NEW DRUG UPDATE 2017

Joe Strain, Pharm.D.

SDSU College of Pharmacy – Rapid City Regional Hospital

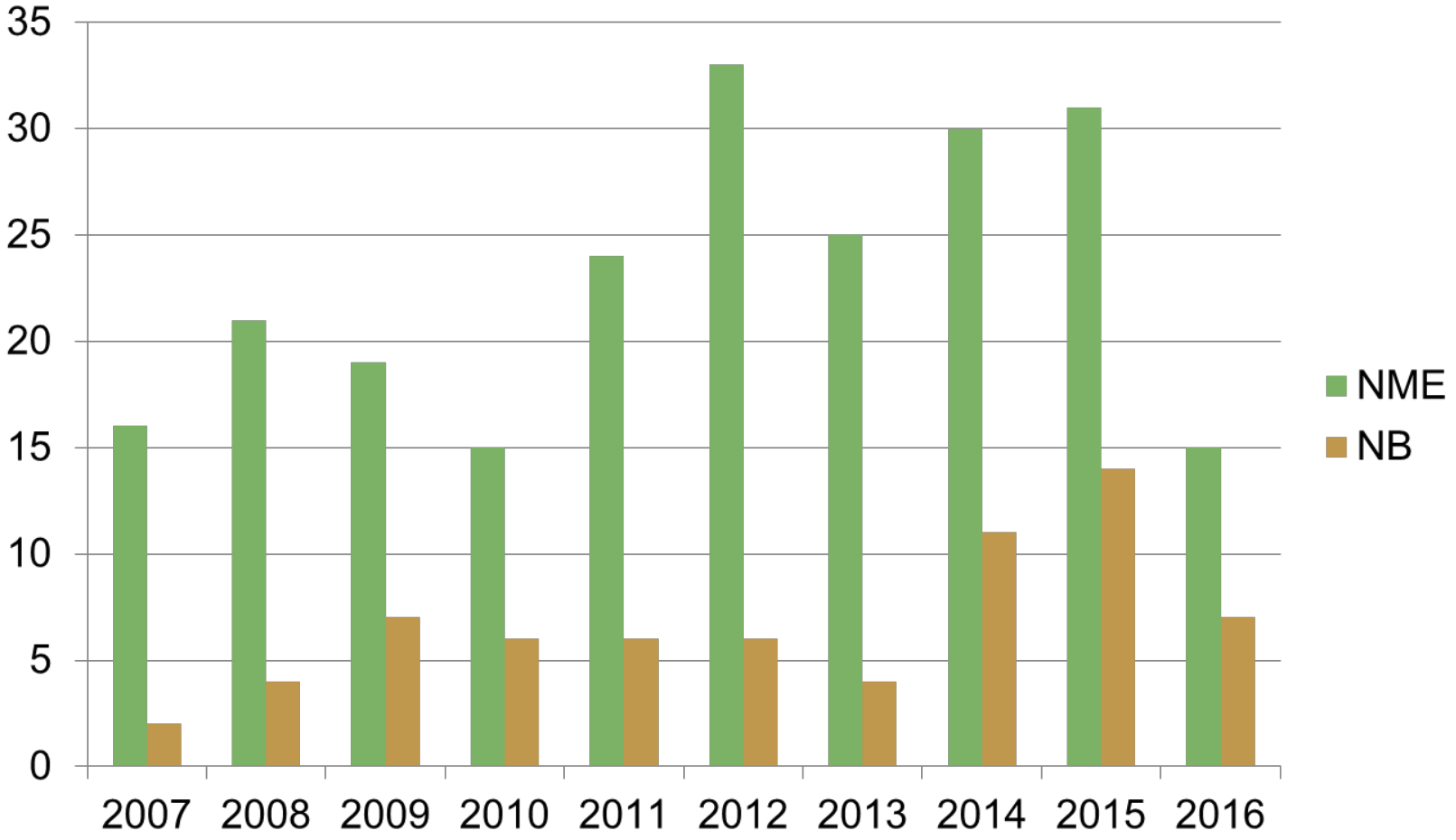
Disclosure

- I have reports no actual or potential conflicts of interest associated with this presentation

Learning Objectives

- *Upon successful completion of this activity, participants should be able to:*
  - Identify therapeutic indications of drugs recently approved by the FDA.
  - Discuss pharmacological properties of the new medications
  - List side effects, warnings, precautions and significant drug interactions associated with each medication.
  - Identify the normal dose and dosage forms of the drugs presented.
  - Describe limitations to implementing the new medications into clinical practice

New Drug Approval Trends



http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm474696.htm

Agenda

- Insulin degludec/liraglutide (Xultophy®)
- Insulin glargine/lixisenatide (Soliqua™)
- Plecanatide (Trulance™)
- Naldemedine (Symproic®)
- Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)
- Glecaprevir/pibrentasvir (Mavyret™)
- Safinamide (Xadago®)
- Valbenazine (Ingrezza™)
- Delafloxacin (Baxdela™)
- Bezlotoxumab (Zinplava™)
- Betrixaban (Bevyxxa®)

The combination of a GLP-1 agonist and long-acting insulin was associated with weight gain in clinical trials.

A. True

B. False

Insulin degludec/Liraglutide (Xultophy®)

- Indication
  - Type 2 diabetes mellitus inadequately controlled on basal insulin (< 50 units) or liraglutide (≤ 1.8 mg daily)
- Pharmacology
  - Ultra long acting insulin
  - GLP-1 agonist
    - Increases glucose-dependent insulin release
    - Decreases glucagon secretion
    - Slows gastric emptying

Xultophy PI 2016.

DUAL V Trial

Endpoint	Glargine N = 279	Liraglutide/degludec N = 278	P-value
A_{1C} reduction at 26 weeks*	1.13%	1.81%	< 0.001
A_{1C} < 7%	47%	71.6%	< 0.001
Hypoglycemia (events/patient-year)	5.05	2.23	< 0.001
Weight change	+ 1.8 kg	- 1.4 kg	< 0.001

Lingvay I, et al. JAMA. 2016;315:898-907.

