三總藥訊
(TSGH Pharmacy Newsletter)

（76）國報字第〇〇一號

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調劑科專欄：健保規定異動

本期要目

發文日期：中華民國九十二年十月二日
發文字號：健保審字第〇九二〇〇三三六二五號
（自九十二年十一月一日起施行）

原給付規定條文	增(修)訂後給付規定條文（92/11/1）
10.9.2. moxifloxacin(如 Avelox film-coated tablet) 1.限用於成人(十八歲以上)之慢性支氣管炎的急性惡化或社區性肺炎。 2.每日限使用一粒(400mg)，使用期間以不超過十天為原則。	10.9.2. moxifloxacin 口服劑型(如 Avelox film-coated tablet) 1.限用於成人(十八歲以上)之慢性支氣管炎的急性惡化或社區性肺炎。 2.每日限使用一粒(400mg)，使用期間以不超過十天為原則。

備註:畫底線為增訂條文

發文日期：中華民國九十二年十月十三日
發文字號：健保審字第〇九二〇〇三三六二六號
（自九十二年十一月一日起施行）

原給付規定條文	增(修)訂後給付規定條文（92/11/1）
13.皮膚科製劑　Dermatological preparation 13.9 Tacrolimus(如 Protopic Ointment 0.03%) 給付規定： 1.限下列病患使用：中、重度異位性皮膚炎，且患部面積>30%。 2.使用規範： (1) 成人患部面積 30%~50%， 1tube/30g/wk；患部 面積>50% 2tube/30g/wk。 (2) 小孩患部面積 30%~50%，1tube/30g/2wk； 患部 面積>50% 1tube/30g/wk 3.面積計算：成人依照 rule of nines，由部位乘予大約比例之總和，小孩依比例(Barkin 公式)修訂。 4.使用一個月後，症狀若無改善，應改用其他藥 物治療。 5.以三個月為一個療程，若需繼續治療，與第二 療程應間隔九個月。	13.皮膚科製劑　Dermatological preparation 13.11 Pimecrolimus (Elidel 1%) 給付規定： 1.限二至十七歲孩童及青少年之下列病患使用： 中、重度異位性皮膚炎，且患部面積>30%。 2.使用規範： (1) 二至十七歲孩童及青少年之患部面積 30%~50%，1tube/30g/2wk；患部面積>50%， 1tube/30g/wk。 (2) 面積計算：兒童依比例(備註 Barkin 公式)修 訂。 (3) 使用一個月後，症狀若無改善，應改用其他藥物治療。 (4) 以三個月為一個療程，若需繼續治療，與第二療程應間隔九個月。

備註:畫底線為增訂條文

ADR 專欄：綜整 92-4 ADR 案例(52 cases)總表

No	年齡	姓別	ADR日期	Naranjo score	懷疑藥物	ADR症狀
1	37	女	920713	8	Rifater EMB	Skin eruption

