New Drug Review – Fall 2011

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Cardiovascular

azilsartan medoxomil (Edarbi®) – Takeda

Category: angiotensin II receptor blocker (ARB)

Indication: treatment of hypertension; either alone or in combination with other antihypertensive agents

Pharmacology: Azilsartan antagonizes angiotensin II at the AT_1 receptor subtype in tissues like vascular smooth muscle and the adrenal gland. Azilsartan exhibits more than 10,000-fold greater affinity for the AT_1 receptor than the AT_2 receptor. Angiotensin II is a potent vasoconstrictor; which also stimulates the synthesis and release of aldosterone. By selectively blocking the AT_1 receptor, azilsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

Pharmacokinetics: Azilsartan medoxomil is a prodrug that is hydrolyzed in the GI tract to azilsartan, the active metabolite. The estimated absolute bioavailability is approximately 60%. Peak plasma concentrations are reached within 1.5-3 hours. Food does not affect bioavailability. It is highly bound (>99%) to plasma proteins and is primarily metabolized by CYP2C9 to inactive metabolites. Half-life is approximately 11 hours, and steady state is achieved within 5 days.

Clinical Trials: A 6-week randomized, double-blind, multicenter, placebo- and active-controlled trial was designed to evaluate the efficacy and safety of azilsartan medoxomil, 40 or 80 mg, compared to placebo, olmesartan, and valsartan in patients with stage 1 or 2 hypertension.[1] A total of 1291 patients were randomized to the various treatment groups. The primary efficacy endpoint was the change from baseline in 24-hour mean systolic blood pressure (BP). (see tables below).

Table 2. Changes From Baseline in 24-Hour Mean Ambulatory Systolic BP

Parameter	Placebo (N=134)	AZL-M 40 mg (N=237)	AZL-M 80 mg (N=229)	Valsartan 320 mg (N=234)	Olmesartan 40 mg (N=254)
Baseline SBP, mm Hg	144.3 (0.9)	144.4 (0.6)	144.6 (0.7)	146.3 (0.6)	144.4 (0.6)
Change from baseline, mm Hg	−0.3 (0.9)	−13.4 (0.7)	−14.5 (0.7)	−10.2 (0.7)	−12.0 (0.7)
Mean difference vs placebo		−13.2	−14.3	−10.0	−11.7
95% CI		−15.4 to −10.9	−16.5 to −12.0	−12.2 to −7.7	−14.0 to −9.5
P value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
Mean difference vs olmesartan		−1.4	−2.5		
95% CI		−3.3 to 0.5	−4.4 to −0.6		
P value vs olmesartan		0.136	0.009*		
Mean difference vs valsartan		−3.2	−4.3		
95% CI		−5.1 to −1.3	−6.3 to −2.4		
P value vs valsartan		0.001	<0.001*		

Values are expressed as least significant mean from baseline and SE of the mean. AZL-M indicates azilsartan medoxomil; SBP, systolic BP.
*Data indicate significant difference at the 0.05 level and significant within the framework of the stepwise analysis for azilsartan medoxomil comparisons (see Figure 1); superiority of 40 mg of azilsartan vs 320 mg of valsartan was not examined, because the stepwise testing sequence was halted at a previous step.

Black Box Warning: AVOID USE IN PREGNANCY – When pregnancy is detected, discontinue Edarbi as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. Azilsartan is listed as Pregnancy Category C (first trimester) and D (second and third trimesters).

Contraindications: None

Warnings: *Hypotension* – In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients, symptomatic hypotension may occur after initiation of treatment. Correct volume or salt depletion prior to administration, or start treatment at 40 mg. *Impaired renal function* – In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g., patients with severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with an ARB has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death.

Drug Interactions: Co-administration of NSAIDs (including COX-2 inhibitors) may result in deterioration of renal function, including possible acute renal failure. NSAIDs can also attenuate the antihypertensive effects of ARBs.

Adverse Reactions: Diarrhea (2%) was the most commonly reported adverse reaction in clinical trials. Other adverse reactions noted were nausea, asthenia, fatigue, muscle spasm, dizziness, and cough.

Dosing: Recommended adult dose is 80 mg PO once daily; with or without food. Consider using a starting dose of 40 mg PO once daily in patients on high-dose diuretics.

How Supplied: 40 mg and 80 mg tablets. Do not repackage; dispense and store in original container.

Cost: Drugstore.com - $2.87 per tablet ($86.10 for 30 day supply)

dabigatran etexilate mesylate (Pradaxa®) – Boehringer Ingelheim

Category: Direct thrombin inhibitor

Indication: to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Pharmacology: Dabigatran is a competitive, direct thrombin inhibitor. Because thrombin enables the conversion of fibrinogen to fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin and thrombin-induced platelet aggregation are inhibited.

Pharmacokinetics: Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Bioavailability is about 3 to 7% with peak levels occurring approximately 1 hour after administration. Bioavailability increases by 75% if the pellets are taken out of the capsule. Dabigatran is 80% renally eliminated, and the half-life is 12-17 hours.

Clinical Trials: RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy)[2] was a non-inferiority, multicenter, multinational, randomized trial comparing two blinded doses of dabigatran (110 mg BID and 150 mg BID) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-

valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more risk factor(s) for stroke. A total of 18,113 patients were randomized and followed for a median of 2 years. The primary outcome was stroke or systemic embolism. Rates of the primary outcome were 1.69% per year in the warfarin group, compared with 1.53% per year in the 110 mg dabigatran group (RR 0.91, 95% CI 0.74-1.11; P<0.001 for non-inferiority) and 1.11% per year in the 150 mg group (RR 0.66, 95% CI 0.53-0.82; P<0.001 for superiority). Rate of major bleeding was 3.36%, 2.71%, and 3.11% per year, respectively. The mortality rate was 4.13%, 3.75%, and 3.64% per year, respectively. (see tables below for more results)

Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority, unless otherwise indicated. The modified Rankin scale (on which scores can range from 0 [no neurologic disability] to 5 [severe disability], with 6 indicating a fatal stroke) was used to categorize stroke: nondisabling stroke was defined by a score of 0 to 2, and disabling or fatal stroke, a score of 3 to 6.

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Contraindications: Active pathological bleeding; history of serious hypersensitivity reaction to dabigatran

Warnings: Dabigatran increases the *risk of bleeding* and can cause significant and, sometimes, fatal bleeding. *Temporary discontinuation* of dabigatran increases the risk of stroke; if therapy is discontinued for any reason, it should be restarted as soon as possible. *Concomitant use of P-gp inducers* (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided.

Drug Interactions: Concomitant use with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided.

Adverse Reactions: Most common adverse effects include bleeding and gastrointestinal (GI) events (dyspepsia, nausea, upper abdominal pain, gastritis, gastrointestinal hemorrhage, and diarrhea). Hypersensitivity reactions were noted in < 0.1% of patients receiving dabigatran.

Dosing: CrCl > 30 ml/min – 150 mg PO twice daily; CrCl = 15-30 ml/min – 75 mg PO twice daily; no dosing available if CrCl < 15 or on dialysis. Dabigatran may be administered with or without food. Capsules must be swallowed whole.

Converting from warfarin: Discontinue warfarin and start dabigatran when the INR is below 2

Converting to warfarin: Conversion based on patients CrCl (see below)

CrCl	Warfarin Recommendation
> 50 ml/min	start warfarin 3 days before discontinuing dabigatran
31-50 ml/min	start warfarin 2 days before discontinuing dabigatran
15-30 ml/min	start warfarin 1 day before discontinuing dabigatran
< 15 ml/min	no recommendations can be made

Converting from parenteral anticoagulants: Start dabigatran 0 to 2 hours prior to the next scheduled dose of parenteral anticoagulant, or at the time of discontinuation of a continuous IV infusion (i.e. heparin drip).

Converting to parenteral anticoagulants: Wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant

Surgery planning: If possible, discontinue dabigatran 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding.

How Supplied: 75 & 150 mg capsules in 60-count bottles and blister packs; store in the original package to protect from moisture; the bottle is good for 60-days once opened

Cost: Drugstore.com - $4.10 per capsule ($245.99 for 30 day supply)

rivaroxaban (Xarelto®) – Janssen

Category: Factor Xa inhibitor

Indication: Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

Pharmacology: Rivaroxaban is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

Pharmacokinetics: Oral bioavailability is 80-100% after oral administration. It is absorbed rapidly with peak levels occurring within 2-4 hours. Approximately, 92-95% is bound to plasma proteins.

Rivaroxaban is significantly metabolized via CYP3A4/5, CYP2J2 and hydrolysis. It is a substrate of the efflux transporter proteins P-gp and ABCG2. Half-life = 5 to 9 hours.

Clinical Trials: Rivaroxaban was studied in 9011 patients (4487 rivaroxaban-treated, 4524 enoxaparin-treated patients) in the RECORD-1, 2, and 3 studies.[3,4,5] RECORD-1 and 2 were randomized, double-blind clinical trials in patients undergoing elective total hip replacement surgery that compared rivaroxaban 10 mg once daily started 6-8 hours post-op to enoxaparin 40 mg once daily started 12 hours post-op. The RECORD-2 treatment duration differed between the two groups, with patients receiving 31-39 days of rivaroxaban versus 10-14 days of enoxaparin. RECORD-3 was a randomized, double-blind clinical trial comparing the same doses of rivaroxaban and enoxaparin in patients undergoing elective total knee replacement surgery. The primary efficacy outcome measure was the composite of any deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause. Results are presented in the tables below. The safety comparison showed similar risk of bleeding events in all the trials.