Insulin degludec/Liraglutide (Xultophy®)

- Dosing
  - Start at 16 units (16 units of degludec and 0.58 mg of liraglutide)
  - Titrate every 3-4 days by 2 units
  - Max dose of 50 units (50 units of degludec and 1.8 mg of liraglutide)
- Availability
  - Only available as a 3 ml pen; packs of 5 pens
  - 100 units/ml of degludec and 3.6 mg/ml of liraglutide

Xultophy PI 2016.

Insulin degludec/Liraglutide (Xultophy®)

- Administration
  - Attach needle
  - Select priming symbol "··—" prior to each use
  - Press button until liquid comes out of needle (may repeat up to 6 times)
  - Then select dose and administer similar to insulin shot
  - Hold button until dose says "0" then count to 6
- Stability/storage
  - Refrigerator until first use then at room temp or refrigerator; protect from light/direct heat
  - Discard 21 days after first use

Xultophy PI 2016.

Insulin glargine/Lixisenatide (Soliqua™)

- Indication
  - Type 2 diabetes mellitus uncontrolled on lixisenatide or basal insulin (< 60 units daily)
- Pharmacology
  - Long acting insulin
  - GLP-1 agonist
    - Increases glucose-dependent insulin release
    - Decreases glucagon secretion
    - Slows gastric emptying

Soliqua PI. 2016.

LixiLan-L Trial

Endpoint	Glargine N = 365	Glargine/Lixi N = 366	P-value
A_{1C} reduction at 30 weeks*	0.6%	1.1%	< 0.0001
A_{1C} < 7%	30%	55%	< 0.0001
Hypoglycemia (events/patient-year)	4.22	3.03	NR
Weight change	+ 0.7 kg	- 0.7 kg	< 0.0001

Diabetes Care 2016;39:1972-1980.

* Primary outcome

Insulin glargine/Lixisenatide (Soliqua™)

- Starting dose
  - If on lixisenatide or less than 30 units of basal insulin
    - Insulin glargine 15 units/ 5 mcg lixisenatide
    - Displayed as “15” in the dosing window
  - If on 30-60 units of basal insulin
    - Insulin glargine 30 units/10mcg lixisenatide
    - Displayed as “30” in the dosing window
- Availability
  - Only available as a 3 ml pen; packs of 5 pens
  - 100 units/ml of glargine, 33 mcg/ml lixisenatide

Soliqua PI 2016.

Insulin glargine/Lixisenatide (Soliqua™)

- Administration
  - Alcohol swab to rubber seal prior to attaching needle
  - Select “2” units prior to each use
  - Press button until liquid comes out of needle (may repeat up to 3 times)
  - Then select dose and administer similar to insulin shot
  - Hold button until dose says “0” then count to 10
- Stability/storage
  - Store in refrigerator until first use then at room temperature; Protect from light
  - Discard 14 days after first use

Soliqua PI 2016.

Pricing

- Insulin glargine/Lixisenatide (Soliqua)
  - $120 for each 3ml pen

- Insulin degludec/Liraglutide (Xultophy)
  - $160 for each 3 ml pen

www.cardinal .com. Accessed August 10th 2017.

Insulin glargine/Lixisenatide (Soliqua™)

Insulin degludec/Liraglutide (Xultophy®)

- Bottom line
  - Combination, once-daily injections
  - Lowers A_{1C} vs. insulin monotherapy
  - Useful for patients not controlled on basal insulin and oral agents
  - Rare pancreatitis
  - Weight loss vs. weight gain with insulin monotherapy
- Additional review
  - Wilding JP, Bain SC. Diabet Med. 2016;33:864-76.

Which of the following is a contraindication to plecanatide?

A. Cancer

B. Age less than 6

C. Urinary tract infection

D. Constipation

Plecanatide (Trulance™)

- Indications
  - Chronic idiopathic constipation (CIC)
- Pharmacology
  - Uroguanylin analog
  - Stimulates guanylate cyclase type-C (GC-C) receptors→ increases cGMP → activates CFTR → efflux of chloride from lining of GI tract leading to increased fluid secretion into intestinal lumen

Plecanatide (Trulance™)

- Pharmacokinetics
  - Not systemically absorbed
  - Metabolized to active metabolite in GI tract
  - Degraded into smaller peptides in the GI tract
- Contraindications
  - Bowel obstruction
  - Ages < 6 (due to risk of dehydration; mice data)
- Warnings and precautions
  - Ages 6-17
  - Diarrhea

Trulance PI 2017

Diarrhea Reported from Phase III Trials

Adverse reaction	Plecanatide N = 863	Placebo N = 870
Diarrhea	5%	1%
Severe diarrhea	0.6%	0.3%
Discontinued due to diarrhea	2%	0.5%

Trulance PI 2017

Efficacy in Chronic Idiopathic Constipation

Outcome	Plecanatide 3 mg N = 453	Plecanatide 6 mg N = 441	Placebo N = 452
*Response Rate	21%†	19.5%†	10.2%
First week responders	35.8%†	29.3%†	16.6%
CSBM within 24 hours	28.7%†	25.2%†	13.3%

*more than 3 complete spontaneous bowel movements (CSBM) per week, and increase of more than 1 CSBM/week in 9 of the 12 weeks

† $p < 0.001$ vs. placebo

Miner, et al. Am J Gastroenterol 2017;112:613-21.

Plecanatide (Trulance™)

- Dosing
  - 3 mg PO once daily with or without food
  - May be crushed and mixed in applesauce or water
- Cost
  - Plecanatide = $329.44 per month
  - Linaclotide = $329.38 per month

Trulance PI 2017

Plecanatide (Trulance™)

- Bottom line
  - Similar to linaclotide
  - No data beyond 12 weeks
  - Contraindicated in pediatric patients
  - Likely for refractory cases of constipation
  - Irritable bowel data pending
- Additional review
  - Brancale A, et al. Pharmacol Res Perspect 2017; 5;e00295.

Why is naldemedine a Schedule II controlled substance?