2	57	男	920802	4	Maxipime	Multiple skin rash
3	67	女	920718	7	Vibramycin	Skin rash & itching
4	45	女	920728	7	Conray	Facial rash and itching
5	26	女	920722	4	Dilantin	Skin rash over abdomen region
6	45	男	920729	7	Angiografin	Hand rash
7	76	男	920728	7	Ultravist	Skin rash over face and neck
8	51	男	920729	7	Ultravist	Skin rash over face and itching
9	57	男	920712	8	Rifater	Skin rash
10	65	女	920805	7	Lonine Mydocalm	Skin rash and itching
11	27	女	920823	8	Keto	SOB and eye swelling
12	73	女	920827	7	Vioxx	Itching and swelling
13	1	女	920827	4	Tripacel	Swelling over left thigh
14	21	男	920812	7	Bromazepam rivotril depakine	Dizziness and standing unstable
15	34	男	920808	7	Depain X	Nausea and vomiting
16	60	女	920801	7	Peysan	Dizziness and headache
17	1月	男	920814	7	Ventol syrup	Hyperactivity
18	80	男	920804	7	Cozaar	Malaise
19	89	男	920914	4	Dilantin depakine Tienam	Skin rash
20	34	男	920829	7	Ultravist	Skin rash
21	79	男	920824	4	Kefadin	Skin rash
22	52	女	920829	5	Rifater	Jaundice hyperbilirubinemia
23	57	男	920719	4	Rifater	Skin rash
24	48	女	920722	6	Rivotril depakine	Acute respiratory failure
25	1	男	920914	7	Antiphen syrup	Skin rash
26	22	女	920822	7	Demerol	Skin rash and itching
27	22	女	921002	7	Keflex	itching
28	70	男	920811	7	Harnalidge proscar	Skin rash
29	61	男	921002	7	Imdur	Severe headache
30	28	女	920822	7	Flagyl	Skin rash
31	45	男	921002	7	Keto	Itching and swelling
32	40	男	920930	7	Xanthium	CNS disturbance arrythmia
33	50	女	920915	7	Oruvail	Skin rash and itching
34	39	女	920927	7	Ponston clindamycin	Eye swelling
35	30	男	920930	7	Ultravist	Eyelid rash and swelling
36	33	男	921005	5	Dilantin	Skin rash
37	87	女	920813	4	Capotil	Cough
38	64	女	921014	7	Lasix prepulside digoxin	Severe vomiting and arrythmia
39	53	女	921007	7	Ultravist	Skin rash
40	49	男	921015	7	Betaloc zok	Hypotension bradycardia
41	34	男	920806	5	Depain X	Nausea drowsiness
42	68	女	921004	7	Depain X	Severe vomiting and dizziness
43	56	男	920801	6	Mydocalm glucophage	Skin rash and itching
44	20	女	920820	5	Propylthiouracil(PTU)	fever and thrombocytopenia
45	22	男	920904	4	Keto mydocalm	Skin rash and swelling
46	64	女	920819	7	Navelbine platinex	Neutropenia

47	65	女	920930	7	Epirubicin Platinex	Neutropenia
48	49	女	920922	7	Navelbine platinex	Neutropenia (921022 同症狀)
49	35	男	920606	7	Endoxan Adriblastina Vincristine	Neutropenia (920707同症狀)
50	39	男	920915	7	Fluarix (GSK 廠)	Fever
51	36	女	920915	7	Fluarix (GSK 廠)	Skin swelling and itching
52	36	男	920916	7	Fluarix (GSK 廠)	Skin rash and itching

Naranjo score： ≤ 0存疑　1-4可能　5-8很可能　≥9確定的

專題報導：CCB 之介紹

謝政智藥師

鈣離子通道阻斷劑(Calcium Channel Blockers，CCB)除了熟悉之三類原型藥--- dihydropyridine **類**(Nifedipine)，benzothiazepine**類**(Diltiazeam)，phenylalkylamine**類**(Verapamil)**外，在藥廠對新藥不斷之研發，及對現有藥品劑型之改變後，而開發出愈來愈多的鈣離子通道阻斷劑。**
CCB依各類藥物及各劑型不同之特性可用於高血壓、心絞痛、蜘網膜下腔出血(subarachnoid hemorrhage)**及**paroxysmal supraventricular tachycardias (PSVT)**等之治療。**

本院目前有15種鈣離子通道阻斷劑(表一)，以下就本院現有之品項依適應症(表二)，藥物動力學特性(表三)，藥物交互作用(表四)及藥物不良反應(表五)逐一簡單的介紹於後。

表一：本院現有之CCB**之藥品品項**

學名	**商品名**
Amlodipine	Norvasc 5mg tab
Barnidipine	Hypoca 10mg cap
Diltiazem	Diltelan SR 120mg cap
	Herbesser 30mg tab
	Herbesser 10mg inj
Felodipine	Plendil 5mg tab
Isradipine	Dynacric SRO 5mg cap
Nicardipine	Perdipine 1mg/ml 10ml inj
Nifedipine	Adalat 10mg cap
	Adalat OROS 30mg tab
Nimodipine	Nimotop 30mg tab
	Nimotop 50ml inj
Verapamil	Isoptin 80mg tab
	Verelan SR 120mg cap
	Cintsu SR 240mg tab