Overview of Primary Efficacy Outcome Measure (DVT, PE, or death) in the RECORD trials

Trial	Rivaroxaban [% (95% CI)]	Enoxaparin [% (95% CI)]	Absolute risk reduction [% (95% CI)]	P-value
RECORD-1	1.1 (0.7-1.8)	3.7 (2.8-4.8)	-2.6 (-3.7 to -1.5)	<0.001
RECORD-2	2.0 (1.2-3.1)	9.3 (7.5-11.5)	-7.3 (-9.4 to -5.2)	<0.0001
RECORD-3	9.6 (7.7-11.8)	18.9 (16.4-21.7)	-9.2 (-12.4 to -5.9)	<0.001

Black Box Warning: SURGICAL SETTINGS – SPINAL/EPIDURAL HEMATOMA – Epidural or spinal hematomas may occur in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. An epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban, and the next dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of rivaroxaban is to be delayed for 24 hours.

Contraindications: hypersensitivity to rivaroxaban; active major bleeding

Warnings: Rivaroxaban increases the *risk of bleeding* and can cause serious and fatal bleeding. Use with caution in conditions with increased risk of hemorrhage. Use with caution in *pregnancy* due to risk of related hemorrhage (has not been studied in pregnant patients; Category C). Avoid use in severe *renal impairment* (CrCl < 30 ml/min) and use with caution in moderate renal impairment (CrCl 30-50 ml/min). Discontinue therapy if patient develops acute renal failure. Avoid use in patients with moderate or severe *hepatic impairment*.

Drug Interactions: Avoid concomitant administration with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk. Avoid concomitant use with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Consider increasing the rivaroxaban dose to 20 mg if these drugs must be coadministered. Avoid concurrent use with other anticoagulants due to the increased bleeding risk. NSAIDs/ASA may increase bleeding risk. Avoid concomitant use of clopidogrel unless the benefit outweighs the increased risk of bleeding.

Adverse Reactions: The most common adverse reactions were bleeding complications. Other effects noted in clinical trials include wound secretion, pain in extremity, muscle spasm, syncope, pruritis, and blisters.

Dosing: 10 mg PO once daily; with or without food. Take initial dose at least 6 to 10 hours after surgery, and continue treatment for 12 days for knee replacement or 35 days for hip replacement. Ensure gastric placement of feeding tube if rivaroxaban tablets are crushed and administered via this route; absorption is impaired if administered directly into the small intestine.

How Supplied: 10 mg film-coated tablets

Cost: AWP - $8.10 per tablet ($243 for 30 day supply) [Price Alert – August 15, 2011]

ticagrelor (Brilinta®) – AstraZeneca

Category: $P2Y_{12}$ platelet inhibitor

Indication: to reduce the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction)

Pharmacology: Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Pharmacokinetics: Bioavailability is approximately 36% with a T_{max} of 1.5 hours. CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor. Both are highly protein bound with a Vd = 88 L. The primary route of ticagrelor elimination is hepatic metabolism; half-life = 7 hours (9 hours for the active metabolite).

Clinical Trials: The clinical evidence for the effectiveness of ticagrelor is derived from The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial;[6] a multicenter, randomized, double-blind study comparing ticagrelor (180 mg loading dose, 90 mg BID thereafter) to clopidogrel (300-600 mg loading dose, 75 mg daily thereafter), both given in combination with aspirin and other standard therapy, in 18,624 patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints. Results are presented below. No significant difference was observed in rates of major bleeding (11.6% vs. 11.2%), but ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5% vs. 3.8%, P=0.03)

Table 3. Major Efficacy End Points at 12 Months.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09
Death from vascular causes, MI, stroke — no./total no. (%)				
Invasive treatment planned§	569/6732 (8.9)	668/6676 (10.6)	0.84 (0.75–0.94)	0.003‡
Event rate, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Event rate, days 31–360¶	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Stent thrombosis — no. of patients who received a stent/total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

* The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of end point. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes. MI denotes myocardial infarction, and TIA transient ischemic attack.
† P values were calculated by means of Cox regression analysis.
‡ Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points.
§ A plan for invasive or noninvasive (medical) management was declared before randomization.
¶ Patients with any primary event during the first 30 days were excluded.

Black Box Warning: BLEEDING RISK – Ticagrelor may cause significant, sometimes fatal, bleeding. Do not use in patients with active bleeding, history of intracranial hemorrhage, or planned CABG. When possible, discontinue ticagrelor at least 5 days prior to surgery. If possible, manage bleeding without discontinuing ticagrelor (stopping therapy increases risk of CV events). ASPIRIN (ASA) DOSE AND TICAGRELOR EFFECTIVENESS – Maintenance doses of ASA > 100 mg reduce the effectiveness of ticagrelor. Use ASA 75-100 mg/day for maintenance doses.

Contraindications: history of intracranial hemorrhage, active pathological bleeding, and severe hepatic impairment

Warnings: Ticagrelor has not been studied in *moderate hepatic impairment*; consider risk/benefit of treatment in such patients. *Dyspnea* was reported in 14% of patients treated with ticagrelor and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to ticagrelor, no specific treatment is required; continue treatment without interruption. Avoid *strong inhibitors and inducers of CYP3A4/5*.

Drug Interactions: Strong inhibitors and inducers of CYP3A4/5 should be avoided. Use of ASA doses above 100 mg reduces the effectiveness of ticagrelor. Ticagrelor increases levels of simvastatin and lovastatin; do not exceed 40 mg/day. Monitor digoxin levels when initiating or changing ticagrelor therapy. Ticagrelor can be given with LMWHs, GPIIb/IIIa inhibitors, PPIs, beta-blockers, ACE inhibitors, and ARBs.

Adverse Reactions: The most common adverse reactions are bleeding and dyspnea. Other adverse reaction include headache, cough, dizziness, nausea, atrial fibrillation, hypertension, non-cardiac chest pain, diarrhea, back pain, hypotension, fatigue, chest pain, bradycardia, gynecomastia, and elevations in uric acid and serum creatinine.

Dosing: Loading dose – 180 mg PO; then 90 mg PO twice daily. Use with ASA; loading dose – 325 mg PO; then 75-100 mg PO once daily. Can be given with or without food, and can be started after a loading dose of clopidogrel.

How Supplied: 90 mg film-coated tablets; keep in the container it comes in

Cost: AWP - $4.35 per tablet ($260.78 for 30 day supply) [Price Alert – August 15, 2011]

Central Nervous System

ezogabine (Potiga®) – Valeant / GSK

Category: Anticonvulsant – potassium channel opener

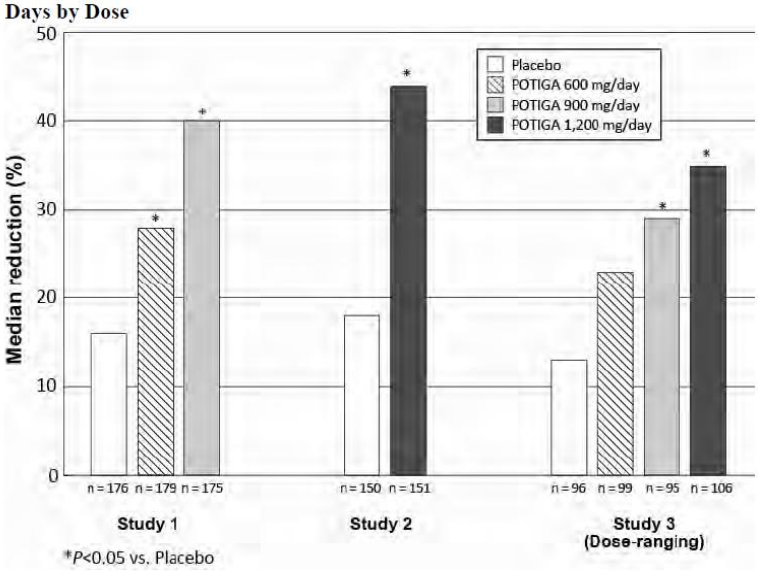
Indication: adjunctive treatment of partial-onset seizures in patients aged 18 years and older

Pharmacology: The mechanism of action has not been fully elucidated. *In vitro* studies indicate that ezogabine enhances transmembrane potassium currents mediated by the KCNQ family of ion channels. By activating KCNQ channels, ezogabine is thought to stabilize the resting membrane potential and reduce brain excitability. It may also exert therapeutic effects through augmentation of GABA-mediated currents.

Pharmacokinetics: Ezogabine is rapidly absorbed with an absolute bioavailability of approximately 60% and T_{max} between 0.5-2 hours. NAMR is a less-potent, active metabolite. Ezogabine and its active metabolite are 80% and 45% bound to plasma protein, respectively. It is extensively metabolized primarily via glucuronidation and acetylation in humans. Renal excretion is the major route of elimination, with about 85% of the dose recovered in the urine as either unchanged drug or metabolites. Half-life = 7 to 11 hours.

Clinical Trials:
The efficacy of ezogabine as adjunctive therapy in partial-onset seizures was established in 3 multicenter, randomized, double-blind, placebo-controlled studies in 1,239 adult patients with partial onset seizures, not adequately controlled with 1 to 3 concomitant anti-epileptic drugs (AEDs). The primary endpoint consisted of the percent change in seizure frequency from baseline in the double-blind treatment phase. Patients were randomized to the total daily maintenance dosages of 600 mg/day, 900 mg/day, or 1,200 mg/day, each administered in 3 equally divided doses. See results below.

