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INTRODUCING

A New Face of Cure* in HCV

For the treatment of chronic genotype 1 (GT1) hepatitis C virus (HCV) infection—an all-oral, interferon-free regimen with 3 distinct direct-acting antivirals

viekira pak™

ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets

*Cure (virologic cure): sustained virologic response (SVR_{12}); HCV ribonucleic acid (RNA) below the lower limit of quantification (<25 IU/mL) 12 weeks after the end of treatment.

INDICATION[1]

VIEKIRA PAK™, with or without ribavirin (RBV), is indicated for the treatment of adult patients with genotype 1 chronic hepatitis C virus infection, including those with compensated cirrhosis.

Limitation of Use:

VIEKIRA PAK is not recommended for use in patients with decompensated liver disease.

IMPORTANT SAFETY INFORMATION

Risks Associated with RBV Combination Treatment

If VIEKIRA PAK is administered with RBV, the contraindications, warnings and precautions (particularly pregnancy avoidance), and adverse reactions for RBV also apply to this combination regimen. Refer to the RBV prescribing information.

CONTRAINDICATIONS

VIEKIRA PAK is contraindicated:

- in patients with severe hepatic impairment due to risk of potential toxicity.
- with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious and/or life-threatening events; strong inducers of CYP3A or CYP2C8, which may lead to reduced efficacy of VIEKIRA PAK; and strong CYP2C8 inhibitors, which may increase dasabuvir levels and the risk of QT prolongation.
- with the following drugs: alfuzosin HCL; carbamazepine, phenytoin, phenobarbital; gemfibrozil; rifampin; ergotamine, dihydroergotamine, ergonovine, methylergonovine; ethinyl estradiol-containing medicines, such as many oral contraceptives; St. John's wort (*Hypericum perforatum*); lovastatin, simvastatin; pimozide; efavirenz; sildenafil (when dosed as Revatio‡ for pulmonary arterial hypertension); triazolam and oral midazolam.
- in patients with known hypersensitivity (e.g., toxic epidermal necrolysis or Stevens-Johnson syndrome) to ritonavir.

WARNINGS AND PRECAUTIONS

Increased Risk of ALT Elevations

- Elevations of ALT to >5x the ULN occurred in 1% of all subjects in clinical trials and were significantly more frequent in females using ethinyl-estradiol-containing medications. In female patients, discontinue ethinyl estradiol-containing medications prior to starting therapy and use alternative methods of contraception during therapy (e.g., progestin only or non-hormonal contraception). Use caution when co-administering VIEKIRA PAK with estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens.

VIEKIRA PAK +/- ribavirin (RBV) cured* chronic HCV in multiple GT1 patient types, including compensated cirrhotics

VIEKIRA PAK +/- RBV was studied in 6 phase III clinical trials that included >2300 adult patients with chronic GT1 HCV[1]

Across patient populations, pooled by recommended treatment regimen† (n=1084), VIEKIRA PAK +/- RBV delivered consistently high cure* rates ranging from 95%–100%[1,2]

SVR_{12} rates

Overall GT1 Patients Cured[1,2*]

(n=1053/1084)

VIEKIRA PAK ⊕/⊖ RBV

(12 OR 24 WEEKS)

Learn more at viekiraHCP.com

†Recommended regimen=ombitasvir, paritaprevir, ritonavir (25/150/100 mg QD) and dasabuvir (250 mg BID) +/- ribavirin (1000 or 1200 mg determined by body weight; divided BID).[1]

- Perform hepatic lab testing on all patients during the first 4 weeks of treatment and as clinically indicated thereafter. If ALT is elevated above baseline levels, repeat testing and monitor closely. Patients should be instructed to consult their doctor without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces. Consider discontinuing VIEKIRA PAK if ALT levels remain persistently >10x the ULN. Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

- The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK and possible development of resistance, or adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

HCV/HIV-1 Co-infected Patients: Risk of HIV-1 Protease Inhibitor Drug Resistance

- The ritonavir component of VIEKIRA PAK is an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance. To reduce this risk, HCV/HIV-1 co-infected patients should also be on a suppressive antiretroviral drug regimen.

ADVERSE REACTIONS

- In subjects receiving VIEKIRA PAK with RBV, the most commonly reported adverse reactions (>10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. In subjects receiving VIEKIRA PAK without RBV, the most commonly reported adverse reactions (≥5% of subjects) were nausea, pruritus, and insomnia.

‡Revatio® is a trademark of its respective owner and not a trademark of AbbVie Inc. The makers of this brand are not affiliated with and do not endorse AbbVie Inc. or its products.

References: 1. VIEKIRA PAK [package insert]. North Chicago, IL. AbbVie Inc. **2.** Data on file. AbbVie Inc.

Please see Brief Summary of Prescribing Information on the adjacent page(s).

abbvie

VIEKIRA PAK™

(ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets)

PROFESSIONAL BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

Limitation of Use:

VIEKIRA PAK is not recommended for use in patients with decompensated liver disease *[see Use in Specific Populations]*.

CONTRAINDICATIONS

- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- VIEKIRA PAK is contraindicated in patients with severe hepatic impairment due to risk of potential toxicity *[see Use in Specific Populations]*.
- VIEKIRA PAK is contraindicated with:
  - Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Drugs that are strong inducers of CYP3A and CYP2C8 and may lead to reduced efficacy of VIEKIRA PAK.
  - Drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation.

Table 1 lists drugs that are contraindicated with VIEKIRA PAK *[see Drug Interactions]*.

Table 1. Drugs that are Contraindicated with VIEKIRA PAK

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antihyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.
Antimycobacterial	Rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions]*.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA PAK may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

- VIEKIRA PAK is contraindicated in patients with known hypersensitivity (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.

WARNINGS AND PRECAUTIONS

Increased Risk of ALT Elevations

During clinical trials with VIEKIRA PAK with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects *[see Adverse Reactions]*. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing of VIEKIRA PAK with or without ribavirin.

These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with VIEKIRA PAK *[see Contraindications]*. Alternative methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA PAK.

Women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with VIEKIRA PAK *[see Adverse Reactions]*.

Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.
- Consider discontinuing VIEKIRA PAK if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risks Associated With Ribavirin Combination Treatment

If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of VIEKIRA PAK and possible development of resistance
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions]*. Consider the potential for drug interactions prior to and during VIEKIRA PAK therapy; review concomitant medications during VIEKIRA PAK therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications and Drug Interactions]*.

Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-infected Patients

The ritonavir component of VIEKIRA PAK is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with VIEKIRA PAK should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

ADVERSE REACTIONS

If VIEKIRA PAK is administered with ribavirin (RBV), refer to the prescribing information for ribavirin for a list of ribavirin-associated adverse reactions.

The following adverse reaction is described below and elsewhere in the labeling:

- Increased Risk of ALT Elevations *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of VIEKIRA PAK cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment was based on data from six Phase 3 clinical trials in more than 2,000 subjects who received VIEKIRA PAK with or without ribavirin for 12 or 24 weeks.

VIEKIRA PAK with Ribavirin in Placebo-Controlled Trials

The safety of VIEKIRA PAK in combination with ribavirin was assessed in 770 subjects with chronic HCV infection in two placebo-controlled trials (SAPPHIRE-I and -II). Adverse reactions that occurred more often in subjects treated with VIEKIRA PAK in combination with ribavirin compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia (see Table 2). The majority of the adverse reactions were mild in severity. Two percent of subjects experienced a serious adverse event (SAE). The proportion of subjects who permanently discontinued treatment due to adverse reactions was less than 1%.

Table 2. Adverse Reactions with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to Placebo for 12 Weeks

	SAPPHIRE-I and -II	
	VIEKIRA PAK + RBV 12 Weeks N = 770 %	Placebo 12 Weeks N = 255 %
Fatigue	34	26
Nausea	22	15
Pruritus*	18	7
Skin reactions[$]	16	9
Insomnia	14	8
Asthenia	14	7

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

[$]Grouped terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, dermatitis, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria.