表二：CCB**之適應症**

Indications √ = labeled X = unlabeled	Amlodipine	Diltiazem	Diltiazem SR	Felodipine	Isradipine	Nicardipine IV	Nifedipine	Nifedipine ER	Nimodipine	Verapamil	Verapamil SR
Angina pectoris											
Vasospastic	√	√					√	√[2]		√	
Chronic stable	√	√					√	√[2]		√	
Unstable										√	
Hypertension	√		√	√	√	√		√		√	√
Subarachnoid hemorrhage									√		
Paroxysmal supraventricular tachycardia										√[4]	
Unlabeled uses											
Prevention of migraine headaches		X								X	
Pulmonary hypertension	X	X		X			X				
Raynaud's phenomenon	X	X		X	X		X				
Preterm labor							X				
Hypertrophic cardiomyopathy										X	

表三：CCB之藥動學特性

Parameters		Amlodipine	Diltiazem	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine	Verapamil
Pharmacokinetics	Extent of absorption (oral) (%)	nd	nd	≅100	90-95	≅100	100	nd	nd	> 90
	Absolute bioavailability (oral) (%)	64-90	40	≅20	15-24	≅35	45-75 (IR) 84-89 (ER)	≅13	≅5	20-35 (IR)
	Volume of distribution	nd	≅305 L (IV)	10 L/kg	3 L/kg	8.3 L/kg (IV)	nd	nd	nd	nd
	T_{max} (h)	6-12	2-4 (IR) 10-14 (ER) 6-11 (SR)	2.5-5	1.5 (IR) 7-18 (CR)	0.5-2 (IR) 1-4 (SR)	0.5 (IR) 6 (ER)	1	6-12	1-2 (IR) ≅11 (ER) ≅7-9(SR)
	Protein binding(%)	93	70-80	> 99	95	> 95	92-98	> 95	> 99	≅90
	Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
	Major metabolites	90% converted to inactive	Desacetyl-diltiazem[2]	6 inactive	Mono acids and cyclic lactone[3]	nd	Inactive	Numerous, inactive	5 major urinary metabolites	Norverapamil[4]
	Half-life, elimination(h)	30-50	3-4.5 (IR) 4-9.5 (ER) 5-7 (SR) ≅3.4 (IV)	11-16	8	2-4	≅2 (IR) ≅7 (ER)	≅8-9[7]	7-12	2.8-7.4[8] 4.5-12[9] ≅12 (SR) 2-5(IV)
	Clearance, systemic	nd	≅65 L/h(IV)	≅0.8 L/min	1.4 L/min	0.4 L/h· kg (IV)	nd	nd	nd	nd
	Excreted unchanged in urine (%)	10	2-4	±	0	< 1	< 0.1	< 1	trace	3-4

	Excreted in urine (%)	nd	nd	70	60-65	60 (oral) 49 (IV)	60-80	nd	60-80	≈70
	Excreted in feces (%)	nd	nd	10	25-30	35 (oral) 43 (IV)	15	nd	nd	≈16
ECG Changes	Heart rate	±	0-↓	↑↑	↑	↑↑	0-↑		±	±
	QRS complex	0	nd	0	0	0	nd		0	nd
	PR interval	0	↑	0	0	0	nd		0	↑
	QT interval	0	nd	0	↑	↑	nd		0	nd
Hemodynamics	Myocardial contractility	0-↓	0-↓	0-↓	↓	0-↓	0-↓	na	0-↓	↓↓
	Cardiac output/index	↑	0-↑	nd	↑	↑↑	↑		nd	±
	Peripheral vascular resistance	↓↓	↓↓[10]	↓↓[10]	↓↓	↓↓↓	↓↓↓		↓↓[10]	↓↓