Figure 1. Median Percent Reduction From Baseline in Seizure Frequency per 28 Days by Dose



Contraindications: none

Warnings: Ezogabine may cause *urinary retention* in some patients. Urologic symptoms should be carefully monitored; use with caution in patients with other risk factors for urinary retention. *Confusional state, psychotic symptoms and hallucinations* can occur during treatment (usually in the first 8 weeks). Rapid titration at greater than the recommended doses appears to increase the risk of psychosis and hallucinations; symptoms typically resolved within 7 days of discontinuation. Dose-related increases in *dizziness and somnolence* are possible. Most cases were mild to moderate in intensity and occurred during the titration phase. Dizziness and somnolence appeared to diminish with continued use. Ezogabine produces a small *prolongation in the QT interval*. Close observation is recommended if it is used with other medicines known to prolong the QT interval or patients at increased risk. Antiepileptic drugs (AEDs) increase the risk of *suicidal thoughts or behavior* in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Drug Interactions: Carbamazepine and phenytoin can reduce ezogabine concentrations about approximately 1/3, consider increasing the ezogabine dose. Administration of ezogabine may increase digoxin serum concentrations, due to the N-acetyl metabolite inhibition of P-glycoprotein–mediated transport of digoxin. Serum levels of digoxin should be monitored. Alcohol can increase systemic exposure and worsen dose-related adverse effects. Ezogabine can falsely elevate both serum and urine bilirubin.

Adverse Reactions: The most common adverse reaction occurring in ≥ 4% are dizziness (23%), somnolence (22%), fatigue (15%), confusional state (9%), vertigo (8%), tremor (8%), abnormal coordination (7%), diplopia (7%), disturbance in attention (6%), memory impairment (6%), asthenia (5%), blurred vision (5%), gait disturbance (4%), aphasia (4%), dysarthria (4%), and balance disorder (4%). In most cases the reactions were of mild or moderate intensity.

Dosing: See dosing information in the table below. Ezogabine may be taken with or without food. Tablets should be swallowed whole. If discontinued, dose should be tapered over a 3 week period to prevent withdrawal seizures, unless safety concerns require abrupt withdrawal.

Specific population	Initial dose	Titration	Maximum dose
General Dosing			
General Population (including mild renal or hepatic impairment)	100 mg TID (300 mg/day)	Increase by no more than 50 mg/dose (150 mg/day) at weekly intervals	400 mg TID (1200 mg/day)
Dosing in Specific Populations			
Geriatric (>65 years)	50 mg TID (150 mg/day)	Increase by no more than 50 mg/dose (150 mg/day) at weekly intervals	250 mg TID (750 mg/day)
Renal impairment (CrCl < 50 ml/min or ESRD on dialysis	50 mg TID (150 mg/day)		200 mg TID (600 mg/day)
Hepatic impairment (Child-Pugh > 7-9)	50 mg TID (150 mg/day)		250 mg TID (750 mg/day)
Hepatic impairment (Child-Pugh > 9)	50 mg TID (150 mg/day)		200 mg TID (600 mg/day)

How Supplied: 50, 200, 300, and 400 mg film-coated tablets

Cost: not yet available; awaiting DEA controlled-substance classification

fingolimod (Gilenya®) – Novartis

Category: sphingosine 1-phosphate receptor modulator

Indication: treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability

Pharmacology: Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5 and blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the CNS.

Pharmacokinetics: Oral bioavailability is 93% with a T_{max} of 12-16 hours. Steady-state levels are achieved in 1 to 2 months. Fingolimod highly distributes (86%) in red blood cells; fingolimod-phosphate has significantly less (<17%) uptake. Both are >99.7% bound to plasma proteins and highly distributed to body tissues. Fingolimod undergoes phosphorylation to the active fingolimod-phosphate. It is primarily metabolized via CYP4F2. Half-life = 6-9 days.

Clinical Trials: The Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) study[7] was a 12-month, double-blind, double-dummy, active-controlled study in 1292 patients with relapsing-remitting MS. Patients were randomized to receive either oral fingolimod at a daily dose of either 1.25 or 0.5 mg or IM interferon beta-1a at a weekly dose of 30 mcg. Results showed that the primary endpoint of annualized relapse rate was significantly lower in both groups receiving fingolimod — 0.20 (95% confidence interval [CI], 0.16 to 0.26) in the 1.25-mg group and 0.16 (95% CI, 0.12 to 0.21) in the 0.5-mg group — than in the interferon group (0.33; 95% CI, 0.26 to 0.42; P<0.001 for both comparisons). No significant differences were seen among the study groups with respect to progression of disability (a secondary endpoint).

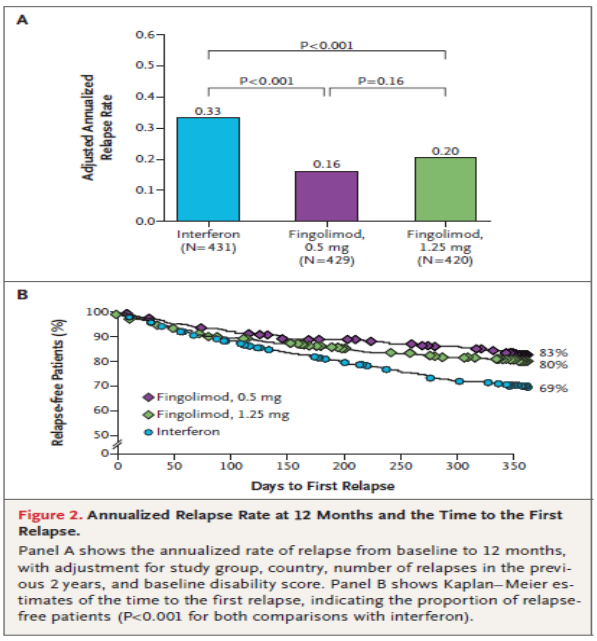


Figure 2. Annualized Relapse Rate at 12 Months and the Time to the First Relapse.
Panel A shows the annualized rate of relapse from baseline to 12 months, with adjustment for study group, country, number of relapses in the previous 2 years, and baseline disability score. Panel B shows Kaplan–Meier estimates of the time to the first relapse, indicating the proportion of relapse-free patients (P<0.001 for both comparisons with interferon).

Contraindications: none

Warnings: *Bradyarrhythmia and Atrioventricular (AV) Blocks* – Initiation of fingolimod treatment results in a decrease in heart rate (mean decrease of 13 bpm). Observe patients for 6 hours for signs and symptoms of bradycardia. Baseline EKG should be done for high-risk patients who have not had an EKG in the previous 6 months. Initiation of therapy may also result in transient AV conduction delays. Most cases resolved within 24 hours, but occasionally required treatment. If fingolimod is discontinued for more than 2 weeks, the same precautions for initial dosing should apply. *Infections* – Fingolimod causes a dose-dependent reduction in peripheral lymphocyte count to 20-30% of baseline values and may therefore increase the risk of infection. Baseline CBC (within the last 6 months) should be obtained. Consider suspending treatment if a serious infection develops and reassess risk/benefit. Effects last for up to 2 months following the last dose. Test for antibodies to varicella zoster virus (VZV) in patients without a history of chickenpox or vaccination, and vaccinate all antibody-negative patients (hold treatment for 1 month after vaccine). *Macular Edema* was reported in 0.4% of patients (history of diabetes or uveitis increases risk). Ophthalmologic exam should be done at baseline, 3-4 months after initiation, and at any time the patient reports visual disturbances. *Respiratory Effects* – Dose-dependent reductions in FEV_1 have been noted (3.1% vs. 2% for placebo). Fingolimod was not studied in MS patients with compromised respiratory function. Monitor respiratory function during therapy if clinically indicated. *Hepatic Effects* – Elevations in liver enzymes (LFTs) occur in patients receiving fingolimod. Baseline LFTs and bilirubin levels should be available before starting therapy and reassessed in patients who develop symptoms suggestive of hepatic dysfunction. *Fetal Risk* – Fingolimod may cause fetal harm. Women of childbearing potential should use effective contraception during and for 2 months after stopping treatment. A pregnancy registry has been established. *Blood Pressure Effects* – Fingolimod caused an average increase of 2 mmHg in systolic blood pressure (SBP) and 1 mmHg in diastolic blood pressure (DBP). Blood pressure should be monitored during therapy.

Drug Interactions: Fingolimod increases the risk of torsades de pointes in patients taking Class Ia and III antiarrhythmic drugs; monitor closely. Ketoconazole increases fingolimod blood levels 1.7-fold; increasing the risk of adverse effects. Avoid use of live-virus vaccines during and for 2 months after fingolimod therapy; all vaccinations may be less effective during treatment. Antineoplastic, immunosuppressive, or immunomodulating therapies increase the risk of immunosuppression and

possible infection. Heart rate-lowering drugs (beta blockers, etc) may increase the risk of bradyarrhythmia.

Adverse Reactions: The most common adverse reactions include headache, influenza, diarrhea, back pain, LFT elevations, and cough. The only adverse event leading to treatment interruption reported at an incidence >1% was LFT elevations (3.8%). Vascular events (including stroke) and lymphomas were reported in premarketing trials in patients receiving higher than recommended doses; but not with the recommended 0.5 mg dose.

Dosing: 0.5 mg PO once daily; observe patient for 6 hours after first dose to monitor for bradycardia; may be taken with or without food.

How Supplied: 0.5 mg hard capsule

Cost: drugstore.com - $138.57 per capsule ($3,880.04 for 28 cap dispense pack)

vilazodone (Viibryd®) – Forest Labs

Category: Antidepressant

Indication: Treatment of major depressive disorder (MDD)

Pharmacology: The exact mechanism of the antidepressant effect of vilazodone is not fully understood, but is thought to be related to increasing serotonergic activity in the CNS through selective inhibition of serotonin reuptake (SSRI). Vilazodone also has partial agonist effects at the serotonin 5-HT_{1A} receptor.

Pharmacokinetics: Oral bioavailability is approximately 72% when given with food, and the T_{max} is 4-5 hours. Steady-state is achieved in about 3 days. Vilazodone is widely distributed and highly protein bound (96-99%). Elimination is primarily through hepatic metabolism (CYP3A4 primarily). Half-life = 25 hours.

Clinical Trials: The efficacy of vilazodone in the treatment of MDD was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies. Patients were titrated over 2 weeks to a dose of 40 mg of vilazodone with food (n=436) or placebo (433) once daily. The primary outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS). Vilazodone showed significantly more improvement on the MADRS when compared to placebo.