A. High potential for abuse

B. Structurally similar to morphine

C. Easily converted to fentanyl

D. Have no idea—doesn’t make any sense

Naldemedine (Symproic®)

- Indication
  - Opioid-induced constipation in chronic non-cancer pain
- Pharmacology
  - Structurally related to naltrexone
  - Side chain increases size & polarity
  - Decreases ability to penetrate blood-brain barrier

Naldemedine (Symproic®)

- Pharmacokinetics
  - T ½ ~ 11 hours
  - Primarily metabolized by CYP3A
  - Majority excreted via kidneys
- Contraindications
  - GI obstruction

Naldemedine (Symproic®)

- Warnings and precautions
  - GI perforation
  - Opioid withdrawal
  - No data in severe hepatic impairment
- Drug interactions
  - Avoid CYP3A inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort)
  - CYP3A inhibitors increase plasma levels (e.g. diltiazem, clarithromycin, fluconazole)
  - P-glycoprotein inhibitors increase plasma levels (e.g. amiodarone, verapamil)

Symproic PI 2017

Adverse Reactions from 12-week Clinical Trials

Reaction	Naldemedine N = 542	Placebo N = 546
Abdominal pain	8%	2%
Diarrhea	7%	2%
Nausea	4%	2%
Gastroenteritis	2%	1%

Symproic PI 2017

Efficacy for Opioid Induced Constipation

Compose 1 Trial	Naldemedine N = 273	Placebo N = 272	p-value (95% CI)
Response rate*	47.6	34.6	0.002 (4.8-21.3)
Compose 2 Trial	**Naldemedine N = 276**	**Placebo N = 274**	**p-value (95% CI)**
Response rate*	52.5%	33.6%	< 0.0001 (10.8-27)

*at least 3 SBMs/wk, and increase of at least 1 SBM/wk in 9 of the 12 weeks & 3 out of the last 4 weeks

Hale M, et al. Lancet Gastroenterol Hepatol. 2017;2:555-64.

Naldemedine (Symproic®)

- Dosing
  - 0.2 mg once daily with or without food
- Cost
  - #30 0.2 mg tablets = ???
- Availability
  - Expected summer 2017
- Schedule II controlled substance
  - Current proposal to deschedule

Naldemedine (Symproic®)

- Bottom line
  - Another agent for opioid-induced constipation
  - Likely 2nd line after less expensive laxatives
  - Currently a C-II

- Additional review
  - Hale M, et al. Lancet Gastroenterol Hepatol. 2017;2:555-64.

Which of the following is a contraindication to using sofosbuvir/velpatasvir/voxilaprevir?

A. Mild cirrhosis (Child-Pugh A)

B. Rifampin use

C. Failed previous hepatitis C treatment

D. Hepatitis Genotype-3

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- Indication
  - Treatment of hepatitis genotypes 1-6, previously treated with an NS5A inhibitor
  - Treatment of hepatitis genotypes 1a or 3 previously treated with sofosbuvir without an NS5A inhibitor
- Pharmacology
  - Block steps of viral replication
  - Sofosbuvir: HCV NS5B RNA polymerase inhibitor
  - Velpatasvir: HCV NS5A protein inhibitor
  - Voxilaprevir: NS3/4A protease inhibitor

Vosevi PI 2017

Pharmacokinetics

Parameter	Sofosbuvir	Velpatasvir	Voxilaprevir
Effect of food on absorption	↑ 64-144%	↑ 40-166%	↑ 112-435%
T ½	29h*	17h	33h
Urinary excretion	80%*	0.4%	0%
Metabolism	Cathepsin A CES1 HINT1	CYP2B6 CYP2C8 CYP3A4	CYP3A4

Vosevi PI 2017

* Active metabolite

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- Contraindications
  - Rifampin
- Warnings/precautions
  - Moderate to severe hepatic impairment
    - Child-Pugh B & C
  - Hepatitis B reactivation
  - Drug interactions
    - Next slide

Vosevi PI 2017

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- Drug interactions
  - Many, many many…
    - http://www.hep-druginteractions.org/
  - Amiodarone—bradycardia
  - Avoid with P-gp inducers and moderate-potent CYP inducers
    - Reduces levels of all 3 agents
  - Avoid OATP inhibitors
    - Increases voxilaprevir
  - Acid-reducing drugs decrease velpatasvir absorption