*↑↑↑ or ↓↓↓= pronounced effect; ↑↑ or ↓↓= moderate effect; ↑ or ↓= slight effect; ±=negligible amount or effect; nd = no data(**無相關資料**); na = not applicable(**適應症不在** CV). [1]Activity of metabolites is unknown. [2]25% to 50% as potent a coronary vasodilator as diltiazem; plasma levels are 10% to 20% of the parent drug. [3]Of 6 metabolites identified, accounting for > 75%. [4]Major metabolite; cardiovascular activity is ≈20% that of verapamil. [5]Following cessation of multiple dosing. [6]During a given dosing interval. [7]Earlier elimination rates are much more rapid, equivalent to a half-life of 1 to 2 hours. [8]After single doses. [9]After repetitive doses. [10]Dose-related.

表四：CCB之藥物交互作用

Precipitant drug	Object drug*		Description
Amiodarone	Diltiazem, verapamil	↑	Coadministration may result in cardiotoxicity with bradycardia and decreased cardiac output. Monitor closely.
Azole antifungals-Itraconazole	Felodipine, isradipine, nifedipine	↑	Serum concentrations of the calcium channel blocker may be increased. Observe clinical response, monitor cardiovascular status, and adjust calcium channel blocker dose accordingly.
Barbiturates	Felodipine, nifedipine, verapamil	↓	Pharmacologic effects of the calcium channel blocker may be decreased.
Beta-blockers	Calcium channel blockers	↑	Coadministration may cause additive or synergistic effects. Diltiazem, isradipine, nicardipine, nifedipine, and verapamil may inhibit the metabolism of certain beta-blockers. Monitor cardiac function and adjust dosages as needed.
Calcium channel blockers-Diltiazem, isradipine, nicardipine, nifedipine, verapamil	Beta-blockers		
Calcium salts	Verapamil	↓	Clinical effects and toxicities of verapamil may be reversed by calcium.
Carbamazepine, Oxcarbazepine	Felodipine	↓	Pharmacologic effects of felodipine may be decreased. Patients may require higher doses of felodipine.
Cisapride	nifedipine	↑	Cisapride may increase nifedipine serum concentrations. Monitor closely and adjust dose of nifedipine as needed.
Cyclosporine	Nifedipine, felodipine	↑	Pharmacologic and toxic effects of nifedipine or felodipine may be increased. Cyclosporine levels and toxicity may be increased when given concurrently with diltiazem, felodipine, nicardipine, or verapamil. However, verapamil may be nephroprotective when given before cyclosporine. Monitor cyclosporine levels and adjust the dose as needed.
Diltiazem, felodipine, nicardipine, verapamil	Cyclosporine		
Erythromycin	Felodipine	↑	Coadministration may increase the effects of felodipine. Monitor cardiovascular status closely and adjust felodipine dose as needed.
H_2 antagonists-Cimetidine, ranitidine	Diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, verapamil	↑	Serum concentrations of the calcium channel blocker may be increased when given concurrently with cimetidine. Ranitidine also has been shown to affect diltiazem concentrations. Monitor cardiovascular status closely. Adjust dose as needed.
Hydantoins (eg, phenytoin)	Felodipine, nisoldipine, verapamil	↓	The pharmacologic effects of the calcium channel blocker may be decreased. Monitor cardiovascular status closely. Adjust dose as needed.
Melatonin	Nifedipine	↓	Concurrent use may decrease the antihypertensive effects of nifedipine.
Nafcillin	Nifedipine	↓	Nafcillin administration results in a large reduction in the plasma concentration of nifedipine; loss of efficacy is likely to result. Nafcillin would be expected to reduce the plasma concentrations of other calcium channel blockers as well. Avoid coadministration.
Quinupristin/Dalfopristin	Nifedipine	↑	Concurrent use may increase the plasma concentration of nifedipine. The metabolism of other calcium channel blockers would likely be reduced by quinupristin/dalfopristin

