UWTASP

tele-antimicrobial stewardship program

Oseltamivir (Tamiflu)

1.) Renal adjustment guidelines recommend 30mg daily-BID. Can I give 75 mg instead?

2.) What is your policy on continuing treatment > 5 days for inpatients with severe disease?

Tamiflu dosing

2008 and 2012

- Treatment
  - CrCl>30: 75mg BID
  - CrCl 10-30: 75mg QD
- Prophylaxis
  - CrCl>30: 75mg QD
  - CrCl 10-30:
    - 75mg every other day or
    - 30mg QD

2016 and 2019

- Treatment
  - CrCl 60-90: 75mg BID
  - CrCl 30-60: 30mg BID
  - CrCl 10-30: 30mg QD
- Prophylaxis
  - CrCl 60-90: 75mg QD
  - CrCl 30-60: 30mg QD
  - CrCl 10-30: 30mg every other day

Oseltamivir (Tamiflu) Package Insert

2016 and 2019 PKPD

Table 7 Simulated Median Treatment Exposure Metrics of Oseltamivir Carboxylate in Patients with Normal Renal Function, with Renal Impairment and ESRD Patients on Hemodialysis

Renal Function/ Impairment	Normal Creatinine Clearance 90-140 mL/min (n=57)	Mild Creatinine Clearance 60-90 mL/min (n=45)	Moderate Creatinine Clearance 30-60 mL/min (n=13)	Severe Creatinine Clearance 10-30 mL/min (n=11)	ESRD Creatinine Clearance <10 mL/min on Hemodialysis (n=24)
Recommended Treatment Regimens					
PK exposure parameter	**75 mg twice daily**	**75 mg twice daily**	**30 mg twice daily**	**30 mg once daily**	**30 mg every HD cycle**
C_{min} (ng/mL)	145	253	180	219	221
C_{max} (ng/mL)	298	464	306	477	1170
AUC_{48} (ng·h/mL)*	11224	18476	12008	16818	23200
Recommended Prophylaxis Regimens					
PK exposure parameter	**75 mg once daily**	**75 mg once daily**	**30 mg once daily**	**30 mg every other day**	**30 mg alternate HD cycle**
C_{min} (ng/mL)	39	62	57	70	42
C_{max} (ng/mL)	213	311	209	377	903
AUC_{48} (ng·hr/mL)*	5294	8336	6262	9317	11200

*AUC normalized to 48 hours.

Oseltamivir (Tamiflu) Package Insert

A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

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	PCR Neg, Day 5/ Culture Neg, Day 5	Length of stay	Death
75 mg PO BID n = 85	39.7%/ 98.7%	4.0 (3.0-6.5) days	1.1%
150 mg PO BID n = 70	43.3%/ 98.6%	6.0 (3.0-8.0) days	1.4%

Clinical Infectious Diseases 2013;57(11):1511-9.

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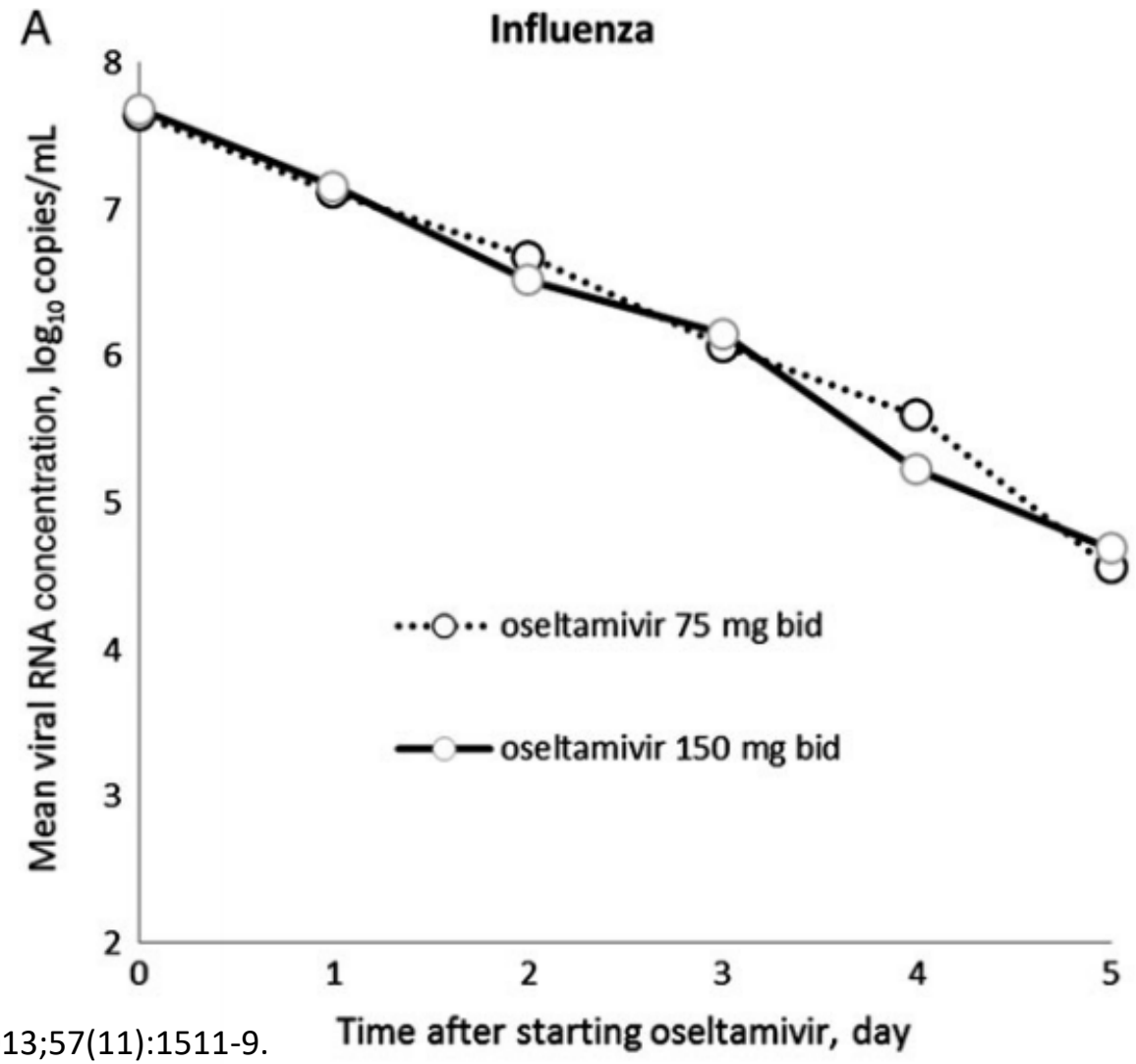