Vosevi PI 2017

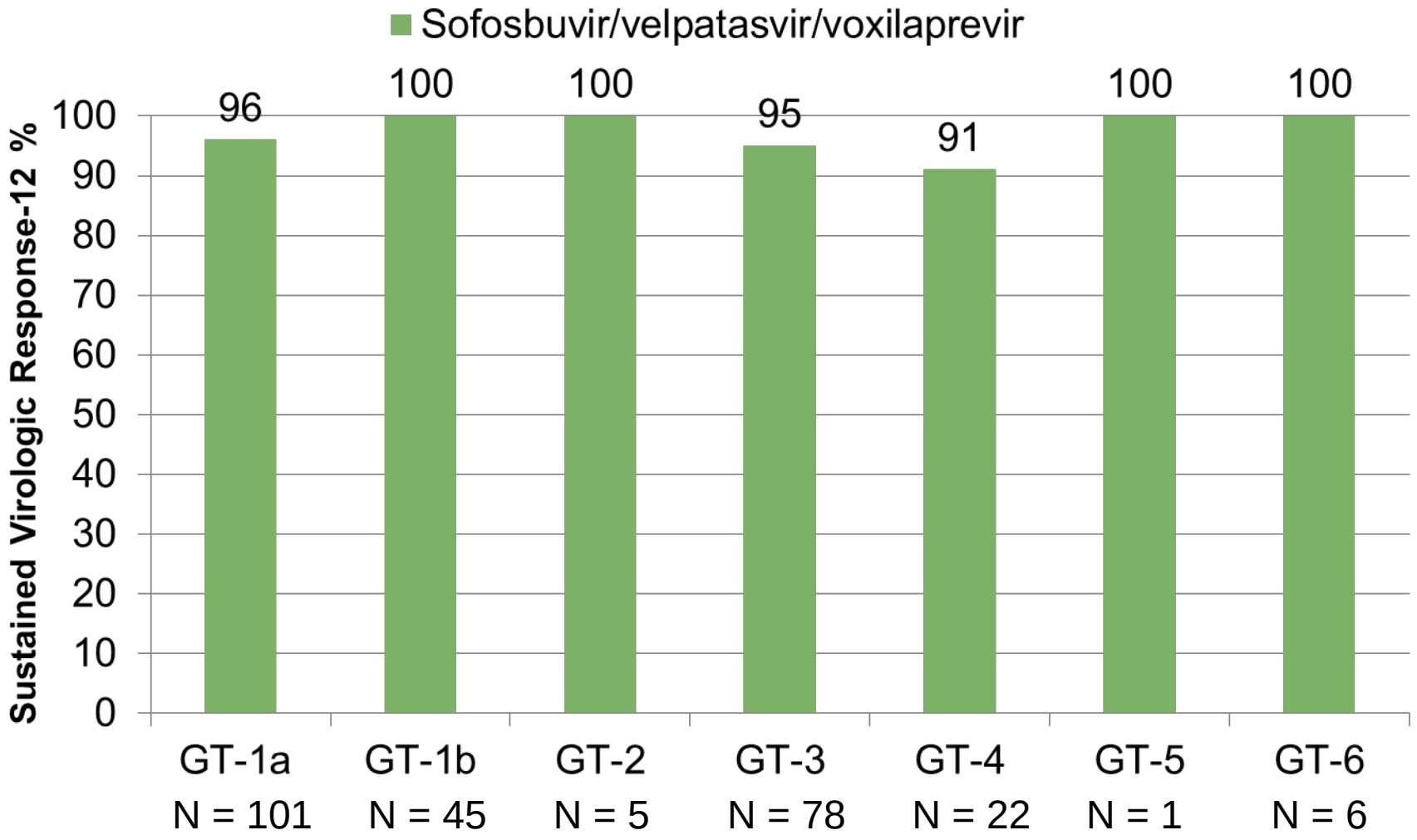
Common Adverse Reactions

	POLARIS-1		POLARIS-4	
	Sof/Vel/Vox N = 263	Placebo N = 152	Sof/Vel/Vox N = 182	Placebo N = 151
Headache	21%	14%	23%	23%
Fatigue	17%	15%	19%	23%
Diarrhea	13%	9%	14%	3%
Nausea	13%	7%	10%	3%
Insomnia	6%	3%	3%	1%

Vosevi PI 2017

Sof/Vel/Vox = Sofosbuvir/velpatasvir/voxilaprevir

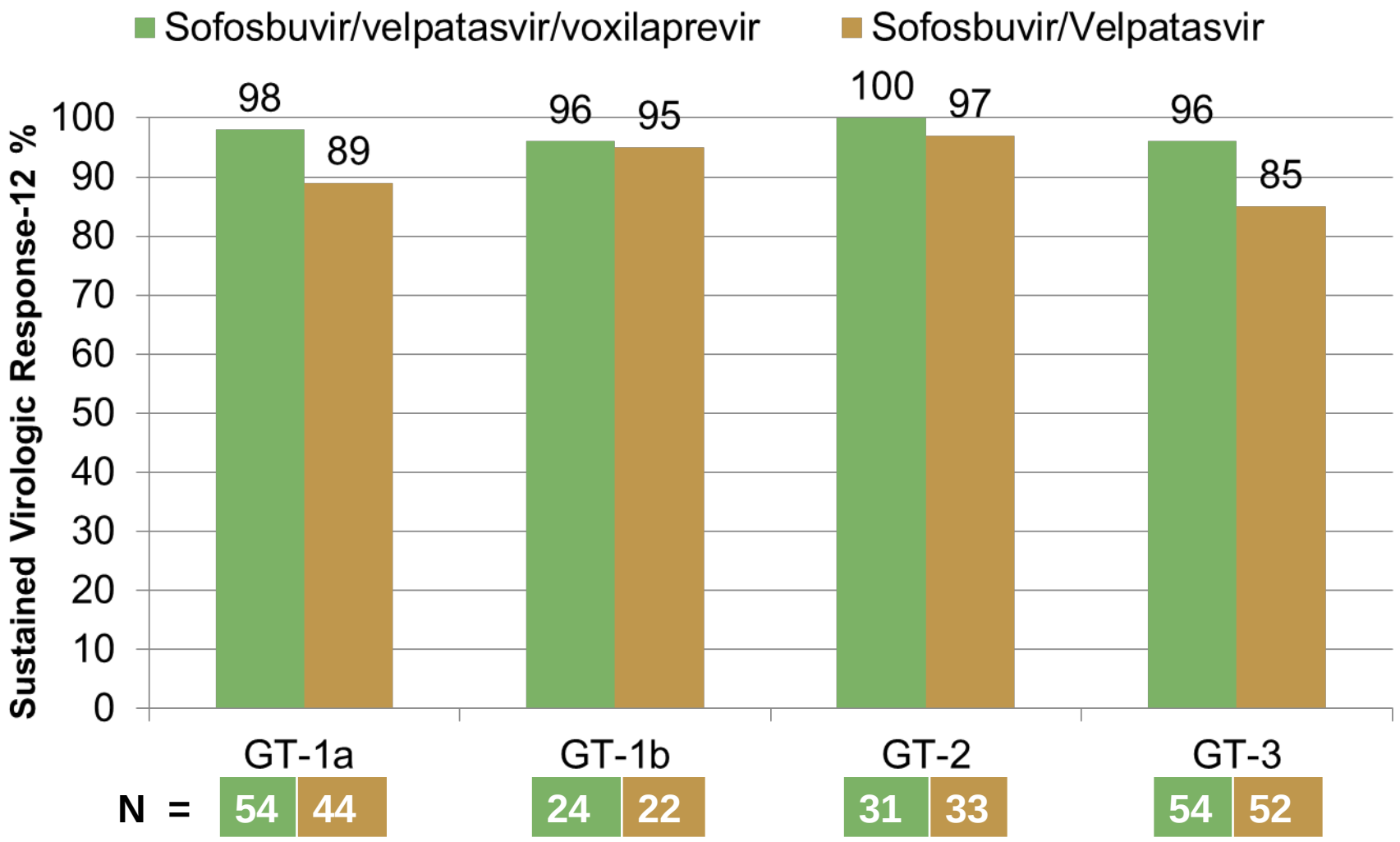
POLARIS-1 Trial



N Engl Med 2017; 376:2134-46

GT = genotype

POLARIS-4 Trial



N Engl Med 2017; 376:2134-46

GT = genotype

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- Dosing
  - One tablet daily **with food** x 12 weeks
  - 400mg/100mg/100mg tablets
- Cost
  - $74,760 for 12 weeks

Vosevi PI 2017

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

- Bottom line
  - First agent approved for those failing other new treatments
  - Convenient dosing
  - Expensive
- Additional review
  - http://www.hcvguidelines.org/

Which of the following is true regarding glecaprevir/pibrentasvir?