Rifampin	Diltiazem, isradipine, nicardipine, nifedipine, verapamil	↓	Coadministration may decrease the therapeutic effects of the calcium channel blocker. Monitor cardiovascular status closely. Adjust dose as needed.
St. John's Wort	Calcium channel blockers-Nifedipine	↓	Coadministration may reduce the plasma concentration of nifedipine. The metabolism of other calcium channel blockers would likely be increased by St. John's Wort as well.
Valproic acid	Nimodipine	↑	Valproic acid increases the AUC of nimodipine with no effect on the elimination half-life. Monitor closely.
Calcium channel blockers	Anesthetics	↑	Calcium channel blockers may potentiate the cardiac effects and vascular dilation associated with anesthetics. Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Titrate doses carefully.
Verapamil	Antiarrhythmic agents-Disopyramide, flecainide	↑	Concomitant use of verapamil and flecainide may have additive effects. Until data on possible interactions between verapamil and disopyramide are obtained, the manufacturer recommends not administering disopyramide within 48 h before or 24 h after verapamil administration.
Verapamil	Antineoplastics-Doxorubicin	↑	Verapamil appears to increase doxorubicin serum concentrations.
Antineoplastics	Verapamil	↓	The absorption of verapamil can be reduced by the cyclophosphamide, oncovin, procarbazine, prednisone (COPP) and the vindesine, adriamycin, cisplatin(VAC) drug regimens.
Diltiazem, verapamil	Benzodiazepines-Midazolam, triazolam	↑	Effects of certain benzodiazepines may be increased.
Diltiazem, verapamil	Buspirone	↑	Coadministration may increase the effects of buspirone. Monitor closely and adjust buspirone dose as needed.
Calcium channel blockers-Diltiazem, verapamil	Carbamazepine	↑	Serum carbamazepine concentrations may be increased. Monitor serum levels and adjust dosage as necessary.
Nifedipine	Diltiazem	↑	Diltiazem increases nifedipine plasma concentrations and nifedipine increases diltiazem plasma concentrations.
Diltiazem	Nifedipine		
diltiazem, nifedipine, verapamil	Digoxin	↑	Serum digoxin concentrations may be elevated, causing increased toxicity. Coadministration with diltiazem or nifedipine has produced conflicting reports. Monitor digoxin levels and adjust the dose as needed.
Verapamil	Dofetilide	↑	Concurrent use may increase dofetilide plasma concentration with increased risk of ventricular arrhythmias. Coadministration is contraindicated.
Verapamil	Ethanol	↑	Verapamil may cause increased and prolonged CNS effects of ethanol.
Diltiazem, verapamil	HMG-CoA reductase inhibitors	↑	Plasma concentrations of certain HMG-CoA reductase inhibitors(eg, atorvastatin) may be elevated. If coadministration cannot be avoided, administer a conservative dose of the HMG-CoA reductase inhibitor.
Isradipine	Lovastatin	↓	Plasma concentrations of lovastatin may be reduced, decreasing pharmacologic effect. Monitor clinical response and adjust therapy as needed.
Diltiazem, verapamil	Imipramine	↑	Coadministration increases imipramine serum concentrations.
Diltiazem, verapamil	Lithium	↑↓	Coadministration with verapamil has caused a reduction in lithium levels and toxicity. Coadministration with diltiazem has caused neurotoxicity.
Diltiazem	Methylprednisolone	↑	Pharmacologic and toxic effects of methylprednisolone may be increased.
Diltiazem	Moricizine	↑	Concurrent use may increase moricizine concentrations, while moricizine may decrease diltiazem concentrations.
Moricizine	Calcium channel blockers-Diltiazem	↓	
Verapamil	Nondepolarizing muscle relaxants	↑	Nondepolarizing muscle relaxant effects may be enhanced. Respiratory depression may be prolonged. Avoid concurrent use if possible.
Verapamil	Prazosin	↑	Concurrent use may increase serum prazosin concentrations and may increase the sensitivity to prazosin-induced postural hypotension.
Diltiazem, verapamil	Quinidine	↑	Coadministration may increase the therapeutic and adverse effects of quinidine. Use quinidine with verapamil only when no other alternative exists. Closely monitor quinidine serum levels and cardiac effects. Quinidine decreased the AUC of nisoldipine by 26% but not the peak concentration.
Nifedipine	Quinidine	↓	Serum levels and actions of quinidine may be decreased. Serum concentrations and actions of nifedipine may be increased.
Quinidine	Nifedipine	↑	
Diltiazem, verapamil	Sirolimus	↑	Coadministration may increase sirolimus plasma concentrations.
Diltiazem, nifedipine, verapamil	Tacrolimus	↑	Tacrolimus levels may be elevated, increasing toxicity. Monitor serum levels and adjust dosage as needed.
Diltiazem, verapamil	Theophyllines	↑	Pharmacologic and toxic effects of theophyllines may be increased. Monitor serum levels and adjust dosage as needed.
Nifedipine	Vincristine	↑	Vincristine levels may be elevated, possibly increasing toxicity.