Clinical Infectious Diseases 2013;57(11):1511-9.

Dose-Adjusting Oseltamivir (Do we have to?)

Table 7 Oseltamivir Carboxylate Exposures in Subjects With Normal and Reduced Serum Creatinine Clearance

Parameter	Normal Renal Function			Impaired Renal Function				
	75 mg once daily	75 mg twice daily	150 mg twice daily	Creatinine Clearance <10 mL/min		Creatinine Clearance >10 and <30 mL/min		
				CAPD	Hemodialysis			
				30 mg weekly	30 mg alternate HD cycle	75 mg daily	75 mg alternate days	30 mg daily
C_{max}	259*	348*	705*	766	850	1638	1175	655
C_{min}	39*	138*	288*	62	48	864	209	346
AUC_{48}†	7476*	10876*	21864*	17381	12429	62636	21999	25054

*Observed values. All other values are predicted.

†AUC normalized to 48 hours.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf
Revised 12/2012, accessed 10/21/19.

	Description of events	Management and outcomes	Oseltamivir treatment
1	Diarrhoea	Antibacterial stopped; symptoms resolved	Continued
2	Diarrhoea	Antibacterial stopped; symptoms resolved	Continued
3	Diarrhoea	Antibacterial stopped; symptoms resolved	Continued*
4	Diarrhoea	C. difficile positive; antibacterials stopped and metronidazole started; symptoms resolved	Continued
5	Vomiting	Antib…	
6	Vomiting		
7	Vomiting a… diarrhoea	…ymptoms later …solved	Stopped after 1 day*
8	Vomiting and watery stool	Antibacterial stopped; symptoms later resolved	Dose reduced*
9	Dizziness	Symptomatic treatment; resolved	Continued*
10	Dizziness	Symptomatic treatment; resolved	Dose reduced*
11	Insomnia	Symptoms later resolved	Continued*
12	Rash	Antibacterial and NSAID stopped; resolved	Continued
13	Rash	Symptoms later resolved	Stopped after 3 days
14	Abnormal liver function	Antibacterial stopped; resolved	Continued*
15	Asymptomatic bradycardia	Beta-blocker stopped; resolved	Dose reduced*

Overall, 15 patients experienced adverse events during treatment…75mg vs 150mg, 5.3% vs 22.0%, p=.004

Dose-Adjusting Oseltamivir: Do we have to?

Table 4 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Subjects 13 Years of Age and Older

Adverse Event[a]	Treatment				Prophylaxis			
	Placebo N=716		TAMIFLU 75 mg twice daily N=724		Placebo/ No Prophylaxis[b] N=1688		TAMIFLU 75 mg once daily N=1790	
Nausea (without vomiting)	40	(6%)	72	(10%)	56	(3%)	129	(7%)
Vomiting	21	(3%)	68	(9%)	16	(1%)	39	(2%)
Diarrhea ☆	70	(10%)	48	(7%)	40	(2%)	50	(3%)
Bronchitis	15	(2%)	17	(2%)	22	(1%)	15	(1%)
Abdominal pain	16	(2%)	16	(2%)	25	(1%)	37	(2%)
Dizziness	25	(3%)	15	(2%)	21	(1%)	24	(1%)
Headache ☆	14	(2%)	13	(2%)	306	(18%)	326	(18%)
Cough	12	(2%)	9	(1%)	119	(7%)	94	(5%)
Insomnia	6	(1%)	8	(1%)	15	(1%)	22	(1%)
Vertigo	4	(1%)	7	(1%)	4	(<1%)	4	(<1%)
Fatigue	7	(1%)	7	(1%)	163	(10%)	139	(8%)

[a] Adverse events included are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg twice daily group.

[b] The majority of subjects received placebo; 254 subjects from a randomized, open-label postexposure prophylaxis study in households did not receive placebo or prophylaxis therapy.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf
Revised 12/2012, accessed 10/21/19.

Dose-Adjusting Oseltamivir (UW)

ClCr (ml/min)	>60 ml/min	30 – 60 ml/min	10 – 30 ml/min	< 10 ml/min
Treatment	75 mg q 12h	30 mg q 12h	30 mg q 24h	30 mg q 24h
Prophylaxis	75 mg q 24h	30 mg q 24h	30 mg q 48h	30 mg q 48h

UW Medicine Renal Dosing Guidelines, 10.2019