A. Relatively cheaper vs. other hepatitis C agents

B. Approved as an 8-week therapy

C. Approved for multiple hepatitis C genotypes

D. All of the above

Glecaprevir/Pibrentasvir (Mavyret™)

- Indication
  - Hepatitis C genotypes 1-6, treatment naïve, may have mild cirrhosis
  - Hepatitis C genotype 1, previously failed an NS5A inhibitor OR an NS3/4A protease inhibitor
- Pharmacology
  - Glecaprevir: HCV NS3/4A protease inhibitor
  - Pibrentasvir: HCV NS5A inhibitor

Mavyret PI 2017

Pharmacokinetics

Parameter	Glecaprevir	Pibrentasvir
Effect of food on absorption*	↑ 83-163%	↑ 40-53%
T ½	6h	13h
Urinary excretion	0.7%	0%
Metabolism	CYP3A4 (secondary)	None

Mavyret PI 2017

*moderate-high fat meal

Glecaprevir/Pibrentasvir (Mavyret™)

- Contraindications
  - Severe hepatic impairment (Child-Pugh C)
  - Rifampin and atazanavir
- Warnings/precautions
  - Moderate hepatic impairment (Child-Pugh B)
  - Hepatitis B reactivation
  - Carbamazepine, efavirenz, & St. John’s wort

Mavyret PI 2017

Glecaprevir/Pibrentasvir (Mavyret™)

- Drug interactions
  - http://www.hep-druginteractions.org/
  - Both inhibit P-glycoprotein, BCRP and OATP
  - Both are substrates of P-gp and PCRP
  - Specific medication interactions listed in package insert
  - Specific list of medications NOT interacting listed in package insert

Mavyret PI 2017

Adverse Reactions from ENDURANCE-3 Trial

Reaction	Glecaprevir/ Pibrentasvir 8 weeks N = 157	Glecaprevir/ Pibrentasvir 12 weeks N = 233	Daclatasvir/ sofosbuvir 12 weeks N = 115
Headache	16%	17%	15%
Fatigue	11%	14%	12%
Nausea	9%	12%	12%
Diarrhea	7%	3%	3%

Mavyret PI 2017

Study (Genotype)	Population	SVR12	Treatment Duration
ENDURANCE-4 /SURVEYOR-1 (5, 6)	Treatment Naïve and IFN/RBV/Sof Experienced without cirrhosis	100% (57/57)	12 weeks
Surveyor-2 (2,4,5,6)	Treatment Naïve and IFN/RBV/Sof Experienced without cirrhosis	97% (248/255)	8 weeks
ENDURANCE-1 (1)	Treatment Naïve and IFN/RBV/Sof Experienced without cirrhosis	99% (348/351)	8 weeks
EXPEDITION-1 (1,2,4,5,6)	Treatment Naïve and IFN/RBV/Sof Experienced + cirrhosis	99% (145/146)	12 weeks

Mavyret PI 2017

SVR12 = sustained virologic response at 12 weeks after end of treatment

ENDURANCE-3
(Treatment Naïve, Genotype 3, without cirrhosis)

Outcome	Glecaprevir/ Pibrentasvir 8 weeks N = 157	Glecaprevir/ Pibrentasvir 12 weeks N = 233	Daclatasvir/ sofosbuvir 12 weeks N = 115
SVR12	94.9%	95.3%	96.5%

SVR12 = sustained virologic response at 12 weeks after end of treatment

Mavyret PI 2017

Glecaprevir/Pibrentasvir (Mavyret™)

- Dosing
  - 100mg/40mg tablets
  - Take 3 tablets once daily **with food**
  - 4-week or 8-week supply
    - Wallets of 3 tablets each
- Cost
  - $26,400 for 8 weeks
  - $39,600 for 12 weeks

Mavyret PI 2017

Glecaprevir/Pibrentasvir Duration: Treatment Naïve Patients

HCV Genotype	Treatment Duration	
	No cirrhosis	Child-Pugh A
1-6	8 weeks	12 weeks

Glecaprevir/Pibrentasvir Duration: Treatment-Experienced Patients

HCV Genotype	Previous regimen	No cirrhosis	Child-Pugh A
1	NS5A inhibitor	16 weeks	16 weeks
	NS3/4A protease inhibitor	12 weeks	12 weeks
1,2,4,5,6	Interferon, ribavirin or sofosbuvir	8 weeks	12 weeks

Mavyret PI 2017

Glecaprevir/Pibrentasvir (Mavyret™)

- Bottom line
  - First 8-week treatment for all genotypes
  - Certain subtypes require 12 or 16 weeks
  - GT-1 patients failing previous treatment with new agents
  - Significantly cheaper list price vs. other approved treatments
  - May be used in renal failure
- Additional review
  - http://www.hcvguidelines.org/

Safinamide’s mechanism is similar to which agent?