*↑ = Object drug increased. ↓= Object drug decreased.

表五：CCB**之藥物不良反應**

Adverse Reactions		Amlodipine	Diltiazem Oral (IV)[1]	Felodipine	Isradipine[1]	Nicardipine Oral (IV)[1]	Nifedipine[1]	Nimodipine	Verapamil Oral (IV)[1]
Cardiovascular	Angina/Angina pectoris		< 2	0.5-1.5		†	≤1		≤1
	Angina increased					5.6[2]	≤1		
	Arrhythmia	≤1	< 2 (1[3])	0.5-1.5			≤1		
	Arrhythmia, ventricular		< 1				< 0.5		
	Atrial fibrillation	≤1	1.4		≤1		< 1		
	AV block (1°, 2°, or 3°)		7.6 (< 1)			(†)			0.8-1.7
	Bradycardia	≤1	≤6 (< 1)				< 1	≤1	1.4 (1.2)
	Chest pain	≤1	< 1	0.5-1.5	≤2.7	(0.7)	≤3		≤1
	CHF		< 2 (< 1)					< 1	1.8
	Edema	1.8-14.6[4]	≤6 (<1)		3.5-35.9[2]	0.6-1	10-30[2]	≤1.2[2]	1.7-3
	ECG abnormalities		≤4.1			0.6 (1.4)		≤1.4	2
	Facial edema			0.5-1.5			≤1		
	Hypertension		< 1			(0.7)		< 1	1.7
	Hypotension	≤1	< 2	0.5-1.5	≤1	† (5.6)	< 1	≤8.1[2]	0.7-2.5
	Hypotension, postural	≤1	< 1			≤0.9 (1.4)	< 1		0.4
	Hypotension, symptomatic		(3.2)						(1.5)
	MI		< 1	0.5-1.5	≤1				≤1
	Palpitations	0.7-4.5[2]	≤2	0.4-2.5	1-5.1[2]	2.8-4.1	≤7	< 1	≤1
	Peripheral edema		2-15 (4.3)	2-17.4		(†)	7-29[2]		3.7
	Sinus bradycardia		< 1						
	Supraventricular tachycardia					(0.7)			
	Syncope	≤1	< 2 (< 1)	0.5-1.5	≤1	0.8 (0.7)	≤1		≤1
	Tachycardia	≤1	< 2	0.5-1.5	≤3.4	0.8-3.4 (3.5)	≤1	≤1.4	
	Vasculitis	≤1							≤1
	Vasodilation		≤3			4.7-5.5 (0.7)			
	Ventricular extrasystoles	≤0.1	≤2			† (1.4)			
	Ventricular tachycardia	≤1	(< 1)			† (0.7)			
CNS	Abnormal dreams	≤1	< 2			0.4			
	Amnesia	≤0.1	< 2						
	Anxiety/Anxiety disorders	≤1		0.5-1.5		†	≤1		
	Asthenia	1-2	≤4 (< 1)	2.2-3.9		0.9-5.8 (0.7)	≤4		2
	Ataxia	≤0.1					≤1		
	Confusion					† (†)	< 1		≤1
	Depression	≤1	< 2	0.5-1.5	≤1	†	≤1	≤1.4	(†)
	Dizziness/Lightheadedness	≤3.4[2]	≤10 (< 1)	2.7-3.7	3.4-8	1.6-6.9 (1.4)	4-27	< 1	3-4.7 (1.2)
	Drowsiness				≤1				
	Equilibrium disturbances						≤2		≤1
	Fatigue/Lethargy	4.5[2]			≤8.5[2]		4-5.9		1.7-4.5
	Headache	7.3	≤12 (< 1)	10.6-14.7	10.3-22	6.2-8.2	10-23	≤4.1[2]	2.2-12.1 (1.2)
	Hypesthesia	≤1				(0.7)	≤1		
	Insomnia	≤1	< 2	0.5-1.5	≤1	0.6	< 3		≤1
	Malaise	≤1	< 1			0.6	≤1		
	Migraine	≤0.1					≤1		
	Nervousness	≤1	≤2	0.5-1.5	≤1	0.6	≤7		
	Paresthesia	≤1	< 2 (< 1)	1.2-1.6	≤1	1 (0.7)	≤3		≤1
	Shakiness/Jitteriness						≤2		≤1
	Sleep disturbances						≤2		1.4
	Somnolence	1.3-1.6[4]	< 2	0.5-1.5		1.1-1.4	< 3		≤1
	Tremor	≤1	< 2			0.6	≤8		
	Vertigo	≤1	< 1			†	≤3		(†)
	Weakness				≤1.2		10-12		
Dermatologic	Acne							≤1.4	
	Dermatitis	≤0.1	≤1				≤2		
	Erythema multiforme	≤1	< 1						≤1
	Hair loss	≤0.1	†				≤1		≤1