VIEKIRA PAK with and without Ribavirin in Regimen-Controlled Trials

VIEKIRA PAK with and without ribavirin was assessed in 401 and 509 subjects with chronic HCV infection, respectively, in three clinical trials (PEARL-II, PEARL-III and PEARL-IV). Pruritus, nausea, insomnia, and asthenia were identified as adverse events occurring more often in subjects treated with VIEKIRA PAK in combination with ribavirin (see Table 3). The majority of adverse events were mild to moderate in severity. The proportion of subjects who permanently discontinued treatment due to adverse events was less than 1% for both VIEKIRA PAK in combination with ribavirin and VIEKIRA PAK alone.

Table 3. Adverse Events with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to VIEKIRA PAK for 12 Weeks

	PEARL-II, -III and -IV	
	VIEKIRA PAK + RBV 12 Weeks N = 401 %	VIEKIRA PAK 12 Weeks N = 509 %
Nausea	16	8
Pruritus*	13	7
Insomnia	12	5
Asthenia	9	4

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

VIEKIRA PAK with Ribavirin in Subjects with Compensated Cirrhosis

VIEKIRA PAK with ribavirin was assessed in 380 subjects with compensated cirrhosis who were treated for 12 (n=208) or 24 (n=172) weeks duration (TURQUOISE-II). The type and severity of adverse events in subjects with compensated cirrhosis was comparable to non-cirrhotic subjects in other phase 3 trials. Fatigue, skin reactions and dyspnea occurred at least 5% more often in subjects treated for 24 weeks. The majority of adverse events occurred during the first 12 weeks of dosing in both treatment arms. Most of the adverse events were mild to moderate in severity. The proportion of subjects treated with VIEKIRA PAK for 12 and 24 weeks with SAEs was 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.

Skin Reactions

In PEARL-II, -III and -IV, 7% of subjects receiving VIEKIRA PAK alone and 10% of subjects receiving VIEKIRA PAK with ribavirin reported rash-related events. In SAPPHIRE-I and -II 16% of subjects receiving VIEKIRA PAK with ribavirin and 9% of subjects receiving placebo reported skin reactions. In TURQUOISE-II, 18% and 24% of subjects receiving VIEKIRA PAK with ribavirin for 12 or 24 weeks reported skin reactions. The majority of events were graded as mild in severity. There were no serious events or severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS).

Laboratory Abnormalities

Serum ALT Elevations

Approximately 1% of subjects treated with VIEKIRA PAK experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. The incidence increased to 25% (4/16) among women taking a concomitant ethinyl estradiol containing medication *[see Contraindications and Warnings and Precautions]*. The incidence of clinically relevant ALT elevations among women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy was 3% (2/59).

ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range 8-57 days) and most resolved with ongoing therapy. The majority of these ALT elevations were assessed as drug-related liver injury. Elevations in ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT *[see Warnings and Precautions]*.

Serum Bilirubin Elevations

Post-baseline elevations in bilirubin at least 2 x ULN were observed in 15% of subjects receiving VIEKIRA PAK with ribavirin compared to 2% in those receiving VIEKIRA PAK alone. These bilirubin increases were predominately indirect and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with serum ALT elevations.

Anemia/Decreased Hemoglobin

Across all Phase 3 studies, the mean change from baseline in hemoglobin levels in subjects treated with VIEKIRA PAK in combination with ribavirin was -2.4 g/dL and the mean change in subjects treated with VIEKIRA PAK alone was -0.5 g/dL. Decreases in hemoglobin levels occurred early in treatment (Week 1-2) with further reductions through Week 3. Hemoglobin values remained low during the remainder of treatment and returned towards baseline levels by post-treatment Week 4. Less than 1% of subjects treated with VIEKIRA PAK with ribavirin had hemoglobin levels decrease to less than 8.0 g/dL during treatment. Seven percent of subjects treated with VIEKIRA PAK in combination with ribavirin underwent a ribavirin dose reduction due to a decrease in hemoglobin levels; three subjects received a blood transfusion and five required erythropoietin. One patient discontinued therapy due to anemia. No subjects treated with VIEKIRA PAK alone had a hemoglobin level less than 10 g/dL.

VIEKIRA PAK in HCV/HIV-1 Co-infected Subjects

VIEKIRA PAK with ribavirin was assessed in 63 subjects with HCV/HIV-1 co-infection who were on stable antiretroviral therapy. The most common adverse events occurring in at least 10% of subjects were fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%).

Elevations in total bilirubin greater than 2 x ULN (mostly indirect) occurred in 34 (54%) subjects. Fifteen of these subjects were also receiving atazanavir at the time of bilirubin elevation and nine also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases *[see Warnings and Precautions and Adverse Reactions]*. No subject experienced a grade 3 ALT elevation.

Seven subjects (11%) had at least one post-baseline hemoglobin value of less than 10 g/dL, and six of these subjects had a ribavirin dose modification; no subject in this small cohort required a blood transfusion or erythropoietin.

Median declines in CD4+ T-cell counts of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively, and most returned to baseline levels post-treatment. Two subjects had CD4+ T-cell counts decrease to less than 200 cells/mm^3 during treatment without a decrease in CD4%. No subject experienced an AIDS-related opportunistic infection.

VIEKIRA PAK in Selected Liver Transplant Recipients

VIEKIRA PAK with ribavirin was assessed in 34 post-liver transplant subjects with recurrent HCV infection. Adverse events occurring in more than 20% of subjects included fatigue 50%, headache 44%, cough 32%, diarrhea 26%, insomnia 26%, asthenia 24%, nausea 24%, muscle spasms 21% and rash 21%. Ten subjects (29%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten subjects underwent a ribavirin dose modification due to decrease in hemoglobin and 3% (1/34) had an interruption of ribavirin. Five subjects received erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion.

DRUG INTERACTIONS

See also Contraindications and Warnings and Precautions.

Potential for VIEKIRA PAK to Affect Other Drugs

Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration of VIEKIRA PAK with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

Potential for Other Drugs to Affect One or More Components of VIEKIRA PAK

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. Co-administration of VIEKIRA PAK with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Dasabuvir is primarily metabolized by CYP2C8 enzymes. Co-administration of VIEKIRA PAK with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. Ombitasvir, paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of the various components of VIEKIRA PAK.

Established and Other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with VIEKIRA PAK, doses should be re-adjusted after administration of VIEKIRA PAK is completed. Dose adjustment is not required for VIEKIRA PAK.

Table 4 provides the effect of co-administration of VIEKIRA PAK on concentrations of concomitant drugs and the effect of concomitant drugs on the various components of VIEKIRA PAK. See *Contraindications* for drugs that are contraindicated with VIEKIRA PAK. Refer to the ritonavir prescribing information for other potentially significant drug interactions with ritonavir.

Table 4. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
ANTIARRHYTHMICS		
amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with VIEKIRA PAK.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	When VIEKIRA PAK is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.
voriconazole	↓ voriconazole	Co-administration of VIEKIRA PAK with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
CALCIUM CHANNEL BLOCKERS		
amlodipine	↑ amlodipine	Consider dose reduction for amlodipine. Clinical monitoring is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone	↑ fluticasone	Concomitant use of VIEKIRA PAK with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide (C_{max})	Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.
HIV-ANTIVIRAL AGENTS		
atazanavir/ ritonavir once daily	↑ paritaprevir	When coadministered with VIEKIRA PAK, atazanavir 300 mg (without ritonavir) should only be given in the morning.
darunavir/ ritonavir	↓ darunavir (C_{trough})	Co-administration of VIEKIRA PAK with darunavir/ritonavir is not recommended.
lopinavir/ ritonavir	↑ paritaprevir	Co-administration of VIEKIRA PAK with lopinavir/ritonavir is not recommended.
rilpivirine	↑ rilpivirine	Co-administration of VIEKIRA PAK with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
HMG CoA REDUCTASE INHIBITORS		
rosuvastatin	↑ rosuvastatin	When VIEKIRA PAK is co-administered with rosuvastatin, the dose of rosuvastatin should not exceed 10 mg per day.

