurement/dosing device. If dispensing different strength solution to different members of the same household, ensure these are clearly labelled and differentiated.
- Advise dose should be mixed with equal quantity of sweetened liquid to mask bitter taste.
- Advise dose best taken with or after food to reduce chance of side effects such as nausea and/or vomiting.
- Advise on storage requirements and stability periods.