	Injection site reactions		(3.9)			(1.4)			
	Leukocytoclastic vasculitis		†	0.5					
	Pruritus	1-2	< 2 (< 1)		≦1		< 3	< 1	
	Rash	1-2	≦2	0.2-2	≦2.6	0.4-1.2	≦3	≦2.4	≦2.4
	Rash maculopapular	≦1							
	Stevens-Johnson syndrome		†				< 0.5		≦1
	Urticaria	≦0.1	< 1	0.5-1.5	≦1		≦2		≦1 (†)
GI	Abdominal discomfort	1.6	1	0.5-1.5	≦5.1	(0.7)	< 3		(0.6)
	Abdominal distention		≦2		1.2				
	Acid regurgitation			0.5-1.5					
	Anorexia	≦1	< 2						
	Appetite increase	≦0.1							
	Constipation	≦1	≦3.6 (< 1)	0.3-1.5	≦3.8	0.6	≦3.3		3.9-11.7
	Diarrhea	≦1	≦2	0.5-1.5	≦3.4		< 3	≦4.2	≦2.4
	Dry mouth	≦1	< 2 (< 1)	0.5-1.5	≦1	0.4-1.4	< 3		≦1
	Dysgeusia	≦0.1	< 2				≦1		
	Dysphagia	≦1							
	Dyspepsia	1-2	≦6	0.5-3.9		0.8-1.5 (†)	< 3		2.5-2.7
	Flatulence	≦1	< 1	0.5-1.5			< 3		
	Gastritis	≦0.1							
	GI distress								≦1
	GI hemorrhage		< 1				< 1	< 1	
	Gingival hyperplasia	≦1	†	< 0.5			≦1		≦1
	Nausea	2.9[2]	≦2.2 (<1)	1-1.7	1-5.1	1.9-2.2 (4.9)	2-11	0.6-1.4	1.7-2.7 (0.9)
	Thirst	≦1	< 2						
	Vomiting	≦1	≦2 (< 1)	0.5-1.5	≦1.3	0.4-0.6 (4.9)	≦1	< 1	
GU	Decreased libido			0.5-1.5	≦1		≦1		
	Dysuria	≦0.1		0.5-1.5			≦1		
	Gynecomastia		< 2	0.5-1.5			< 0.5		
	Hematuria					(0.7)	≦1		
	Impotence		≦2	0.5-1.5	≦1	†	≦3		≦1
	Nocturia	≦1	< 2		≦1	0.4	≦1		
	Polyuria	≦1	< 2	0.5-1.5		(1.4)	< 3		
	Sexual difficulties	≦2	< 2				≦2		
	Urinary frequency	≦1		0.5-1.5	1.3-3.4	≦0.6 (†)	≦3		≦1
Hematologic	Anemia			0.5-1.5			< 0.5	< 1	
	Ecchymosis								≦1
	Leukopenia	≦1	†		≦1		< 0.5		
	Petechiae		< 2						
	Purpura	≦1	< 1				≦1		≦1
	Thrombocytopenia	≦1	†			(†)	< 0.5	< 1	
Musculoskeletal	Arthralgia	≦1	1.4	0.5-1.5		†	< 3		≦1
	Arthritis						< 1		
	Back pain	≦1	1.7-2.9	0.5-1.5			≦1		
	Hypertonia	≦0.1	< 1			(†)	≦1		
	Leg cramps				≦1		≦3		
	Leg pain			0.5-1.5			≦3		
	Muscle cramps	1-2	< 2	0.5-1.5			≦8	≦1.4	≦1
	Myalgia	≦1	≦2.3	0.5-1.5		1	≦1		1.1
	Neck pain		< 1			(†)	< 1		
	Rigors	≦1					≦1		
Respiratory	Bronchitis		≦4	0.5-1.5					
	Cough	≦0.1		0.8-1.7	≦1		≦6		
	Cough increased		1-3				< 1		
	Dyspnea	1-2	≦6 (< 1)	0.5-1.5	≦3.4	0.6 (0.7)	≦6	≦1.2	1.4
	Epistaxis	≦1	< 2	0.5-1.5			≦3		
	Nasal congestion		< 2				≦6		