Study Number	Primary Endpoint	Least Squares Mean (95% CI) difference from placebo in change from baseline
1	MADRS	-3.2 (-5.2, -1.3)
2	MADRS	-2.5 (-4.4, -0.6)

Black Box Warning: SUICIDALITY AND ANTIDEPRESSANT DRUGS – Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of MDD and other psychiatric disorders. Monitor and observe closely for clinical worsening, suicidality, or unusual changes in behavior when antidepressant therapy is started. Vilazodone is not approved for use in pediatric patients.

Contraindications: Concomitant use of monoamine oxidase inhibitors (MAOIs) or use within 14 days of starting or stopping therapy

Warnings: *Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions* – These reactions are not likely to occur unless vilazodone is used with other serotonergic drugs, MAOIs, antipsychotics or other dopamine antagonists. Use with caution in patients with *seizure disorders*. Vilazodone was not studied in this patient population. *Abnormal bleeding* may occur in patients taking vilazodone. Use of other drugs that can cause bleeding may add to this risk. *Activation of mania/hypomania* may occur; monitor patients for manic symptoms. Withdrawal symptoms may occur if therapy is *abruptly discontinued*; tapering therapy gradually is recommended. *Hyponatremia* due to SIADH has been reported with other SSRI antidepressants and may be possible with vilazodone (no reports were noted in the clinical trials).

Drug Interactions: Use caution when prescribed with other CNS-active agents.
MAOIs are contraindicated. Use with other serotonergic drugs increases the risk of serotonin syndrome. Aspirin, NSAID, or warfarin concomitant use may increase the risk of bleeding. CYP3A4 inhibitors increase vilazodone concentrations. Reduce dose to 20 mg daily if used with moderate-strong inhibitors. CYP3A4 inducers may reduce concentrations, but this has not been evaluated.

Adverse Reactions: The most common adverse effects (≥ 5%) included diarrhea, nausea, vomiting, and insomnia.

Dosing: Vilazodone dosing must be titrated (see below). Take each dose with food (blood concentrations are 50% lower if taken on empty stomach). Taper dose if therapy is discontinued.

Vilazodone initial dose titration

Days	Dose
1-7	10 mg PO once daily
8-14	20 mg PO once daily
15+	40 mg PO once daily

How Supplied: 10, 20, and 40 mg film-coated tablets; starter kit available for dose titration

Cost: Drugstore.com - $4.53 per tablet ($135.99 for 30 day supply)

Endocrine/Metabolic

linagliptin (Tradjenta®) – Boehringer Ingelheim

Category: dipeptidyl peptidase-4 (DPP-4) inhibitor

Indication: Linagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It should not be used with type 1 diabetes and has not been studied in combination with insulin.

Pharmacology: Linagliptin is a reversible inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). This inhibition increases the concentrations of active incretin hormones, stimulating the release of

insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis.

Pharmacokinetics: Oral bioavailability is approximately 30% with a T_{max} of 1.5 hours. Linagliptin is highly (99%) bound to plasma protein and undergoes extensive distribution. Primary route of elimination is in the feces via the enterohepatic system. Plasma concentrations decline in a biphasic manner, with a long terminal half life of > 100 hours related to the saturable binding of linagliptin. However, this prolonged elimination phase does not contribute to drug accumulation. The effective half-life for linagliptin is 12 hours.

Clinical Trials:
In a review of clinical trial data published in The Medical Letter,[8] linagliptin either alone or in combination with metformin, a sulfonylurea or pioglitazone was shown to lowered A_1C 0.4-0.7%, which is similar to the decrease with sitagliptin and saxagliptin. See table below for combination trial results.

Table 1. Combination Therapy Trials with Linagliptin

Drug Combination	A1C % Baseline	A1C % Change
Metformin[5]	7.5-10%	
(12 weeks; n= 333)		
+ Linagliptin 5 mg		-0.50%
+ Glimepiride 1-3 mg		-0.68%
+ Placebo		+0.24%
Metformin >1500 mg daily[6]	8.1%	
(24 weeks; n=701)		
+ Linagliptin 5 mg		-0.49%
+ Placebo		+0.15%
Pioglitazone 30 mg daily[7]	8.6%	
(24 weeks; n=389)		
+ Linagliptin 5 mg		-1.06%
+ Placebo		-0.56%
Sulfonylurea[8]	8.6%	
(18 weeks; n=240)		
+ Linagliptin 5 mg		-0.5%
+ Placebo		-0.1%
Metformin + Sulfonylurea[9]	8.2%	
(24 weeks; n=1058)		
+ Linagliptin 5 mg		-0.7%
+ Placebo		-0.1%

Contraindications: history of hypersensitivity reaction to linagliptin, such as urticaria, angioedema, or bronchial hyperreactivity

Warnings: Use with an insulin secretagogues (e.g. sulfonylureas) was associated with a higher rate of hypoglycemia. Lower doses of insulin secretagogues may be required. No clinical trial has established evidence of macrovascular risk reduction with linagliptin (or any other antidiabetic drug).

Drug Interactions: Strong P-gp or CYP3A4 inducers (e.g. rifampin) decrease linagliptin exposure and efficacy. Use alternative diabetes therapy in patients that require these types of medications.

Adverse Reactions: Nasopharyngitis was the most commonly reported adverse effect. Hypoglycemia may occur if linagliptin is combined with a sulfonylurea. Although uncommon, pancreatitis and hypersensitivity reactions (e.g. urticaria, localized skin exfoliation, or bronchial hyperreactivity) were reported with linagliptin use.

Dosing: 5 mg PO once daily; with or without food

How Supplied: 5 mg film-coated tablets

Cost: Drugstore.com - $7.67 per tablet ($229.99 for 30 day supply)

Infectious Disease

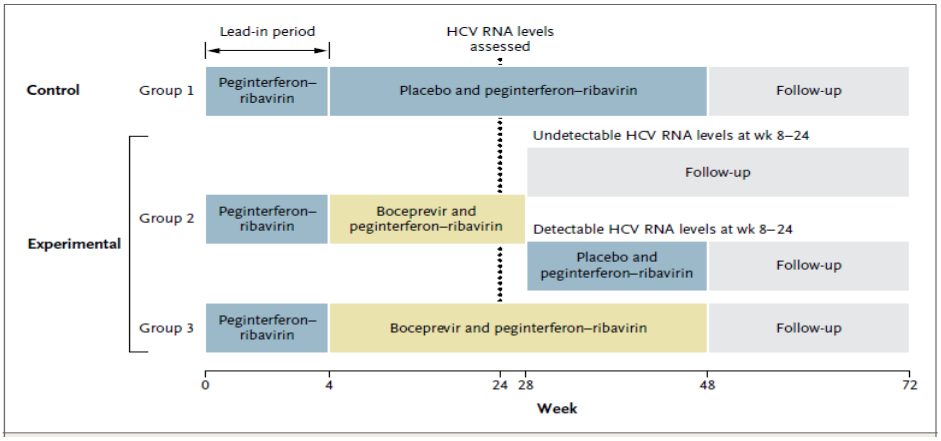
boceprevir (Victrelis®) – Merck

Category: hepatitis C virus (HCV) NS3/4A protease inhibitor

Indication: Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. Boceprevir must not be used as monotherapy and has not been studied in patients documented as null responders to prior therapy with peginterferon alfa and ribavirin. Poor responders to previous peginterferon/ribavirin therapy who were treated with boceprevir have a lower likelihood of achieving a sustained virologic response (SVR) and a higher rate of resistance upon treatment failure.

Pharmacology: Boceprevir is an inhibitor of the HCV NS3/4A protease that is necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins. Boceprevir covalently, yet reversibly, binds to the NS3 protease active site serine (S139) through an (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells.

Clinical Trials: The SPRINT-2 trial[9] was a randomized, double-blind, placebo-controlled study comparing two therapeutic regimens of boceprevir 800 mg orally three times daily in combination with PR [Pegylated interferon alpha 1.5 mcg/kg/week subcutaneously and weight-based dosing with ribavirin (600-1400 mg/day orally divided twice daily)] to PR alone in 938 nonblack and 159 black patients with chronic hepatitis C (HCV genotype 1) infection with detectable levels of HCV-RNA and were *not previously treated* with interferon alfa therapy. Patients were randomly assigned to one of three treatment groups in a 1:1:1 ratio, illustrated below. All subjects with detectable HCV-RNA in plasma at TW24 discontinued treatment.

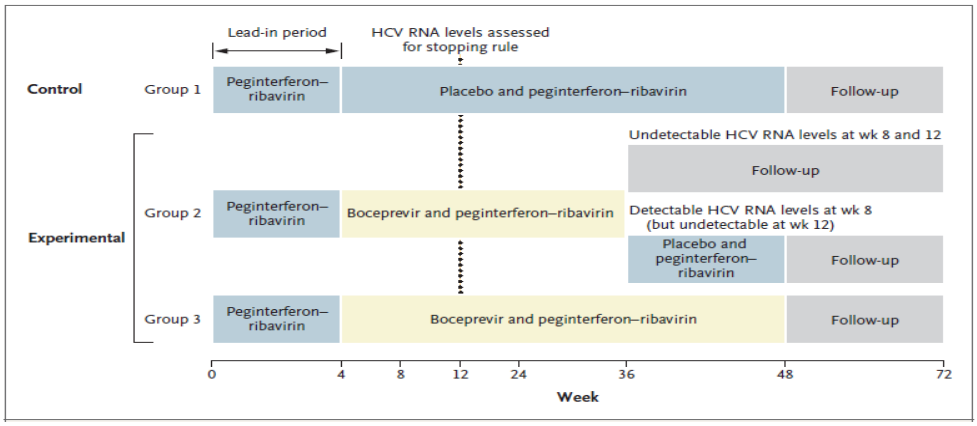


Results of the SPRINT-2 trial are presented in the table below.