(continued)

Table 4. *continued*

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
HMG CoA REDUCTASE INHIBITORS		
pravastatin	↑ pravastatin	When VIEKIRA PAK is co-administered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When initiating therapy with VIEKIRA PAK, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
tacrolimus	↑ tacrolimus	When initiating therapy with VIEKIRA PAK, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day VIEKIRA PAK is initiated. Beginning the day after VIEKIRA PAK is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.
LONG ACTING BETA-ADRENOCEPTOR AGONIST		
salmeterol	↑ salmeterol	Concurrent administration of VIEKIRA PAK and salmeterol is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS		
buprenorphine/ naloxone	↑ buprenorphine ↑ norbuprenorphine	No dose adjustment of buprenorphine/ naloxone is required upon co-administration with VIEKIRA PAK. Patients should be closely monitored for sedation and cognitive effects.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.

The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC) (↑ = *increase of more than 20%*, ↓ = *decrease of more than 20%*, ↔ = *no change or change less than 20%*).

Drugs without Clinically Significant Interactions with VIEKIRA PAK

No dose adjustments are recommended when VIEKIRA PAK is co-administered with the following medications: digoxin, duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, methadone, progestin only contraceptives, raltegravir, warfarin and zolpidem.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Pregnancy Exposure Registry

There is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Adequate and well controlled studies with VIEKIRA PAK have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir, ritonavir (mice and rats), or dasabuvir (rats and rabbits) at exposures higher than the recommended clinical dose [see Data]. Because animal reproduction studies are not always predictive of human response, VIEKIRA PAK should be used during pregnancy only if clearly needed.

If VIEKIRA PAK is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir, ritonavir, or dasabuvir. For ombitasvir, the highest dose tested produced exposures approximately 28-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26-fold the exposures in humans at the recommended clinical dose. For paritaprevir, ritonavir, the highest doses tested produced exposures approximately 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures approximately 48-fold (rat) or 12-fold (rabbit) the exposures in humans at the recommended clinical dose.

Nursing Mothers

It is not known whether any of the components of VIEKIRA PAK or their metabolites are present in human milk. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIEKIRA PAK and any potential adverse effects on the breastfed child from VIEKIRA PAK or from the underlying maternal condition.

If VIEKIRA PAK is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen (see prescribing information for ribavirin).

Pediatric Use

Safety and effectiveness of VIEKIRA PAK in pediatric patients less than 18 years of age have not been established.

Geriatric Use

No dosage adjustment of VIEKIRA PAK is warranted in geriatric patients. Of the total number of subjects in clinical studies of VIEKIRA PAK, 8.5% (174/2053) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK is not recommended in HCV-infected patients with moderate hepatic impairment (Child-Pugh B). VIEKIRA PAK is contraindicated in patients with severe (Child-Pugh C) hepatic impairment *[see Contraindications]*.

Renal Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild, moderate or severe renal impairment. VIEKIRA PAK has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for information regarding use in patients with renal impairment.

Other HCV Genotypes

The safety and efficacy of VIEKIRA PAK has not been established in patients with HCV genotypes other than genotype 1.

OVERDOSAGE

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients to review the Medication Guide for ribavirin *[see Warnings and Precautions]*.

Risk of ALT Elevations

Inform patients to watch for early warning signs of liver inflammation, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discolored feces, and to consult their health care professional without delay if such symptoms occur *[see Warnings and Precautions and Adverse Reactions]*.

Pregnancy

Advise patients to avoid pregnancy during treatment with VIEKIRA PAK with ribavirin. Inform patients to notify their health care provider immediately in the event of a pregnancy. Inform pregnant patients that there is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals *[see Use in Specific Populations]*.

Drug Interactions

Inform patients that VIEKIRA PAK may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products *[see Contraindications, Warnings and Precautions, and Drug Interactions]*.

Inform patients that contraceptives containing ethinyl estradiol are contraindicated with VIEKIRA PAK *[see Contraindications and Warnings and Precautions]*.

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C virus infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment should be taken.

Missed Dose

Inform patients that in case a dose of ombitasvir, paritaprevir, ritonavir is missed, the prescribed dose can be taken within 12 hours.

In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours.

If more than 12 hours has passed since ombitasvir, paritaprevir, ritonavir is usually taken or more than 6 hours has passed since dasabuvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

Instruct patients not to take more than their prescribed dose of VIEKIRA PAK to make up for a missed dose.

Manufactured by AbbVie Inc., North Chicago, IL 60064.

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GASTROENTEROLOGY & HEPATOLOGY

THE GASTRO & HEP REPORT

Comprehensive Reports on the Latest Advances in Gastroenterology & Hepatology From:

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  October 17-22, 2014 • Philadelphia, Pennsylvania

- 65th Annual Meeting of the American Association for the Study of Liver Diseases

  November 7-11, 2014 • Boston, Massachusetts

- Advances in Inflammatory Bowel Diseases Conference

  December 4-6, 2014 • Orlando, Florida

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Presentations in GERD

Implanted Device Restores Lower Esophageal Sphincter Function and Improves Quality of Life

The magnetic sphincter augmentation device is used to restore functioning of the lower esophageal sphincter and is an alternative to tissue fundoplication. At the American College of Gastroenterology (ACG) Annual Scientific Meeting, Philip Katz, MD, of the Einstein Medical Center Philadelphia in Philadelphia, Pennsylvania presented clinical findings in patients with gastroesophageal reflux disease (GERD) who were implanted with a magnetic sphincter augmentation device (Abstract 42).

The study included patients with chronic GERD who had an incomplete response to proton pump inhibitors (PPIs), abnormal acid exposure, small or no hiatal hernia, no Barrett esophagus, normal motility, and esophagitis of Los Angeles grade B or lower. All patients completed a GERD health-related quality of life (HRQL) questionnaire at baseline, while they were still taking PPIs. The questionnaire was again completed 4 years after implantation of a magnetic sphincter augmentation device, when patients were not taking PPIs. The GERD-HRQL score ranges from 0 to 50, with a higher number indicating worse symptoms.

Data were available for 86 patients. GERD-HRQL scores at baseline (when patients were receiving PPIs) were compared with scores 4 years after implantation of a magnetic sphincter augmentation device (when patients were not receiving PPIs). At 4 years postimplantation, the median total GERD-HRQL score improved from 11 to 4 (P<.0001; Table 1). For heartburn-related questions, the median GERD-HRQL score improved from 8 to 3 (P<.0001). The percentage of patients experiencing heartburn causing them to wake from sleep each night improved from 14% to 1% (P=.004). Many more patients reported being "satisfied" (84% vs 13% [P<.0001]). The percentage of patients with bothersome swallowing occurring daily increased from 2% to 7%, but this change was not significant (P=.10). Complaints of bothersome gas or bloating occurring at least daily decreased from 17% to 8%, but the difference was not significant (P=.11). The ability to belch or vomit was retained by 98% and 96% of patients, respectively.

Table 1. Improvement After Magnetic Sphincter Augmentation for GERD

Evaluation	Baseline on PPIs	4-Year Follow-Up Off PPIs	*P* Value
Median total GERD-HRQL score	11	4	<.0001
Median GERD-HRQL score for heartburn questions	8	3	<.0001
Patients waking nightly with heartburn (%)	14	1	.004
Patients satisfied with their present condition (%)	13	84	<.0001

GERD-HRQL, gastroesophageal reflux disease health-related quality of life; PPIs, proton-pump inhibitors.