A. Rasagiline

B. Pramipexole

C. Levodopa

D. Entacapone

Safinamide (Xadago®)

- Indication
  - Add-on treatment for Parkinson’s disease
  - Reduces “off” episodes
- Pharmacology
  - Selective monoamine oxidase B inhibitor
  - Similar to rasagiline and selegiline
  - Also inhibits glutamate

Xadago PI 2017

Safinamide (Xadago®)

- Pharmacokinetics
  - Peaks in 2-3 hours
  - T ½ 20-26 hours
  - Steady-state in 5-6 days
  - Metabolized by 3 oxidative pathways (not CYP450 mediated)
    - Levels increased in hepatic impairment (Child Pugh B)
  - Inactive metabolites excreted via kidneys

Xadago PI 2017

Safinamide (Xadago®)

- Contraindications
  - Hypersensitivity
  - Severe hepatic impairment (Child-Pugh C)
  - MAOI's (including linezolid)
  - Meperidine, tramadol, methadone
  - SNRIs, TCAs, cyclobenzaprine, methylphenidate, amphetamine derivatives, St. John's Wort
  - Dextromethorphan

Xadago PI 2017

Safinamide (Xadago®)

- Warnings/precautions
  - Hypertension
  - SSRI’s
  - Sleep attacks
  - Dyskinesia
  - Psychosis/hallucinations
  - Compulsive behaviors
  - Withdrawal
  - Retinal degeneration

Safinamide (Xadago®)

- Drug interactions
  - Increases levels of BCRP substrates (e.g. methotrexate, rosuvastatin)
  - Dopaminergic antagonists may decrease effectiveness
    - Antipsychotics
    - Metoclopramide

Adverse Reactions from Placebo-controlled Phase III Trials

Reaction	Safinamide 50 mg N = 223	Safinamide 100 mg N = 498	Placebo N = 497
Dyskinesia	21%	17%	9%
Fall	4%	6%	4%
Nausea	3%	6%	4%
Insomnia	1%	4%	2%
Orthostatic hypotension	2%	2%	1%

Xadago PI 2017

“On” Time Without Troublesome Dyskinesia

Measurement (hours/day)	Safinamide 100 mg N = 274	Placebo N = 275
Baseline	9.3	9.06
24 weeks	10.73	9.63
Change	+1.42	+0.57
Mean Difference from Placebo (95% CI)	+0.96 (0.56-1.37)*	NA

JAMA Neurol. 2017;74(2):216-224

* P < 0.001

“On” Time Without Troublesome Dyskinesia

Measurement (hours/day)	Safinamide 50 mg N = 223	Safinamide 100 mg N = 224	Placebo N = 222
Baseline	9.4	9.5	9.3
24 weeks	10.9	11	10.3
Change	1.5	1.5	1
Mean Difference from Placebo (95% CI)	0.51 (0.07-0.94)*	0.55 (0.12-0.99) †	NA

Mov Disord. 2014;29(2):229-237.

* p = 0.0223; † p = 0.013

Safinamide (Xadago®)

- Dosing
  - 50 mg daily for 2 weeks, then increase to 100 mg daily based on tolerability and response
  - Used with or without food
  - If stopping use 50 mg daily x 1 week
  - Max of 50 mg daily if moderate hepatic impairment

MOA-B Inhibitors Monthly Cost Comparison		
Safinamide	Rasagiline	Selegiline
$670	$430	$90

Xadago PI 2017; Pharmacists Letter; 2017

Safinamide (Xadago®)

- Bottom line
  - MAO-B inhibitor w/ glutamate inhibition
  - Likely use when not tolerating rasagiline or selegiline—no direct comparator trials
  - Must be used in combination with carbidopa/levodopa
- Additional Review
  - Muller T. Ther Clin Risk Manag. 2016;12:1151-60.

What is the most common side effect associated with valbenazine?

A. Headache

B. Diarrhea

C. Somnolence

D. Dizziness

Valbenazine (Ingrezza™)

- Indication
  - Treatment of adults with tardive dyskinesia
- Pharmacology
  - Selectively inhibits vesicular monoamine transporter type 2 (VMAT-2)
  - VMAT is a protein in neurons that regulates storage of dopamine in neuronal vesicles
  - Inhibition of VMAT-2 results in reduction of synaptic dopamine levels

Ingrezza PI 2017

Valbenazine (Ingrezza™)

- Pharmacokinetics
  - Hydrolysis and CYP3A4 metabolism
    - Metabolite further metabolized by CYP2D6
  - Peaks in 0.5-1h (4-8 hours for active metabolite)
  - T ½ 15-22 hours
  - Steady-state in 1 week

Ingrezza PI 2017

Valbenazine (Ingrezza™)

- Contraindications
  - None listed
- Precautions/warnings
  - Somnolence
  - QT prolongation
    - Concern if on a strong CYP3A4 or CYP2D6 inhibitor, poor CYP2D6 metabolizer, or baseline QT prolongation
    - 11.7 msec vs 6.7 msec in poor CYP2D6 metabolizers
  - Not recommended in severe renal impairment
    - CrCl < 30 ml/min

Ingrezza PI 2017

Valbenazine (Ingrezza™)

- Drug interactions
  - Monoamine oxidase inhibitors
    - Concomitant use not recommended
  - Strong CYP3A4 inhibitors (e.g. itraconazole) & CYP2D6 inhibitors (e.g. fluoxetine)
    - Reduce dose
  - Strong CYP3A4 inducers (e.g. phenytoin)
    - Avoid use
  - May increase digoxin levels due to P-glycoprotein inhibition

Reactions from 6-week placebo controlled trials

Reaction	Valbenazine N = 262	Placebo N = 183
Somnolence	10.9%	4.2%
Anticholinergic effects	5.4%	4.9%
Falls/balance issues	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia	2.7%	0.5%
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%

Ingrezza PI 2017

KINECT 3 Trial Data

Measure	Valbenazine 40mg N = 70	Valbenazine 80mg N = 79	Placebo N = 76
Baseline AIMS score	9.8	10.4	9.9
AIMS mean change at 6 weeks	-1.9	-3.2	-0.1
Placebo-difference (95% CI)	-1.8 (-3, -0.7) $p < 0.01$	-3.1 (-4.2,-2.0) $p < 0.001$	N/A

Hauser RA, et al. Am J Psychiatry 2017;174:476-84.