	Pharyngitis		1.4-6	0.5-1.5			< 1		3
	Respiratory disorder		< 1			(†)	1		
	Respiratory infection			0.5-1.5			1		
	Rhinitis	0.1	9.6			†			2.7
	Sinusitis		2	0.5-1.5		†	1		3
	Upper respiratory infection			0.7-3.9			1		5.4
	Wheezing						6	< 1	
Special senses	Abnormal vision	1				†	1		
	Amblyopia		(< 1)				< 1		
	Blurred vision		< 1			†	2		1
	Conjunctivitis	1				(†)			
	Tinnitus	1	< 2			† (†)	1		1
Miscellaneous	Accidental injury		1.3						1.5
	Angioedema	1		0.5-1.5			0.5		
	Chills						2		
	Fever		< 1			(†)	2		
	Flu-like illness/syndrome/ symptoms		2.3	0.5-1.5					3.7
	Flushing	0.7-4.5[4]	3 (1.7)	3.9-6.9	1.2-5.1[2]	5.6-9.7	25	2.1	0.6-0.8
	Gout		1-2				1		
	Hot flashes					†	1		
	Hyperglycemia	1	< 2						
	Infection		6			†			12.1
	Pain	1	6			0.6	< 3		
	Sore throat					†	6		
	Sweating		< 1 (< 1)			(1.4)	2	< 1	1
	Sweating increased	1				0.6	1		(†)
	Weight gain	1	< 2				1		
	Weight loss						< 1		

*Data are pooled from separate studies and are not necessarily comparable. [1]Includes data for SR/ER form. [2]Dose-related. [3]Functional rhythm or isorhythmic dissociation. [4]Dose-related and higher in females. †Occurs, no incidence reported.