	Group 1 (PR-48 wks)	Group 2 (RGT)	Group 3 (combo-48wk)
SVR (all)	38%	63%	66%
SVR (non-black)	40%	67%	68%
SVR (black)	23%	42%	53%
Relapse (all)	22%	9%	9%
Relapse (non-black)	23%	9%	8%
Relapse (black)	14%	12%	17%

SVR = sustained virologic response PR = peginterferon/ribavirin therapy RGT=response guided therapy

The RESPOND-2 trial[10] was a randomized, double-blind study comparing two regimens of boceprevir 800 mg PO TID in combination with PR compared to PR alone in 403 patients with chronic hepatitis C (HCV genotype 1) with demonstrated interferon responsiveness (partial responders and relapsers). Null responders to PR were not eligible. Patients were randomized in a 1:2:2 ratio to one of the treatment groups illustrated below. All subjects with detectable HCV-RNA in plasma at TW12 were discontinued from treatment.



Results for all cohorts of the RESPOND-2 trial are presented in the table below.

	Group 1 (PR-48 wks)	Group 2 (RGT)	Group 3 (combo-48wk)
SVR %	21%	59%	66%
Relapse %	28%	14%	12%

Pharmacokinetics: Boceprevir is a 1:1 mixture of two diasteromers (SCH534128 and SCH534129). SCH534128 is the active diasteromer. It is well absorbed following oral administration with a T_{max} of 2 hours; absolute bioavailability has not been studied. Food enhances the exposure of boceprevir by up to 65%. It is ~ 75% bound to plasma proteins. Metabolism of boceprevir includes primarily aldoketoreductase (AKR)-mediated pathway and, to a lesser extent, CYP3A4/5. Elimination is primarily via the liver; half-life = 3.4 hours.

Contraindications: Contraindications to peginterferon alfa and ribavirin also apply to boceprevir combination treatment. *Pregnancy Category X (due to ribavirin)* - Pregnant women and men whose female partners are pregnant should not take boceprevir, due to ribavirin teratogenicity. Do not start therapy until a negative pregnancy test has been obtained immediately prior to dosing. At least two forms of contraception must be used during treatment and for at least 6 months after treatment; hormonal contraceptives may not be as effective in women taking boceprevir. Monthly pregnancy tests

must be performed. Co-administration of drugs highly dependent on CYP3A4/5 for clearance or co-administration of potent CYP3A4/5 inducers is contraindicated (see table below).

Drugs that are contraindicated with boceprevir

Drug class	Drugs Within Class that are Contraindicated	Clinical Comments
Alpha 1-blocker	alfuzosin	↑ alfuzosin concentrations can result in hypotension
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response
Antimycobacterial	rifampin	May lead to loss of virologic response
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity (peripheral vasospasm/ischemia)
GI motility agents	cisapride	Potential for cardiac arrhythmias
Herbal products	St. John's Wort	May lead to loss of virologic response
HMG-CoA reductase inhibitors	lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis
Oral contraceptives	drosperinone	Potential for hyperkalemia
PDE5 enzyme inhibitors	sildenafil or tadalafil when used to treat pulmonary hypertension	Potential for PDE5 inhibitor-associated adverse events (visual abnormalities, hypotension, prolonged erection, syncope)
Neuroleptic	pimozide	Potential for cardiac arrhythmias
Sedative/hypnotics	triazolam, oral midazolam	Prolonged or increased sedation or respiratory depression

Warnings: *Anemia* – The addition of boceprevir to peginterferon alfa / ribavirin therapy caused an additional decrease in hemoglobin concentrations. *Neutropenia* – More patients had low neutrophil counts (7% vs. 4%) when boceprevir was added to peginterferon / ribavirin therapy. CBC (with differential) must be obtained pretreatment, and at TW4, TW8, TW12, and as clinically appropriate.

Drug Interactions: *See contraindication section above.* Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized by this enzyme may have increased exposure if administered with boceprevir. It is a potential inhibitor of p-glycoprotein (P-gp), but drug interactions due to this mechanism have not been evaluated. CYP3A4/5 inhibitors or inducers could increase or decrease exposure to boceprevir.

Adverse Reactions: The most common adverse reactions (>35%) were fatigue, anemia, nausea, headache, and dysgeusia. Other common adverse reactions include neutropenia, diarrhea, vomiting, chills, asthenia, decreased appetite, arthralgia, dizziness, insomnia, irritability, dyspnea, alopecia, dry skin, and rash.

Dosing: *Boceprevir must be given in combination with peginterferon alfa and ribavirin*. The dose is 800 mg (4 capsules) PO TID (every 7-9 hours) with food (meal or snack). Initiate therapy with peginterferon alfa / ribavirin for 4 weeks [Treatment Weeks (TW) 1-4]. Add boceprevir after TW 4; continue based on patient's HCV-RNA counts that are assessed at TW4, TW8, TW12, and TW24 (see table below). Dose reduction is not recommended.

Duration of therapy using response-guided therapy (RGT) guidelines

	Assessment* (HCV-RNA Results)		Recommendation
	At TW 8	At TW 24	
Previously Untreated Patients	Undetectable	Undetectable	Complete three-medicine regimen at TW28
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36 2. Administer peginterferon alfa / ribavirin through TW48
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete three-medicine regimen at TW36
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36 2. Administer peginterferon alfa / ribavirin through TW48
Previous non-responders OR previously untreated patients who are poorly interferon responsive at TW4	RGT not studied	RGT not studied	Complete three-medicine regimen at TW48
Patients with compensated cirrhosis	n/a	n/a	Complete three-medication regimen at TW48
***Treatment Futility** If the patient has HCV-RNA results ≥ 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.			

How Supplied: 200 mg capsules; store refrigerated until dispensed; 3 month expiration if stored at room temperature; packaged in a carton with 28 bottles containing 12 capsules

Cost: AWP - $15.71 per capsule ($188.52 per day OR $31,671.36 for 24-week treatment) [Price Alert – July 15, 2011]

Telaprevir (Incivek®) – Vertex Pharmaceuticals

Category: hepatitis C virus (HCV) NS3/4A protease inhibitor

Indication: Telaprevir, in combination with peginterferon and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers. It MUST NOT be administered as monotherapy and MUST be only prescribed with both peginterferon alfa and ribavirin.
Pharmacology: Telaprevir is an inhibitor of the HCV NS3/4A serine protease, necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins and essential for viral replication.

Clinical Trials: The ADVANCE trial[11] was a randomized, double-blind, parallel-group, placebo-controlled, trial conducted in 1088 patients with HCV genotype 1 infection that were treatment-naïve. Telaprevir was given for the first 8 weeks of treatment (T8/PR regimen) or the first 12 weeks of treatment (T12/PR regimen) in combination with Peg-IFN-alfa-2a/RBV for either 24 or 48 weeks (dependent on rapid virologic response). The control regimen (PR48) consisted of a telaprevir-

matching placebo for the first 12 weeks and Peg-IFN-alfa-2a/RBV for 48 weeks. Results are presented in the table below.

	T12PR (n=363)	T8PR (n=364)	PR (n=361)
SVR all patients	75%	69%	44%
Relapse all patients	9%	9%	28%

The REALIZE trial[12] was a randomized, double-blind, placebo-controlled trial conducted in 663 subjects with HCV genotype 1 who did not achieve SVR with prior treatment with Peg-IFNalfa-2a/RBV or Peg-IFN-alfa-2b/RBV. Patients were randomized in a 2:2:1 ratio to one of three groups: the T12PR48 group, which received telaprevir for 12 weeks and PR for 48 weeks; the lead-in T12PR48 group, which received 4 weeks of PR followed by 12 weeks of telaprevir and PR for a total of 48 weeks; and the control group (PR48), which received PR for 48 weeks. Results are presented in the table below.

SVR Rates

Patient Group	T12PR48	Lead-inT12PR48	PR48
Previous relapsers	83%	88%	24%
Partial responders	59%	54%	15%
No previous response	29%	33%	5%

Virologic Failure Rates

Patient Group	T12PR48	Lead-inT12PR48	PR48
Previous relapsers	1%	1%	26%
Partial responders	18%	19%	70%
No previous response	57%	47%	84%

Pharmacokinetics: Telaprevir is orally available, most likely absorbed in the small intestine. T_{max} is 4-5 hours. When administered with a standard fatty meal, telaprevir AUC increased by 237%. It is approximately 59-76% bound to plasma proteins and is extensively metabolized in the liver (CYP3A4 plays major role). Half-life = 9-11 hours.

Contraindications: Contraindications to peginterferon alfa and ribavirin also apply to telaprevir combination treatment. *Pregnancy Category X (due to ribavirin)* - Pregnant women and men whose female partners are pregnant should not take boceprevir, due to ribavirin teratogenicity. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended. Hormonal contraceptives may not be reliable during treatment and up to 2 weeks after telaprevir therapy; other methods should be used during this time. Monthly pregnancy tests are required during this same time. Telaprevir is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and have a narrow therapeutic index. Also, drugs that are strong CYP3A inducers may lower exposure to telaprevir and should not be used (see table below).