Valbenazine (Ingrezza™)

- Dosing
  - Initially 40 mg once daily with or without food
  - After 1 week increase to 80 mg once daily
  - Dose adjustments
    - Moderate to severe hepatic impairment (40mg daily)
    - CYP3A4 inhibitors (40 mg daily)
    - Poor CYP 2D6 metabolizers (“reduce dose”)
    - CYP2D6 inhibitors (“reduce dose”)
- Cost
  - #30, 40mg capsules = $6330

Ingrezza PI 2017

Valbenazine (Ingrezza™)

- Bottom line
  - First agent approved for tardive dyskinesia
  - Benefit seen as soon as 2 weeks
  - Limited data up to 48 weeks
  - Somnolence most common side effect
- Additional review
  - Citrome L. Int J Clin Pract 2017;e12964.

Delafloxacin is a broad-spectrum fluoroquinolone antibiotic currently approved for pneumonia.

A. True

B. False

Delafloxacin (Baxdela™)

- Indication
  - Acute bacterial skin and skin structure infections
- Pharmacology
  - Fluoroquinolone antimicrobial
  - Lacks strong basic group at the C-7 position
  - “anionic” vs. “zwitterionic”
  - Increased activity in acidic environment

Baxdela PI 2017.
Kocsis, et al. Ann Clin Microbiol Antimicrob 2016;15:34.

Delafloxacin (Baxdela™)

- Spectrum of activity
  - Gram-positive organisms
    - MSSA, MRSA, *Streptococcus pyogenes, E. faecalis*
  - Gram-negative organisms
    - *E. coli. E. cloacae, K. pneumoniae, P. aeruginosa*

Baxdela PI 2017.

Delafloxacin (Baxdela™)

- Pharmacokinetics
  - T ½ ~ 12 hours
  - Oral bioavailability ~ 59%
  - AUC of 450 mg PO similar to 300 mg IV
  - Metabolized primarily via glucuronidation
  - 65% renal elimination
    - Dose adjustments indicated

Baxdela PI 2017.

Delafloxacin (Baxdela™)

- Contraindications
  - Fluoroquinolone allergy
- Warnings and precautions
  - Similar to other fluoroquinolones
  - Tendon rupture, peripheral neuropathy, CNS effects
  - May exacerbate myasthenia gravis
  - *C. difficile*-associated diarrhea
- Drug interactions
  - Antacids, sucralfate, multivitamins

Baxdela PI 2017.

Adverse Reactions from Phase 3 Clinical Trials

Reaction	Delafloxacin N = 741	Vanco/aztreonam N = 751
Nausea	8%	6%
Diarrhea	8%	3%
Headache	3%	6%
Increased transaminases	3%	4%
Vomiting	2%	2%

Baxdela PI 2017.

Clinical Trial Data for Skin Infections

PROCEED 1 Trial	Delafloxacin N = 331	Vancomycin/ aztreonam N = 329	Treatment Difference (95% CI)
*Clinical Response rate	78.2%	80.9%	-2.6 (-8.8, 3.6)
PROCEED 2 Trial	**Delafloxacin N = 423**	**Vancomycin/ aztreonam N = 427**	
*Clinical Response rate	83.7%	80.6%	3.1 (-2.0, 8.3)

Baxdela PI 2017.

Delafloxacin (Baxdela™)

- Dosing
  - IV—300 mg every 12 hours over 60 minutes
  - PO—450mg every 12 hours
  - Duration of 5-14 days
  - Give at least 2 hours before or 6 hours after antacids, sucralfate, metal cations
  - Give with or without food
- Renal impairment (CrCl 15-29 ml/min)
  - IV—200 mg every 12 hours
  - PO—No adjustment
- Avoid in end stage renal disease and dialysis (CrCl < 15 ml/min

Baxdela PI 2017.

Delafloxacin (Baxdela™)

- Bottom line
  - Unique fluoroquinolone for skin infections
  - MRSA activity
  - Similar warnings as other fluoroquinolones
  - Available both IV & PO
- Additional review
  - Kocsis, et al. Ann Clin Microbiol Antimicrob 2016;15:34.

Bezlotoxumab has a lower recurrence rate of Clostridium difficile infections compared to vancomycin.

A. True

B. False

Bezlotoxumab (Zinplava™)

- Indication
  - Reduce recurrence of *Clostridium difficile* infection (CDI)
  - Patients MUST be receiving treatment for *Clostridium difficile* and at high risk of recurrence
  - NOT indicated for the treatment of CDI
- Pharmacology
  - Human monoclonal antibody
  - Binds to *Clostridium difficile* toxin B
  - Not fully understood why it prevents recurrence
- Pharmacokinetics
  - T ½ ~ 19 days

Zinplava PI 2016

Bezlotoxumab (Zinplava™)

- Contraindications
  - None
- Warnings and Precautions
  - Heart failure exacerbations
    - 12.7% (15/118) bezlotoxumab vs. 4.8% (5/104) placebo
  - Deaths in patients with a history of heart failure
    - 19.5% (23/118) bezlotoxumab vs. 12.5% (13/104) placebo
  - Risk vs. benefit
- Drug interactions
  - None identified

Adverse Reactions from Modify I and II Trials

Reaction	Bezlotoxumab N = 786	Placebo N = 781
Overall infusion-related	10%	8%
Nausea	7%	5%
Pyrexia	5%	3%
Headache	4%	3%
Heart failure	2.3%	1%

Zinplava PI 2016

MODIFY I and MODIFY II Efficacy Results

Recurrent CDI	Bezlotoxumab N = 781	Placebo N = 781
Overall*	16.5% (129/781)	26.6% (206/773)
Hx of CDI in past 6 month	25% (54/216)	41.1% (90/219)
Hypervirulent strain	22% (22/100)	32.1% (35/109)
Age ≥ 65 years	15.4% (60/390)	31.4% (127/405)

*primary endpoint; NNT = 10; p-value < 0.0001
All subjects received vancomycin, metronidazole or fidaxomicin for 10-14 days

http://ofid.oxfordjournals.org/content/2/suppl_1/67.full.pdf+html

Bezlotoxumab (Zinplava™)

- Dosing
  - Administer during treatment for CDI
  - Single dose, 10 mg/kg IV infusion over 1 hour
- Availability/storage
  - 1000mg/40ml (25mg/ml) vial stored in refrigerator
  - Dilute in NS or D5 to 1 mg/ml to 10 mg/ml prior to infusion
  - Allow bag to come to room temp prior to use (stable x 16 hours)
  - AWP: $4560 per vial

Zinplava PI 2016

Bezlotoxumab (Zinplava™)

- Bottom line
  - Reduced rate of recurrent CDI vs. placebo
  - Only in conjunction with antibiotic treatment
  - Consider for high risk populations
  - Well-tolerated in trials
  - Caution in heart failure
- Additional review
  - Martin J, Wilcox M. Curr Opin Infect Dis. 2016;29:549-54.