Data from Katz P et al. ACG abstract 42. Presented at: ACG 2014 Annual Scientific Meeting; October 17-22, 2014; Philadelphia, PA.

Radiofrequency Ablation for GERD

Although the majority of GERD cases can be adequately controlled with medication, many patients require further treatment. Radiofrequency ablation with the Stretta system was recently recommended for GERD in guidelines issued by the Society of American Gastrointestinal Endoscopic Surgeons. At the ACG meeting, Seth Lipka, MD, of the Morsani College of Medicine, University of South Florida in Tampa, Florida presented results from a systematic review evaluating the efficacy of the Stretta device for managing GERD (Abstract 40).

Published studies were identified in a search of MEDLINE and the Cochrane Central Register of Controlled Trials from inception until February 28, 2014. Data were pooled using a random effects model. The primary outcomes were physiologic parameters of GERD, including normalization of esophageal pH and augmentation of lower esophageal sphincter pressure. Secondary outcomes included frequency of the use of PPIs and HRQL.

The analysis included 4 trials with a total of 168 patients. Three trials compared the Stretta system vs sham therapy, and 1 trial compared the Stretta system vs PPI therapy. Pooled results yielded no difference between Stretta treatment and sham or PPI therapy for all outcomes.

The studies had several methodologic shortcomings, including failure to provide details on blinding to treatment and failure to report outcomes data. None of the studies reported the proportion of patients who experienced a complete alleviation of GERD symptoms, normalization of esophageal pH, or augmentation of lower esophageal sphincter pressure. The authors concluded

that future studies are needed to characterize the physiologic mechanisms invoked by the Stretta device, and that a high-quality randomized controlled trial is still needed to evaluate the efficacy of this treatment.

Transoral Esophagogastric Fundoplication Effectively Treats GERD Symptoms That Persist Despite PPI Therapy

For some GERD patients with persistent symptoms despite PPI treatment, transoral esophagogastric fundoplication can decrease or eliminate symptoms. At the ACG meeting, Peter Kahrilas, MD, of Northwestern University in Chicago, Illinois presented findings from a study evaluating the efficacy of transoral esophagogastric fundoplication vs PPIs in controlling regurgitation in patients with well-documented GERD (Abstract 41).

The RESPECT (Randomized EsophyX Versus Sham, Placebo-Controlled Transoral Fundoplication) trial was conducted at 8 academic and community medical centers across the United States. After screening 696 patients for GERD symptoms, the trial enrolled 129 patients with proven GERD and a hiatal hernia of 2 cm or less. Patients were randomized 2:1 to receive either transoral esophagogastric fundoplication and 6 months of placebo, or sham surgery and 6 months of omeprazole (40 mg once or twice daily). Assessments were performed at 2, 12, and 26 weeks. The primary study endpoint was the elimination of troublesome regurgitation.

After 6 months, 54 of 80 patients (68%) receiving transoral esophagogastric fundoplication plus placebo reported elimination of troublesome regurgitation compared with 17 of 37 patients (46%) receiving the sham treatment plus PPI (P=.041). Transoral esophagogastric fundoplication was associated with decreased intra-esophageal acid exposure by all parameters measured (P<.001). No improvement in pH was observed in the sham surgery patients. Dysphagia and bloating improved in both groups. Adverse events (AEs) were similar in both arms, with the exception of postoperative epigastric pain and early treatment failure, which were more common in patients randomized to sham surgery.

GERD Symptoms Are More Likely in Patients With Increased Abdominal Obesity Despite Normal Body Mass Index

At the ACG meeting, Shahid Karim, MBBS, of the Liaquat National Hospital and Medical College in Karachi, Sindh, Pakistan described results of a study evaluating whether GERD symptoms correlate to increased abdominal obesity despite a normal body mass index in a multiethnic South Asian population (Abstract P623). The prospective, cross-sectional, multicenter study was conducted from February 2009 to March 2010. The study enrolled nonsmoking, nonalcoholic patients with a normal body mass index, defined as 18.5 to 22.9 kg/m^2 for Asians. Study subjects completed a validated questionnaire to assess the presence of GERD symptoms. Abdominal obesity was defined as waist circumference of at least 90 cm and waist:hip ratio greater than 0.90. Patient data were categorized based on a waist size of 79 cm or less (group A), 80 cm to 90 cm (group B), and 90 cm or greater (group C), and by a waist:hip ratio of 0.90 or less (group 1) vs greater than 0.90 (group 2).

The study included 1260 subjects with a mean age of 36.33 years. GERD symptoms were present in 42.2%. The waist circumference groups A, B, and C included 477, 349, and 434 patients, respectively. The proportion of patients with GERD symptoms rose with increasing waist circumference. GERD symptoms were reported by 30.2% of group A, 37.3% of group B, and 59.5% of group C. The increases were significant between group A vs group B (odds ratio [OR], 1.37; 95% CI, 1.03-1.84; P=.034) and group A vs group C (OR, 3.39; 95% CI, 2.56-4.45; P=.001). Study subjects with the higher waist:hip ratio had significantly more GERD symptoms (OR, 2.03; 95% CI, 1.61-2.56; P=.001). GERD symptoms were present in 32.9% of group 1 and 49.9% of group 2.

A Simple Scoring System to Distinguish Functional Dyspepsia From GERD

The majority of patients who present with epigastric pain have functional dyspepsia and not GERD. However, a misdiagnosis of GERD is common among these patients. Currently, a GERD diagnosis requires the finding of esophagitis based on upper endoscopy or a positive result from a 24-hour pH study. A simpler means for distinguishing between functional dyspepsia and GERD is needed. At the ACG meeting, Neil Marya, MD, of the University of Massachusetts at Worcester described a new scoring system, known as GERDYS, which is based on clinical symptoms to help providers distinguish between functional dyspepsia and GERD (Abstract P1230).

The study retrospectively identified 34 consecutive patients who underwent 24-hour pH monitoring for evaluation of epigastric discomfort. The GERDYS score ranged from -3 to 3. Patient scores increased by 1 point each for ascending chest pain, intermittent symptoms, or nocturnal waking. Scores were reduced by 1 point each for the presence of continuous symptoms, nausea, or bloating. Patients were separated into cohorts based on DeMeester scores of 14.7 or higher for the GERD cohort and scores below 14.7 for the functional dyspepsia cohort.

Based on the DeMeester score, 12 patients were diagnosed with functional dyspepsia and 22 with GERD.

GERDYS scores ranged from -1 to 0 for the functional dyspepsia group and from 0 to 3 for the GERD group. A 1-way analysis of variance revealed a significant difference in patient DeMeester scores by GERDYS scores (*P*=.04). Chi-square analysis demonstrated a significant difference in GERDYS scores for the functional dyspepsia cohort vs the GERD cohort (chi-square value, 14.82; *P*=.005).

The GERDYS score represents the first attempt to provide a quantitative scoring system to distinguish functional dyspepsia from GERD based on clinical criteria. Prospective validation of the GERDYS scoring system could lead to improved identification and management of functional dyspepsia and GERD.

Topical Corticosteroids Improve Histologic But Not Clinical Symptoms in Patients With Eosinophilic Esophagitis

Eosinophilic esophagitis has gained recognition as a clinicopathologic condition characterized by esophageal dysfunction. It is associated with an eosinophil-predominant inflammation of the esophageal mucosa that does not respond to PPI treatment. Topical corticosteroids have shown efficacy in eosinophilic esophagitis and are recommended as a first-line therapy. At the ACG meeting, Ashutosh Gupta, MD, of the John H. Stroger Hospital of Cook County in Chicago, Illinois presented results of a systematic review and meta-analysis investigating the efficacy of topical corticosteroids in treating eosinophilic esophagitis (Abstract 37).

A systematic search of databases from MEDLINE, PubMed, SCOPUS, and the Cochrane library was conducted to identify studies investigating the efficacy of oral viscous budesonide or fluticasone in inducing histologic and clinical remission in children and adults with eosinophilic esophagitis. Only randomized, placebo-controlled trials were included.