Drugs that are contraindicated with telaprevir

Drug Class	Drugs within the class that are contraindicated	Clinical comments
Alpha 1-adrenergic antagonist	alfuzosin	Potential for hypotension or cardiac arrhythmia
Antimycobacterial	rifampin	Significantly reduces telaprevir plasma concentrations
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity (peripheral vasospasm or ischemia)
GI motility agents	cisapride	Potential for cardiac arrhythmias
Herbal products	St. John's wort	Concentrations of telaprevir can be reduced
HMG-CoA reductase inhibitors	atorvastatin, lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis
Neuroleptic	pimozide	Potential for serious/life-threatening adverse reactions (e.g. cardiac arrhythmias)
PDE5 inhibitor	sildenafil or tadalafil (for pulmonary hypertension)	Potential for PDE5 inhibitor-associated adverse events (visual abnormalities, hypotension, prolonged erection, syncope)
Sedative/hypnotics	Orally administered midazolam, triazolam	Prolonged or increased sedations or respiratory depression

Warnings: *Serious skin reactions* including drug rash with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) were reported in <1% of subjects in clinical trials. Stop triple drug therapy immediately if serious skin reaction occurs. *Rash* developed in 56% of subjects in clinical trials. Severe rash was reported in 4%. The severe rash may have a prominent eczematous component. Patients with mild to moderate rash should be followed closely, and telaprevir should be discontinued if the rash progresses and becomes severe. If improvement is not observed within 7 days, discontinue peginterferon and ribavirin. *Anemia* – The addition of telaprevir to peginterferon alfa / ribavirin therapy caused an additional decrease in hemoglobin concentrations. Monitor hemoglobin prior to and at least every 4 weeks during therapy; adjust ribavirin dose if needed. *Laboratory tests* – HCV-RNA should be checked at TW4 and TW12. CBC with differential is recommended at weeks 2, 4, 8, and 12 or as clinically appropriate. Telaprevir is not recommended for patients with moderate or severe *hepatic impairment* or patients with decompensated liver disease.

Drug Interactions: *See contraindication section above.* Telaprevir is an inhibitor of CYP3A. Drugs metabolized by this enzyme may have increased exposure if administered with telaprevir thus increasing the potential for adverse effects. It also inhibits P-gp; drugs that are substrates for P-gp may have increased concentrations and adverse effects. CYP3A and P-gp inhibitors or inducers could increase or decrease exposure to telaprevir.

Adverse Reactions: The most common adverse reactions (incidence at least 5% higher with telaprevir than in controls) were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus.

Dosing: The recommended dose is 750 mg (two tablets) PO TID (7-9 hours apart) with food (at least 20 gm of fat). The recommended duration of treatment is 12 weeks. HCV-RNA levels should be monitored at TW4 and TW12 to determine combination treatment duration and assess for treatment futility (see below)

Treatment-naïve and prior relapse patients			
HCV-RNA	**Triple Therapy telaprevir, peginteferon alpha, and ribavirin**	**Dual Therapy peginteferon alfa and ribavirin**	**Total treatment duration**
Undetectable at TW4 and TW12	First 12 weeks	Additional 12 weeks*	24 weeks
Detectable (≤1000 IU/ml) at TW4 and TW12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients			
All patients	First 12 weeks	Additional 36 weeks	48 weeks
Treatment Futility – All patients TW4 or TW12: HCV-RNA > 1000 IU/ml – discontinue treatment TW24: HCV-RNA detectable – discontinue peginteferon alfa and ribavirin			

* Treatment-naïve patients with cirrhosis who have undetectable HCV-RNA at TW4 and TW12 may benefit from an additional 36 weeks of peginterferon alfa and ribavirin (48 weeks total)

How Supplied: 375 mg film-coated tablets; 28-day blister-pack or 168-count bottle available; store at room temperature. Once bottle is opened, use within 28 days. (*Specialty Pharmacy medication*)

Cost: $117.14 per tablet ($702.84 per day OR $59,038 for 12-week treatment) [AWP per MaxorPlus Clinical Newsletter; June 2011]

Ceftaroline fosamil (Teflaro®) – Forest Labs

Category: Cephalosporin antibacterial

Indication: treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms:
(1) Acute bacterial skin and skin structure infections (ABSSSI) caused by Staphyloccus *aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *E. coli*, *Klebsiella pneumonia*, and *Klebsiella oxytoca*.
(2) community-acquired bacterial pneumonia (CABP) caused by *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca,* and *E. coli*.

Pharmacology: Ceftaroline is a cephalosporin with *in vitro* activity against Gram-positive and -negative bacteria. The bactericidal action of ceftaroline is mediated through binding to essential penicillin-binding proteins (PBPs), thus inhibiting bacterial cell wall synthesis.

Pharmacokinetics: T_{max} occurs around 1 hour after IV administration. Ceftaroline is approximately 20% bound to plasma proteins and has a Vd of 20.3 L. Ceftaroline fosamil is converted into bioactive ceftaroline in plasma by a phosphatase enzyme. Subsequent hydrolysis of the beta-lactam ring results in inactive metabolites. It is primarily eliminated by the kidneys. Half-life = 1.6-2.7 hours

Clinical Trials: Two phase-3, randomized, multicenter, double-blind, non-inferiority trials compared ceftaroline to vancomycin plus aztreonam in 1396 patients with acute bacterial skin and skin structure infections. The modified intent-to-treat (MITT) population included all patients who received any amount of drug, while the clinically evaluable (CE) population demonstrated sufficient adherence to the protocol. Results are presented in the table below.

	Ceftaroline	Vancomycin/Aztreonam	Treatment difference (2-sided 95% CI)
		Trial 1	
Day 3 Responders	74.0%	64.6%	9.4 (0.4, 18.2)
Clinical Cure – CE	91.1%	93.3%	-2.2 (-6.6, 2.1)
Clinical Cure – MITT	86.6%	85.6%	1.0 (-4.2, 6.2)
		Trial 2	
Day 3 Responders	74.0%	68.1%	5.9 (-3.1, 14.9)
Clinical Cure – CE	92.2%	92.1%	0.1 (-4.4, 4.5)
Clinical Cure – MITT	85.1%	85.5%	-0.4 (-5.8, 5.0)

A total of 1231 patients were enrolled in two randomized, multicenter, double-blind, non-inferiority trials comparing ceftaroline with ceftriaxone in patients with CABP. Adjunct clarithromycin therapy was used in trial 1 only. Known or suspected MRSA infections were excluded. The 30-day mortality rate in the two trials combined was 2.0% for ceftaroline and 1.8% for ceftriaxone. Other results are presented in the table below.

	Ceftaroline	Ceftriaxone	Treatment difference (2-sided 95% CI)
		Trial 1	
Day 4 Responders	69.6%	58.3%	11.2 (-4.6, 26.5)
Clinical Cure – CE	86.6%	78.2%	8.4 (1.4, 15.4)
Clinical Cure – MITT	83.8%	77.7%	6.2 (-0.2, 12.6)
		Trial 2	
Day 4 Responders	69.0%	61.4%	7.6 (-6.8, 21.8)
Clinical Cure – CE	82.3%	77.1%	5.2 (-2.2, 12.8)
Clinical Cure – MITT	81.3%	75.5%	5.9 (-1.0, 12.8)

Contraindications: known serious hypersensitivity to ceftaroline or other cephalosporin antibiotic (anaphylaxis and anaphylactoid reactions have been reported with ceftaroline)

Warnings: *Hypersensitivity reactions* – Serious hypersensitivity reactions and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. Use caution in patients listing a cephalosporin, penicillin, or carbapenem allergy because cross-sensitivity has been clearly established. Discontinue ceftaroline immediately if allergic reaction occurs. *Clostridium difficile-associated diarrhea (CDAD)* is possible with ceftaroline therapy. *Direct Coombs' Test Seroconversion* – Seroconversion occurred in 10.8% (vs. 4.4% in comparator) of patients receiving ceftaroline. However, no adverse reactions were reported in any treatment group. If anemia develops during treatment, drug-induced hemolytic anemia should be considered. Use for proven or strongly suspected bacterial infections to avoid the *development of drug-resistant bacteria*.

Drug Interactions: No clinical drug-drug interaction studies have been conducted. There is minimal potential for interactions between ceftaroline and CYP450 substrates, inducers, or inhibitors; drugs that undergo active renal secretion; or drugs that alter renal blood flow.

Adverse Reactions: The most common adverse reactions occurring in > 2% of patients in the pooled phase 3 clinical trials were diarrhea, nausea, and rash.

Dosing: 600 mg IVPB every 12 hours; Infuse over 1 hour. Recommended duration of treatment is 5-14 days for ABSSSI or 5-7 days for CABP.

Ceftaroline Dosing in Patients with Renal Impairment

Estimated CrCl (ml/min)	Recommended ceftaroline dose
> 50	No dose adjustment necessary
> 30 to ≤ 50	400 mg IVPB every 12 hours
≥ 15 to ≤ 30	300 mg IVPB every 12 hours
End-stage renal disease*	200 mg IVPB every 12 hours

*hemodialyzable – administer after dialysis on dialysis days

IVPB preparation: Vials should be reconstituted with 20 ml of sterile water for injection. The constituted solution must be further diluted in 250 ml of NS, D_5W, ½NS, or lactated ringers. Resulting solution is stable for 6 hours at room temperature or 24 hours refrigerated.

How Supplied: 400 and 600 mg vials of sterile powder for injection; store refrigerated (unreconstituted vials can be stored at room temperature for up to 7 days)

Cost: $82/day (Pharmacist's Letter; January 2011; Vol. 27)

fidaxomicin (Dificid®) – Optimer Pharmaceuticals

Category: Macrolide antibacterial

Indication: treatment of *Clostridium difficile*-associated diarrhea (CDAD) in adult patients (≥18 years of age).

Pharmacology: Fidaxomicin is bactericidal against *C. difficile* in vitro, inhibiting RNA synthesis by RNA polymerases**.**

Pharmacokinetics: Fidaxomicin has minimal systemic absorption following oral administration, with plasma levels of fidaxomicin and OP-1118 (main metabolite) in the ng/ml range at therapeutic doses. It undergoes hydrolysis to form OP-1118. Metabolism is not dependent on CYP P450 enzymes. Elimination is primarily in the feces (~92%). Half-life = 9 hours (10 hours for OP-1118).