Which of the following is an approved duration of betrixaban?

A. Duration of hospitalization

B. 6 weeks

C. 3 months

D. 6 months

Betrixaban (Bevyxxa®)

- Indication
  - Prophylaxis of venous thromboembolism in hospitalized medical patients

- Pharmacology
  - Factor Xa inhibitor

Betrixaban (Bevyxxa®)

- Pharmacokinetics
  - Peaks in 3-4 hours
  - Food decreases absorption for up to 6 hours after a meal
  - T ½ 19-27 hours
  - 85% GI, 11% renal elimination
  - Minimal metabolism
  - Renal impairment increases AUC 2-3x

Bevxxa PI 2017

Betrixaban (Bevyxxa®)

- Contraindications
  - Active bleeding
- Warnings/precautions
  - Spinal/epidural anesthesia
    - Wait 72 hours after last dose to remove epidural catheters
    - Wait 5 hours after catheter removal before giving next dose
  - Severe renal impairment (CrCl 15-29 ml/min)
  - Hepatic impairment

Bevxxa PI 2017

Betrixaban (Bevyxxa®)

- Drug interactions
  - P-glycoprotein inhibitors
    - Amiodarone, azithromycin, verapamil
    - Requires a dose reduction
  - Other anticoagulants/antiplatelets

APEX Trial Cohort 1	Betrixaban N = 1914	Enoxaparin N = 1956	RR (95% CI)
Composite	6.9%	8.5%	0.81 (0.65-1.00) p = 0.054
Asymptomatic DVT	5.5%	6.6%	NR
Symptomatic DVT	0.7%	0.1%	NR
Non-fatal PE	0.3%	0.9%	NR
VTE-related death	0.6%	0.6%	NR
Symptomatic events	1.3%	1.9%	0.67 (0.42-1.07) p = 0.09

Cohen, et al. N Eng J Med 375:534-44.

Overall Population	Betrixaban N = 3112	Enoxaparin N = 3174	RR (95% CI)
Composite	5.3%	7%	0.76 (0.63-0.92) p = 0.006
Asymptomatic DVT	4.2%	5.5%	NR
Symptomatic DVT	0.4%	0.7%	NR
Non-fatal PE	0.3%	0.6%	NR
VTE-related death	0.4%	0.5%	NR
Symptomatic events	0.9%	1.5%	0.64 (0.42-0.98) P = 0.04
Ischemic stroke	0.48%	0.91%	0.53 (0.3-0.94) p = 0.026

Cohen, et al. N Eng J Med 2016;375:534-44.
Gibson, et al. Ciruculation; 2017;135:648-655.

Overall Safety Outcomes	Betrixaban N = 3716	Enoxaparin N = 3716	RR (95% CI)
Major Bleeding	0.67%	0.57%	1.19 (0.67-2.12) p = 0.55
Gastrointestinal	0.51%	0.24%	NR
Intracranial hemorrhage	0.05%	0.19%	NR
Fatal bleeding	0.03%	0.03%	NR
Major or CRNM Bleeding	3.1%	1.6%	1.97 (1.44-2.68) p < 0.001

Cohen, et al. N Eng J Med 375:534-44.
Bevxxa PI 2017

CRNM = clinically relevant non-major bleeding

Betrixaban (Bevyxxa®)

- Dosing
  - 160 mg x 1 then 80 mg once daily
  - Give with food
  - Duration of 35-42 days
  - If CrCl 15-29 ml/min
    - 80 mg x 1 then 40 mg once daily
  - Concomitant P-gp inhibitor
    - 80mg x 1 then 40 mg once daily

Bevxxa PI 2017

Betrixaban (Bevyxxa®)

- Availability & Cost
  - 40 mg and 80 mg capsules
  - ? Release date

Bevxxa PI 2017

Betrixaban (Bevyxxa®)

- Bottom line
  - First agent approved for extended prophylaxis in hospitalized medically ill patients
  - Use for 35-42 days
  - Watch for renal impairment and P-gp inhibitors
  - Potential to reduce ischemic stroke post hospitalization
- Additional review
  - Quinlan D, et al. Circulation 2017;135:656-658.

Aspirin/Omeprazole (Yosprala™)

- Indication
  - Secondary prevention of cardiovascular and cerebrovascular events in patients at risk for aspirin-associated ulcers
- Dosage form
  - Intelli-COAT system
  - Immediate release omeprazole 40mg
  - Delayed-release, enteric-coated aspirin (dissolves at pH > 5.5)

Yosprala PI 2016.

Cumulative Incidence of Gastric Ulcers

Months	Study 1		Study 2	
	ASA + OME N = 265	EC ASA N = 265	ASA + OME N = 259	EC ASA N = 260
0-1	1.1%	3.8%	0.4%	3.1%
0-3	3%	6.8%	0.4%	6.5%
0-6	3.8%*	8.7%	2.7%**	8.5%

ASA = aspirin; OME = omeprazole; EC = enteric coated

Yosprala PI 2016.

* p-value = 0.02; ** p-value 0.005

Aspirin/Omeprazole (Yosprala™)

- Dosing
  - 81/40 mg
  - 325/40 mg
- Price
  - ~$140 per month
  - ~ $40 for a month of omeprazole 40mg + ASA E.C. 325 mg
- Compliance vs. Cost

Yosprala PI 2016.

www.cardinal.com

Final Exam

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