The analysis identified 5 studies including 161 patients with a clinical and histologic diagnosis of eosinophilic esophagitis. Fluticasone was administered in 3 studies (n=101), and oral viscous budesonide was administered in 2 studies (n=60). Compared with placebo, topical corticosteroids were associated with a higher rate of complete histologic remission (OR, 20.81; 95% CI, 7.03-61.63) as well as partial histologic remission (OR, 32.20; 95% CI, 6.82-152.04). Corticosteroids were associated with a nonsignificant improvement over placebo for clinical symptoms—defined as an improvement in dysphagia or composite scores of upper gastrointestinal (GI) symptoms (OR, 2.72; 95% CI, 0.90-8.23).

Presentations in IBS

Rifaximin Treatment Can Be Successfully Repeated to Treat Patients With IBS-D Symptoms

Final data from the TARGET 3 (Targeted, Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for Non-C IBS) study demonstrated for the first time that rifaximin treatment can be repeated to successfully re-treat patients with recurrent diarrhea-predominant irritable bowel syndrome (IBS-D). Findings from the TARGET 3 trial were presented by Anthony Lembo, MD, of Beth Israel Deaconess Medical Center in Boston, Massachusetts at the ACG 2014 Annual Scientific Meeting (Abstract 45).

The study enrolled IBS-D patients who met the Rome III criteria. All patients were experiencing IBS-related abdominal pain and bloating. During the 7-day baseline period, the patients had at least 2 bowel movements that corresponded to type 6 or 7 on the Bristol Stool Scale. During the initial 14-day open-label phase, patients were treated with rifaximin (550 mg 3 times daily), followed by a 4-week treatment-free follow-up period to assess response. The composite primary endpoint, as required by the US Food and Drug Administration (FDA), was a decrease from baseline of at least 30% in the mean abdominal pain score and a decrease from baseline of at least 50% in the number of days per week that stool consistency can be categorized as type 6 or 7 on the Bristol Stool Scale.

Of the 2579 patients enrolled during the open-label phase, 1074 (42%) responded. Recurrent IBS-D symptoms were reported in 692 of these responding patients (64%); 636 were randomized to receive rifaximin retreatment (n=328) or placebo (n=308) for 14 days followed by a 4-week treatment-free period. Rifaximin induced significantly more responses compared with placebo (33% vs 25%; P=.02). During the second double-blind retreatment phase, rifaximin was again associated with a significantly greater proportion of responders (37% vs 29%; P=.04). The key secondary endpoint of prevention of recurrence also favored rifaximin (13.2% vs 7.1%; P=.0068). AEs were similar in the 2 treatment groups.

Plecanatide Demonstrates Efficacy at Tolerable Doses in Patients With IBS-C

Plecanatide is a minimally absorbed peptide of uroguanylin, the ligand for the human intestinal guanylate cyclase-C receptor. At the ACG meeting, Philip Miner, Jr, MD, of the Oklahoma Foundation for Digestive Research in Oklahoma City, Oklahoma presented results from a dose-finding clinical trial that assessed the safety and efficacy of plecanatide (Abstract 14).

The trial was a multicenter, double-blind, placebo-controlled, parallel-group study of 424 patients with constipation-predominant IBS (IBS-C). Patients were randomized to receive placebo or oral plecanatide dosed at 0.3 mg, 1.0 mg, 3.0 mg, or 9.0 mg once daily for 12 weeks. The primary efficacy endpoint was the change from baseline in complete spontaneous bowel movements. Key secondary efficacy endpoints included the change from baseline in worst abdominal pain intensity; the FDA's overall responder endpoint for IBS-C; and the change in stool consistency using the Bristol Stool Scale.

All but the lowest dose of plecanatide yielded improvement in the weekly frequency of complete spontaneous bowel movements compared with placebo, with increases of 2.12, 2.74, and 2.44 for plecanatide doses of 1.0 mg, 3.0 mg, and 9.0 mg, respectively (P≤.05 for each comparison). Plecanatide dosed at 3.0 mg daily significantly improved the secondary endpoints of change from baseline of worst abdominal pain intensity, FDA overall responder endpoint, and stool consistency and straining. The most common AE was diarrhea, which was observed in 9.4%, 9.3%, and 11.8% of patients at the plecanatide doses of 1.0 mg, 3.0 mg, and 9.0 mg, respectively.

Urgency as a Measure of Eluxadoline Treatment Effect

Eluxadoline is a locally acting μ-opioid receptor agonist and δ-opioid receptor antagonist that has been shown to improve symptoms associated with IBS-D in 2 randomized, double-blind, phase 3 clinical trials. These trials showed that eluxadoline yielded higher responder rates with concomitant improvements in stool consistency and pain at weeks 12 and 26 compared with placebo. At the ACG 2014 meeting, Anthony Lembo, MD, of Beth Israel Deaconess Medical Center in Boston, Massachusetts presented results of a post hoc study of phase 3 data, which evaluated urgency-free days as reported in patient diaries to assess treatment effect (Abstract 13).

The study pooled data from 2324 patients diagnosed with IBS-D from the phase 3 trials of eluxadoline. During the primary treatment period of 26 weeks, patients completed daily diaries to record IBS-D symptoms. Patients

were considered responders if they were free of urgency on at least half of the days. Cumulative distribution functions for urgency-free days showed differentiation between eluxadoline (75 mg or 100 mg) vs placebo for weeks 1 to 12 and weeks 1 to 26. At the median and 75th percentile of the populations, treatment with eluxadoline showed a 16% to 18% increase in days without urgency. Moderate correlations were observed between the definition of responder used in the study and the FDA's responder endpoint (for 50% of trial weeks, patients report ≥30% decrease in abdominal pain at its worst and, in the same week, an increase in complete spontaneous bowel movements of ≥1 from baseline). The measurement of urgency-free days may provide a valuable addition to the assessment of IBS-D severity and treatment outcome. Eluxadoline demonstrated a significant reduction in urgency over placebo.

Social Stress and Sex Differences in IBS

Approximately two-thirds of IBS patients are female. At the ACG 2014 meeting, Elyse Thakur, MA, of Wayne State University in Detroit, Michigan presented results of a study examining whether personal stress differed in female vs male IBS patients (Abstract P506).

The study included 284 patients with Rome III IBS, 80% of whom were female. The patients' median age was 41 years. All patients completed tests assessing social support (Interpersonal Support Evaluation List), interpersonal problems (Inventory of Interpersonal Problems), negative interactions (Negative Interaction Scale), and IBS symptom severity during the baseline phase of a trial conducted by the National Institutes of Health.

Overall, interpersonal distress was similar for male and female IBS patients. In the test assessing personal problems, men were more likely to report concerns with fighting with other people and keeping other people at a distance, which reflects a hostile-dominant interpersonal pattern. Male patients with vindictive and/or self-centered interpersonal problems reported less support and more negative interactions than female patients. Male patients generally reported less social support. The quality of relationship problems correlated with IBS symptom severity as measured by gastroenterologists but not patients. The increased interpersonal difficulties in male IBS patients may influence estimations of symptoms and impact the doctor-patient relationship.

Polyethylene Glycol Vs Antibiotics for Treating IBS-C Patients With a Positive Lactulose Breath Test

Although antibiotics are commonly prescribed for treating IBS-C, polyethylene glycol has demonstrated efficacy for treating IBS-C and represents an attractive alternative, due to its low cost and favorable side effect profile. At the ACG 2014 meeting, Bingru Xie, MD, of the University of Medicine and Dentistry in Newark, New Jersey presented findings of a study comparing polyethylene glycol vs antibiotics for the treatment of patients with IBS-C as confirmed by a lactulose breath test (Abstract P494).