Clinical Trials: A 10-day course of fidaxomicin (200 mg PO BID) was compared to vancomycin (125 mg PO QID) in a randomized, double-blind, multicenter, phase-3 clinical trial. A total of 629 patients with acute symptoms of *C. difficile* infection and positive stool toxin test were enrolled. The primary endpoint was clinical cure (resolution of symptoms and no need for further therapy by 2 days after treatment course). Secondary endpoints included recurrence of *C. difficile* infection (diarrhea and a positive stool test within 4-weeks after treatment) and global cure (cure with no recurrence). See figure below for results.

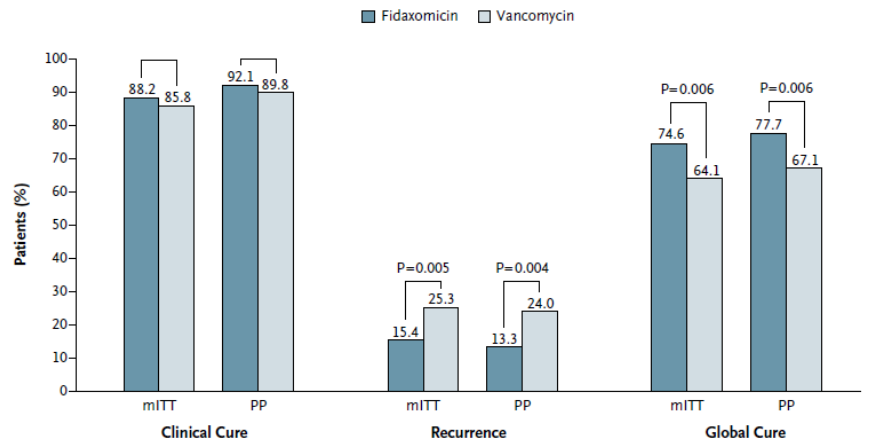


Figure 2. Rates of Primary and Secondary End Points.

mITT = modified intention to treat PP=per protocol

Contraindications: none

Warnings: *Not for systemic infections* – Fidaxomicin is minimally absorbed and thus would not be effective for treatment of systemic infections. *Development of drug resistant bacteria* – To reduce the development of drug-resistance, only use fidaxomicin to treat infections that are proven or strongly suspected to be caused by *Clostridium difficile*.

Drug Interactions: Fidaxomicin is a substrate for P-glycoprotein (P-gp) but may be co-administered with P-gp inhibitors with no dose adjustment necessary.

Adverse Reactions: The most common adverse reactions are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%)

Dosing: 200 mg PO BID for 10 days; may be given with or without food.

How Supplied: 200 mg film-coated tablets

Cost: AWP - $168 per tablet ($3360 for 10-day treatment) [First DataBank, June 2011]

spinosad (Natroba®) – ParaPRO / Pernix

Category: Topical Pediculicide

Indication: Topical treatment of head lice infestation in patients 4 years of age and older; use as part of an overall lice management program

Pharmacology: Spinosad, the active ingredient, is derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. It is a mixture of spinosyn A and spinosyn D in a ratio of approximately 5 to 1. Spinosad causes neuronal excitation in insects. After periods of hyper-excitation, lice become paralyzed and die.

Pharmacokinetics: When used as recommended, spinosad blood concentrations were not detectable after use. The bioavailability of benzyl alcohol was not assessed.

Clinical Trials: Two randomized, investigator-blinded, active-controlled studies were conducted in 1038 patients 6 months of age and older with head lice infestation. The youngest patient from each household was considered to be the primary subject and only these patients were evaluated for efficacy. Spinosad was compared to permethrin 1% in the study; retreatment was allowed if live lice were found on day-7. See table below for results.

Portion of subjects free of live lice 14 days after last treatment

Study 1		Study 2	
spinosad (n=91)	Permethrin 1% (n=89)	spinosad (n=83)	Permethrin 1% (n=84)
77 (84.6%)	40 (44.9%)	72 (86.7%)	36 (42.9%)

Contraindications: none

Warnings: *Benzyl alcohol toxicity* – Benzyl alcohol is contained in this product and is not recommended for neonates and infants <6 months of age.

Drug Interactions: None mentioned in product information

Adverse Reactions: Most common adverse events were application site erythema and irritation and ocular erythema.

Dosing: Shake bottle well before using. Apply sufficient amount to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 ml (1 bottle) to adequately cover scalp and hair. Leave on for 10 minutes, and then thoroughly rinse off with warm water. If live lice are seen after 7 days, a second treatment should be applied. Avoid contact with eyes.

How Supplied: 0.9% topical suspension – 4 oz (120 ml) bottles

Cost: AWP - $262.80 per bottle (Price Alert – July 15, 2011)

Respiratory

indacaterol (Arcapta Neohaler®) – Novartis

Category: long-acting $beta_2$-adrenergic agonist (LABA)

Indication: Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is not indicated to treat acute deteriorations of COPD and is not indicated to treat asthma.

Pharmacology: Indacaterol is a LABA that acts locally in the lung as a bronchodilator. The pharmacological effects of $beta_2$-adrenoceptor agonist drugs are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of ATP to cyclic-AMP. Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. Indacaterol has 24-fold greater agonist activity at $beta_2$-receptors compared to $beta_1$-receptors (similar to formoterol).

Pharmacokinetics: Absolute bioavailability of indacaterol after inhaled doses was on average 43-45%. Systemic exposure results from a composite of pulmonary and intestinal absorption. Peak levels occur at 15 minutes post dose. It is extensively distributed and is ~95% bound to plasma proteins. Primary route of elimination was the fecal rout. Average terminal half-life ranges from 45.5 to 126 hours, effective half-life = 40 to 56 hours. Steady state is reached in approximately 12-15 days.

Clinical Trials: There were 6 indacaterol confirmatory trials that were randomized, double-blinded, placebo- and active-controlled in design. However, only two utilized the 75 mcg once daily FDA-approved dose, and both were placebo-controlled. The primary outcome measure was 24-hour post-dose trough FEV_1 after 12-weeks of treatment. Indacaterol was more effective than placebo in this regard [1.38 vs. 1.26 L, treatment difference 0.12 (0.08-0.15, 95% CI) in one trial and 1.49 vs. 1.35, treatment difference 0.14 (0.10-0.18) in the other].

Black Box Warning: ASTHMA-RELATED DEATH – LABA increase the risk of asthma-related death. Previous studies compared the safety of salmeterol or placebo in asthma patients and showed an increase in asthma-related death. This finding is considered a class effect of LABA, including indacaterol.

Contraindications: All LABA are contraindicated in asthma patients without use of a long-term asthma control medication; indacaterol is not indicated for the treatment of asthma.

Warnings: *Deterioration of disease and acute episodes* – Indacaterol should not be initiated in patients with acutely deteriorating COPD. It has not been studied in this patient population. Do not use for the relief of acute symptoms. Short-acting $beta_2$-agonists should also be prescribed for relief of acute respiratory symptoms. *Excessive use and use with other LABA* – Do not use more often, at higher doses than recommended, or in conjunction with other LABA, as an overdose may result. *Cardiovascular effects* – Indacaterol can produce significant cardiovascular effects in some patients; including increases in pulse rate, blood pressure, or symptoms. Use with caution in patients with cardiovascular disorders; consider discontinuing if symptoms develop. *Coexisting conditions* – Use with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. *Hypokalemia and Hyperglycemia* – $Beta_2$-agonists may produce significant hypokalemia and hyperglycemia. However, clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical trials with indacaterol.

Drug Interactions: Use with other adrenergic drugs may potentiate the sympathetic effects of indacaterol. Concomitant use of xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of indacaterol. Use with extreme caution with MAOIs, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonist on the CV system may be potentiated. Beta-blockers and indacaterol may interfere with the effects of each other when administered concurrently.

Adverse Reactions: Most common adverse reactions (>2% and more common than placebo) are cough, oropharyngeal pain, nasopharyngitis, headache and nausea**.**

Dosing: Inhale 75 mcg (contents of 1 capsule) by mouth once daily using the Neohaler inhaler device; do not swallow the capsule. Store capsules in the blister pack, only remove immediately before use.

How Supplied: 75 mcg capsules containing powder for inhalation; Neohaler® inhaler (always use the new inhaler provided with each new prescription)

Cost: AWP - $195.84 (30 capsules + Neohaler®) [Price Alert – August 15, 2011]

roflumilast (Daliresp®)- Forest Labs

Category: Phosphodiesterase-4 (PDE4) inhibitor

Indication: treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Pharmacology: Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of PDE4 (a major cyclic AMP-metabolizing enzyme in lung tissue). This inhibition of PDE4 activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism(s) by which roflumilast exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells.

Pharmacokinetics: Oral bioavailability is ~80% with T_{max} occurring in approximately 1 hour after dosing. Roflumilast is highly bound to plasma proteins (99%). It is extensively metabolized via CYP450 enzymes and by conjugation. The N-oxide metabolite is active and peak concentrations occur approximately 8 hours after dosing. The median half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state is reached in 4 days and 6 days, respectively.

Clinical Trials: Two randomized, double-blind, placebo-controlled trials were conducted that assessed roflumilast and its effects on reducing the rate of moderate to severe COPD exacerbations in patients with severe COPD with chronic bronchitis and exacerbations within the previous year and at least a 20 pack-year smoking history. The use of inhaled corticosteroids was prohibited. One enrolled 1525 subjects, while the other enrolled 1571. In both trials, roflumilast demonstrated significant reduction in the rate of moderate to severe exacerbations compared to placebo. There was also a significant improvement on FEV_1 which averaged 50 ml across the studies. See tables below for details. In studies in patients with less severe disease, roflumilast did not significantly reduce exacerbations compared to placebo.