A review of medical records from 2011 to 2013 at the authors' GI treatment center yielded 36 patients with an IBS-C diagnosis based on the Rome III criteria and positive results on a lactulose breath test. Ten patients received polyethylene glycol, and 12 patients received antibiotics for 14 days. The lactulose breath test was used to evaluate levels of CH_4, H_2, and CO_2 at baseline, and again at 60 minutes and 120 minutes after ingestion of lactulose. The test was administered before treatment and 2 weeks after.

Before polyethylene glycol treatment, the lactulose breath test showed a mean H_2 increase of 17.6 ppm and a mean CH_4 increase of 25.4 ppm at 60 minutes. After treatment with polyethylene glycol, the test showed a mean H_2 increase of 9.2 ppm and a mean CH_4 decrease of 24 ppm at 60 minutes. Lactulose breath testing before antibiotic treatment showed a mean H_2 increase of 12 ppm and a mean CH_4 increase of 33 ppm at 60 minutes. After antibiotic treatment, the test showed a mean H_2 increase of 8.4 ppm and a mean CH_4 decrease of 1.03 ppm at 60 minutes. Therefore, the mean H_2 level and the mean CH_4 level were reduced from baseline in both groups after treatment. When the differences in levels of H_2 and CH_4 before and after treatment were compared for the 2 treatment groups, polyethylene glycol yielded the greater improvement for CH_4 levels ($P<.05$). Reductions in H_2 levels, however, were similar ($P>.05$).

For the treatment of HCV in GT 1 patients

HARVONI®

ledipasvir/sofosbuvir
90 mg/400 mg tablets

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INDICATION

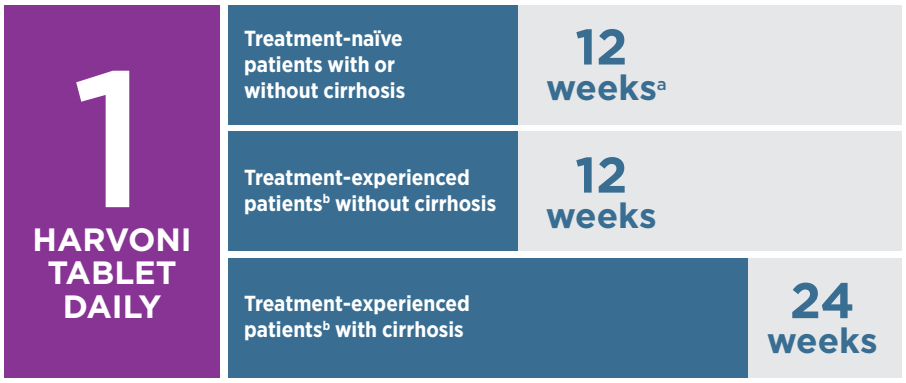
HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

Please see Brief Summary of full Prescribing Information on the following pages.

harvoni.com/hcp

HARVONI is a once-daily single-tablet regimen for HCV GT 1 patients[1]

Recommended treatment duration for HARVONI[1]



[a]HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.[1]

[b]Treatment-experienced patients who failed treatment with either peginterferon (Peg-IFN) alfa + ribavirin (RBV) or an HCV protease inhibitor + Peg-IFN + RBV.[1]

HCV = hepatitis C virus

HARVONI is the first and only IFN- and RBV-free regimen available in one tablet taken once a day[1]

- HARVONI is IFN- and RBV-free for GT 1 treatment-naïve and treatment-experienced patients with or without cirrhosis, regardless of GT 1a or 1b subtype[1]
- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]
- HARVONI can be taken with or without food[1]
- Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups[1]
- No dose adjustments are required based on advanced age, mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment. The safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis[1]
- No dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite[1]

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir (SOVALDI®).

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue and headache.

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

harvoni.com/hcp

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:

Risk of Reduced Therapeutic Effect Due to P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir (SOVALDI®) is not recommended.

ADVERSE REACTIONS:

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=215), 12 (N=539) and 24 (N=326) weeks. Adverse events led to permanent treatment discontinuation in 0%, <1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively.

Adverse Reactions (adverse events assessed as causally related by the investigator): The most common adverse reactions (≥10%; all grades) were fatigue and headache. Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

- *HARVONI for 8 weeks:* fatigue (16%); headache (11%); nausea (6%); diarrhea (4%); and insomnia (3%)
- *HARVONI for 12 weeks:* fatigue (13%); headache (14%); nausea (7%); diarrhea (3%); and insomnia (5%)
- *HARVONI for 24 weeks:* fatigue (18%); headache (17%); nausea (9%); diarrhea (7%); and insomnia (6%)

Direct comparison across trials should not be made due to differing trial designs.

Laboratory Abnormalities: *Bilirubin Elevations:* Bilirubin elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Lipase Elevations:*** Transient, asymptomatic lipase elevations of greater than 3x ULN were observed in <1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Creatine Kinase:*** Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive. **An alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:**

- **Acid Reducing Agents:** Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration.
  - *Antacids:* Separate HARVONI and antacid administration by 4 hours.
  - *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI.
  - *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
- **Antiarrhythmics (digoxin):** Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HIV Antiretrovirals**
  - *Regimens containing tenofovir disoproxil fumarate (DF) and an HIV protease inhibitor/ritonavir (emtricitabine/tenofovir DF plus atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir):* The safety of increased tenofovir concentrations has not been established.

Brief Summary (cont.)

Consider alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

- *Efavirenz/emtricitabine/tenofovir DF:* Monitor for tenofovir-associated adverse reactions. Refer to VIREAD, TRUVADA or ATRIPLA prescribing information for renal monitoring recommendations.
- *Elvitegravir/cobicistat/emtricitabine/tenofovir DF:* The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.
- *Tipranavir/ritonavir:* Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

- **HCV Products (simeprevir):** Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin):** Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs individually: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir DF or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: HARVONI is Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk but had no effect on nursing pups. It is not known if HARVONI and its metabolites are secreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the nursing child from the drug or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

Reference: 1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. October 2014.

GILEAD

Presentations in Hepatology

Liver Function Improves in Cirrhotic HCV Patients Treated With a 3-Drug Antiviral Combination Plus Ribavirin

Patients infected with hepatitis C virus (HCV) are at increased risk for hepatocellular carcinoma and liver-related mortality. However, the risk is significantly reduced in patients who achieve a sustained virologic response (SVR) to treatment. At the ACG meeting, Priyam Tripathi, MD, of Case Western Reserve University in Cleveland, Ohio presented results of a study examining hepatic function in HCV patients treated with antiviral agents (Abstract 5).

The phase 3 TURQUOISE-II (A Study to Evaluate the Safety and Effect of ABT-450, Ritonavir and ABT-267 [ABT-450/r/ABT-267] and ABT-333 Coadministered With Ribavirin [RBV] in Hepatitis C Virus [HCV] Genotype 1-infected Adults With Compensated Cirrhosis) study evenly randomized 380 patients with Child-Turcotte-Pugh type A cirrhosis to receive the 3-drug combination of ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin (3D plus RBV) for 12 or 24 weeks of treatment. The study included both treatment-naive and treatment-experienced patients. Prior use of pegylated interferon and ribavirin was permitted. All patients had HCV genotype 1 infection and cirrhosis. Laboratory testing, including chemistry, hematology, and urinalysis, was conducted at each study visit during the treatment and afterward.

Treatment for 12 or 24 weeks resulted in SVR rates at week 12 of 92% and 96%, respectively. In most patients, liver enzymes normalized by the end of the 12- or 24-week treatment period, with normalization of alanine transaminase, aspartate transaminase, and gamma-glutamyl transpeptidase in 93.1%, 87.8%, and 92.5% of patients, respectively. Mean liver enzyme values normalized by week 4. Liver function was largely restored after treatment, as demonstrated by the normalization of conjugated bilirubin levels, albumin levels, and prothrombin time. Platelet counts increased in the overall population, consistent with a possible improvement in portal hypertension.

Ledipasvir/Sofosbuvir Plus Ribavirin for HCV Patients With Decompensated Cirrhosis

At the American Association for the Study of Liver Diseases (AASLD) Liver Meeting, Steven Flamm, MD, of the Northwestern University Feinberg School of Medicine in Chicago, Illinois presented preliminary results of a prospective, multicenter study evaluating ledipasvir/sofosbuvir plus ribavirin in HCV patients with decompensated cirrhosis (Abstract 239). The combination of ledipasvir (90 mg/day), sofosbuvir (400 mg/day), and ribavirin (initially 600 mg/day, then escalated) was administered for 12 or 24 weeks. The study included 108 adults with HCV genotype 1 or 4. Patients had a Child-Turcotte-Pugh score of B (n=59) or C (n=49). Six patients were excluded from the analysis because they underwent liver transplantation during the course of the study. SVR12 rates were 87% for 12 weeks of treatment and 89% for 24 weeks of treatment. Among patients with a Child-Turcotte-Pugh score of B, there were 4 relapses and 3 deaths. The group with a Child-Turcotte-Pugh score of C had 2 relapses and 2 deaths (plus 1 patient who was lost to follow-up). The relapse rates were similar to those reported in patients with compensated cirrhosis. The longer treatment duration of 24 weeks did not appear to confer any additional benefit. A virologic response was associated with improvements in bilirubin, albumin, Model for End-Stage Liver Disease scores, and Child-Turcotte-Pugh scores, regardless of the patient's Child-Turcotte-Pugh score at baseline. The 12-week and 24-week regimens were generally well tolerated, with 4 serious AEs attributed to study treatment and 3 patients discontinuing treatment because of an AE.

An All-Oral Regimen of 3 Direct-Acting Antiviral Agents in HCV Genotype 1 Patients With Cirrhosis

The phase 3 TURQUOISE-II trial evaluated a combination regimen of 3 direct-acting antiviral agents in HCV genotype 1 patients with cirrhosis. Results were reported at the AASLD Liver Meeting by Michael Fried, MD, of the University of North Carolina at Chapel Hill School of Medicine (Abstract 81). The study randomized 380 patients to receive a combination of paritaprevir, ombitasvir, and dasabuvir plus ribavirin for 12 or 24 weeks. Follow-up lasted for 48 weeks after the cessation of treatment. Enrolled patients could be treatment-naive or treatment-experienced; a key exclusion criterion, however, was prior therapy with a direct-acting antiviral agent. The overall SVR12 rates were 91.8% after 12 weeks of treatment and 96.5% after 24 weeks of treatment. Analysis of baseline demographic, clinical, and virologic factors did not identify

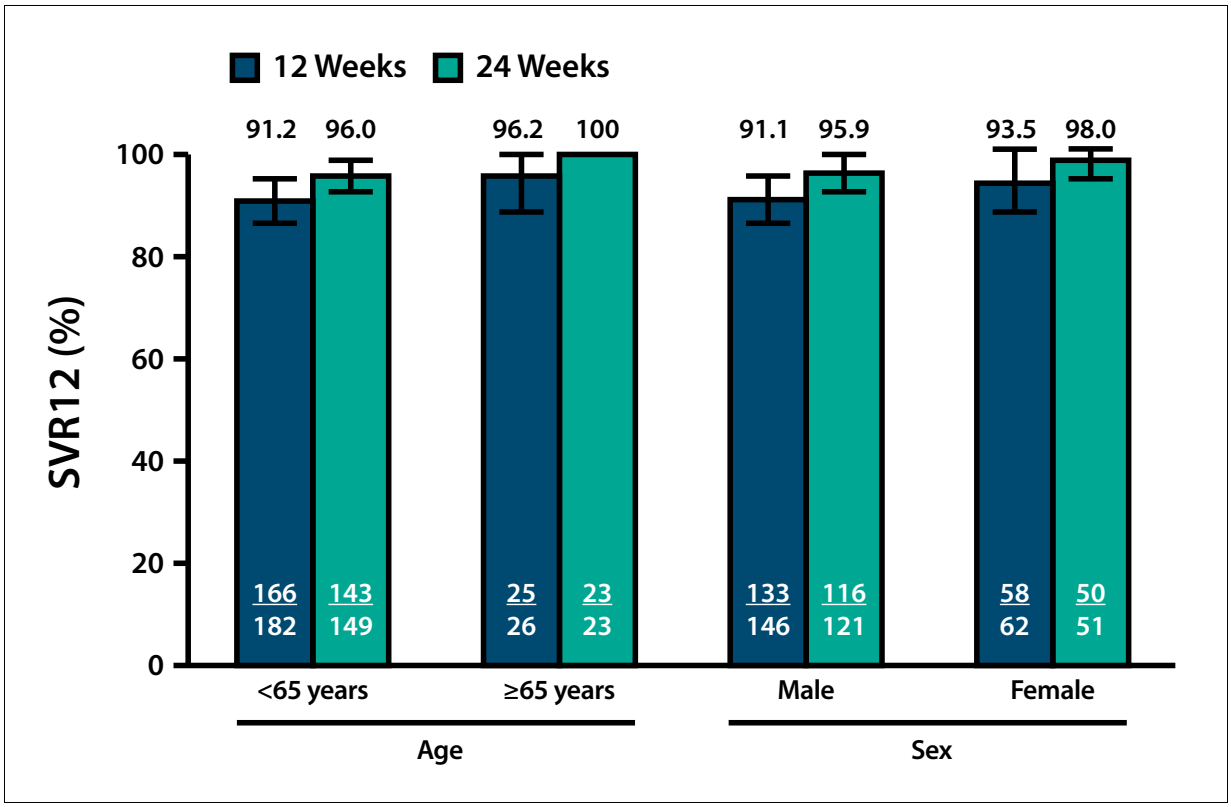


Figure 1. Rates of SVR12 with paritaprevir/ritonavir, ombitasvir, and dasabuvir in the TURQUOISE-II study. SVR12, sustained virologic response at week 12. Adapted from Fried MW et al. AASLD abstract 81. *Hepatology*. 2014;60(4 suppl).

significant differences in SVR12 rates for most comparisons (Figure 1). SVR12 rates were higher with the 24-week regimen than the 12-week regimen in patients who were prior null responders (95.2% vs 86.7%), treatment-naive (95.9% vs 94.2%), genotype 1a (95.0% vs 88.6%), or genotype 1b (100% vs 98.5%).

The study also examined the demographic and disease characteristics of the patients who did not achieve SVR12. In the 12-week treatment arm, 8% of patients failed to achieve SVR12, and 6% of patients relapsed. In the 24-week arm, 3.5% of patients failed to achieve SVR12, and 0.6% of patients relapsed. All but 1 of the patients who relapsed had HCV genotype 1a, and nearly all of the relapsed patients had HCV RNA levels of 800,000 IU/mL or higher. Three factors emerged that were significantly associated with reduced rates of SVR12: interleukin 28B genotype TT (P=.021), prior null response (P=.038), and HCV genotype 1a infection (P=.046).

Sofosbuvir and Simeprevir for the Treatment of Recurrent HCV After Liver Transplantation

Recurrence of HCV after liver transplantation has been associated with increased rates of fibrosis. Among these patients, traditional therapies have been associated with low SVR rates and significant AEs. A study reported at the AASLD Liver Meeting by Heather O'Dell, ANP-BC, from the Vanderbilt University Medical Center in Nashville, Tennessee evaluated the use of sofosbuvir and simeprevir to treat recurrent HCV after liver transplantation (Abstract LB-8).

The 18 patients in this study had undergone transplantation at least 3 months before the study start and had documented recurrence of HCV infection. The patient's mean age was 61 years, 78% of patients were male, and 3 patients had cirrhosis. Patients received treatment with sofosbuvir and simeprevir while continuing to receive standard immunosuppressant therapy, which consisted of tacrolimus in 89% and cyclosporine in 11%. All patients completed 12 continuous weeks of therapy. No patients required adjustments to the immunosuppressant dose or experienced transplant rejection.