Effects on Exacerbations per Patient-Year

	Roflumilast	Placebo	Absolute reduction	Rate Ratio (95% CI)
Study 1	1.1	1.3	0.2	0.85 (0.74-0.98)
Study 2	1.2	1.5	0.3	0.82 (0.71-0.94)

Effects on FEV_1

	Roflumilast	Placebo	Effect (95%CI)
Study 1	46	8	+39 (18-60)
Study 2	33	-25	+58 (41-75)

Contraindications: moderate to severe liver impairment

Warnings: *Psychiatric Events including Suicidality* – Treatment with roflumilast is associated with an increase in psychiatric adverse reaction (5.9% vs. 3.3% compared to placebo). Most commonly reported were insomnia, anxiety, and depression. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Carefully weigh risk/benefit in patients with a history of depression and/or suicidal behavior. *Weight loss* was a common adverse reaction in clinical trials (7.5% vs. 2.1% for placebo). Monitor weight during therapy. If unexplained weight loss occurs, consider discontinuing roflumilast.

Drug Interactions: Use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, and phenytoin) is not recommended as use may result in a decrease in therapeutic effectiveness. Co-administration with CYP3A4 inhibitors or dual CYP3A4 and CYP1A2 inhibitors may increase exposure and adverse reaction from roflumilast; carefully weigh risk/benefit. Co-administration with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and increase risk of side effects.

Adverse Reactions: Most common adverse reactions (≥ 2%) are diarrhea, weight decrease, nausea, headache, back pain, influenza, insomnia, dizziness and decreased appetite.

Dosing: 500 mcg PO once daily, with or without food

How Supplied: 500 mcg tablets

Cost: AWP - $6.90 per tablet ($207 for 30 day supply) [Price Alert – July 15, 2011]

Miscellaneous

belimumab (Benlysta®) – Human Genome Sciences / GSK

Category: B-lymphocyte stimulator (BLyS)-specific inhibitor

Indication: Treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy; *Limitations of use* – Efficacy has not been evaluated in patients with severe active lupus nephritis or severe active CNS lupus. It has not been studied in combination with other biologics or IV cyclophosphamide. Therefore, use is not recommended in these situations.

Pharmacology: Belimumab is a human IgG monoclonal antibody specific for soluble human BLyS, a B-cell survival factor. Belimumab binds to soluble BLyS and thus blocks its binding to receptors on B cells. This inhibits the survival of B cells and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Pharmacokinetics: Following IV infusion, belimumab's distribution half-life is 1.75 days with an apparent Vd of 5.29 L. Terminal half-life is 19.4 days.

Clinical Trials:
Two randomized, double-blind, placebo-controlled trials were conducted in patients with SLE (Trial 2 – 76 weeks, Trial 3 – 52 weeks). Eligible patients had active SLE, defined as a SELENA-SLEDAI score ≥6, and positive autoantibody test results. See results below.

Table 3. Clinical Response Rate in Patients with SLE After 52 Weeks of Treatment

	Trial 2			Trial 3		
Response[1]	Placebo + Standard of Care (n = 275)	BENLYSTA 1 mg/kg + Standard of Care[2] (n = 271)	BENLYSTA 10 mg/kg + Standard of Care (n = 273)	Placebo + Standard of Care (n = 287)	BENLYSTA 1 mg/kg + Standard of Care[2] (n = 288)	BENLYSTA 10 mg/kg + Standard of Care (n = 290)
SLE Responder Index	34%	41% (p = 0.104)	43% (p = 0.021)	44%	51% (p = 0.013)	58% (p < 0.001)
Odds Ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 (1.3, 2.6)
Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

Contraindications: patients who have had anaphylaxis to belimumab

Warnings: *Mortality* – There were more deaths reported with belimumab than placebo during clinical trials [3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) deaths in the placebo, belimumab 1 mg/kg, belimumab 4 mg/kg, and belimumab 10 mg/kg groups, respectively]. *Serious infections* have been reported in patients receiving immunosuppressive agents, including belimumab. Exercise caution when considering use in patients with chronic infections. Consider interrupting therapy in patients who develop a new infection. *Malignancy* – The impact of belimumab on the development of malignancies is not known. However, as with other immunomodulating agents, the mechanism of action of belimumab could increase the risk of development of malignancies. *Hypersensitivity reactions, including anaphylaxis,* were reported in clinical trials. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. *Infusion reactions* also occurred during administration. These symptoms included bradycardia, myalgia, headache, rash, urticaria, and hypotension. *Depression* – Serious psychiatric events were reported more frequently in patients receiving belimumab vs. placebo; including depression. It is unknown if belimumab treatment is associated with increased risks of suicidal behavior. *Immunization* – Live vaccines should not be given for 30 days before or concurrently with belimumab (clinical safety has not been established). Belimumab may interfere with the response to immunizations.

Drug Interactions: Drug-interaction studies have not been performed. No evidence of clinically meaningful interactions was seen in clinical trials.

Adverse Reactions: Common adverse reactions (≥5%) in clinical trials were: nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

Dosing: Recommended dose is 10 mg/kg at 2-week intervals x 3 doses; then at 4-week intervals thereafter. Administer as an IV infusion only over 1 hour; rate may be slowed or interrupted if the patient develops an infusion reaction. Consider administering premedication for infusion reactions and hypersensitivity reactions. Belimumab should be administered by healthcare providers prepared to manage anaphylaxis.

IV Preparation: Allow vial to reach room temperature, then reconstitute with sterile water for injection. Gently swirl, do not shake vial; may take up to 30 minutes for reconstitution. Further dilute dose in 250 ml of NS (dextrose solutions are incompatible). Total time from reconstitution to completion of infusion should not exceed 8 hours.

How Supplied: 120 and 400 mg single-use vials (lyophilized powder for injection)

Cost: AWP - $531.82 for 120 mg vial; $1772.71 for 400 mg vial (MaxorPlus Clinical Newsletter; March 2011)

2011 New Dosage Form Approvals

BRAND	GENERIC	COMPANY	DESCRIPTION
Abstral	fentanyl	ProStrakan	Sublingual tablets for breakthrough pain in cancer patients tolerant to opiate therapy
AndroGel	testosterone	Abbott	New concentrated formulation (1.62%) topical gel for hypogonadism
Banzel	rufinamide	Eisai	New oral suspension formulation for seizures
Complera	emtricitabine/ rilpivirine/tenofovir	Gilead Sciences	New combination for HIV-1 infection in treatment-naïve adults
Duexis	ibuprofen / famotidine	Horizon Pharma	New NSAID-H_2-antagonist combination for patients with rheumatoid and osteo-arthritis
Gralise	gabapentin	Abbott	Once-daily formulation for postherpetic neuralgia
Lazanda	fentanyl	Archimedes Pharma	New nasal spray formulation for breakthrough cancer pain
Lotemax	loteprednol	Bausch and Lomb	New ophthalmic ointment formulation for post-op inflammation and pain
Makena	hydroxy-progesterone	Baxter Pharm.	Injectable progestin to reduce the risk of preterm birth
Nithiodote	sodium nitrite / sodium thiosulfate	Hope Pharm.	Injectable agents for treatment of acute cyanide poisoning
Nucynta ER	tapentadol	Janssen	New extended-release formulation for moderate to severe chronic pain
Oxecta	oxycodone	King Pharm.	Immediate-release tablet formulated to deter abuse (not amenable to crushing/dissolution)
Phoslyra	calcium acetate	Fresenius	Oral solution phosphate binder
Rectiv	nitroglycerin	ProStrakan	0.4% ointment formulation for pain associated with chronic anal fissures
Rezira	hydrocodone / pseudoephedrine	Cypress Pharm.	New combination antitussive/decongestant oral solution for relief of cold symptoms
Suprenza	phentermine	Akrimax Pharm.	Orally disintegrating tablet (ODT) for weight loss
Viramune XR	nevirapine	Boehringer Ingelheim	Extended-release tablet for HIV-1 infection
Zutripro	hydrocodone / chlorpheniramine / pseudoephedrine	Cypress Pharm.	New combination antitussive/antihistamine/ decongestant oral solution for relief of allergy and cold symptoms
Zyclara	imiquimod	Graceway	New lower strength (3.75%) for actinic keratoses and genital warts

2011 Other FDA Approvals

BRAND	GENERIC	COMPANY	DESCRIPTION
Adcetris	brentuximab vedotin	Seattle Genetics	CD30-directed antibody-drug conjugate for certain types of advanced lymphomas
Anascorp	Centruroides immune F(ab)2	Rare Disease Therapeutics	Antivenin for scorpion stings
Caprelsa	vandetanib	AstraZeneca	Oral kinase inhibitor for advanced medullary thyroid cancer
Cortifact	factor XIII	CSL Behring	Concentrate (human) to prevent bleeding in patients with congenital factor XIII deficiency
Edurant	rilpivirine	Tibotec	Non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV-1 infection
Firazyr	icatibant	Shire human Genetic Therapies	Bradykinin B2 receptor antagonist for acute attacks of hereditary angioedema
Fluzone intradermal	influenza virus vaccine	Sanofi Pasteur	Intradermal seasonal influenza vaccine for patients age 18-64 years
Horizant	gabapentin enacarbil	GSK	Gabapentin prodrug for restless leg syndrome
Nulojix	belatacept	BMS	Immunosuppressant to prevent rejection after kidney transplant
Xalkori	crizotinib	Pfizer	Kinase inhibitor for advanced non-small cell lung cancer
Yervoy	ipilimumab	BMS	Cytotoxic T-lymphocyte antigen 4-blocking antibody for late-stage melanoma
Zelboraf	vemurafenib	Genentech	Kinase inhibitor for advanced melanoma
Zytiga	abiraterone	Centocor Ortho Biotech	CYP17 inhibitor for advanced prostate cancer

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All other information in this handout is derived from the FDA-approved manufacturer's prescribing information for each drug.