The rapid virologic response rate was 72%, and all patients achieved an end-of-treatment response. The only reported AEs were mild headache and nausea. There were no interactions that required adjustment of the treatment dosage. Among the 15 patients with HCV RNA at 4 weeks posttreatment, the SVR4 rate was 100%. For the 7 evaluable patients with data at 12 weeks posttreatment,

Table 2. Entecavir and Tenofovir for Chronic HBV Patients Who Failed Previous Nucleos(t)ide Treatment

Efficacy[a]	Week 48, % (n/N)	Week 96, % (n/N)
HBV DNA <50 IU/mL	76 (70/92)[b]	85 (78/92)
HBV DNA <6 IU/mL	19 (17/92)	16 (15/92)
HBeAg loss	5 (3/56)	9 (5/56)
HBeAg seroconversion	4 (2/56)	2 (1/56)
HBsAg loss	0	2 (2/92)
HBsAg seroconversion	0	1 (1/92)

[a] Patients who did not complete treatment were considered nonresponders.

[b] Primary endpoint.

HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Data from Zoulim F et al. AASLD abstract 230. *Hepatology*. 2014;60(4 suppl).

the SVR12 rate was also 100%. The results from this small study support further investigation of new direct-acting antiviral therapies in the liver transplant population.

Entecavir and Tenofovir Combination Therapy for Chronic Hepatitis B

At the AASLD Liver Meeting, Fabien Zoulim, MD, PhD, from Lyon University in Lyon, France described results from the ENTEBE (Safety and Efficacy of Entecavir Plus Tenofovir in Adults With Chronic Hepatitis B and Previous Nucleos(t)ide Treatment Failure) study, a single-arm, open-label, multicenter study evaluating a combination of entecavir and tenofovir as rescue therapy in patients with chronic hepatitis B who had failed prior treatment with a nucleos(t)ide therapy (Abstract 230). Entecavir and tenofovir are both potent agents with resistance profiles that do not overlap.

A regimen of entecavir (1 mg) plus tenofovir (300 mg) was administered for 96 weeks to 92 patients (6 discontinued). Prior nucleos(t)ide therapy included monotherapy with entecavir (53%), lamivudine (22%), tenofovir (12%), adefovir (4%), and telbivudine (2%), or combinations of these agents (7%). More than half of patients (58%) had evidence of single-drug or multidrug resistance mutations.

The primary endpoint—hepatitis B DNA level of less than 50 IU/mL—was achieved by 76% of patients at week 48 and 85% at week 96 (Table 2). The primary endpoint at week 96 was achieved by 100% of patients who had failed adefovir or telbivudine, 88% who had failed entecavir, 82% who had failed tenofovir, 80% who had failed lamivudine, and 83% who had failed combination therapy. Six patients experienced on-treatment serious AEs, none of which were considered related to study treatment. One patient died from hepatocellular carcinoma.

Cognitive Changes in Hepatic Encephalopathy May Not Be Reversible

Results from a multicenter study evaluating the persistence of cognitive impairment in hepatic encephalopathy patients were reported at the AASLD Liver Meeting by Jasmohan Bajaj, MD, of Virginia Commonwealth University in Richmond, Virginia (Abstract 94). This international study included 187 outpatients with cirrhosis from 3 different medical centers (in Virginia, Ohio, and Rome). Cognitive testing included assessment of the psychometric hepatic encephalopathy score and the inhibitory control test. The psychometric hepatic encephalopathy score is based on 6 subtests. The inhibitory control test consists of 2 identical halves that are given one after the other (with a short break in between). Subjects with an intact learning ability should show improvement in the second half as compared with the first half.

At baseline, results of all cognitive tests were worse among patients with hepatic encephalopathy. Patients without hepatic encephalopathy showed significant improvement on the second half of the inhibitory control test as compared with the first half. Patients with hepatic encephalopathy did not improve on the second half. These results were replicated when the patients underwent subsequent testing (performed a median of 20 days later). In addition, subsequent assessment of the psychometric hepatic encephalopathy score showed that patients without hepatic encephalopathy improved on 4 subtests compared with the first assessment, whereas patients with hepatic encephalopathy improved on 2 subtests. Despite adequate medical therapy, patients with prior hepatic encephalopathy showed persistent significant learning impairment compared to those without. The authors concluded that the recognition of these continued cognitive deficits should increase efforts to avoid an initial episode of hepatic encephalopathy and perhaps increase the transplant listing priority for patients with this condition.

Idiosyncratic Drug-Induced Liver Injury

At the ACG meeting, Naga Chalasani, MD, of Indiana University in Indianapolis, Indiana presented results of a prospective study enrolling patients with idiosyncratic drug-induced liver injury in the United States (Abstract 31). Patients with suspected drug-induced liver injury were enrolled prospectively and followed for at least 6 months. Among the 1257 subjects enrolled, causality adjudication was completed in 1091. A diagnosis of drug-induced liver injury was deemed definite in 235 patients, highly likely in 466 patients, and probable in 198 patients. The liver injury was hepatocellular in 54% of these patients, cholestatic in 23%, and mixed in 23%. Approximately

10% of patients died or underwent liver transplantation, and 17.5% developed chronic drug-induced liver injury.

Most cases (86%) of drug-induced liver injury could be attributed to 5 classes of agents: antimicrobials (n=408), herbal and dietary supplements (n=145), cardiovascular agents (n=88), central nervous system agents (n=82), and antineoplastic agents (n=49). The individual agents associated with the most cases were amoxicillin-clavulanate (n=91), isoniazid (n=48), nitrofurantoin (n=42), trimethoprim/sulfamethoxazole (n=31), minocycline (n=28), cefazolin (n=20), azithromycin (n=18), ciprofloxacin (n=16), levofloxacin (n=13), and diclofenac (n=13). The duration of disease latency did not impact outcome. Patients ages 65 years or older had higher rates of drug-induced liver injury than younger patients. Rates of mortality and liver transplantation did not differ according to age. Nine patients developed severe cutaneous reactions (Stevens-Johnson syndrome), which were associated with lamotrigine (n=2), azithromycin (n=2), moxifloxacin (n=1), nitrofurantoin (n=1), diclofenac (n=1), carbamazepine (n=1), and cephalexin/lamotrigine (n=1). Four of these patients died.

Grazoprevir and Elbasvir With or Without Ribavirin in HCV Genotype 1

The randomized, open-label, phase 2 C-WORTHY trial was designed to examine the efficacy and safety of grazoprevir and elbasvir with or without ribavirin in patients with HCV genotype 1 infection. In part A of the C-WORTHY trial, this regimen achieved SVR12 rates of 89% to 100% in 65 treatment-naive, noncirrhotic, HCV genotype 1–infected patients. At the AASLD Liver Meeting, Eric Lawitz, MD, of the University of Texas Health Science Center in San Antonio reported the final results from the subset of treatment-naive, cirrhotic patients and prior null responders enrolled in part B of the study (Abstract 196).

Patients received 12 or 18 weeks of grazoprevir (100 mg/day) plus elbasvir (50 mg/day) with or without ribavirin (dosed according to body weight). In the treatment-naive patients who received 12 weeks of therapy, intent-to-treat analysis yielded SVR12 rates of 90% with ribavirin and 97% without. Among patients who received 18 weeks of treatment, SVR12 rates were 97% with ribavirin vs 94% without. Among the prior null responders, 12 weeks of treatment yielded SVR12 rates of 94% with ribavirin vs 91% without. Eighteen weeks of treatment yielded rates of 100% with ribavirin vs 97% without ribavirin in null responders. When data for the 12-week and 18-week treatment groups were pooled, SVR12 rates were 95% with ribavirin vs 94% without; 93% for HCV genotype 1a patients vs 99% for genotype 1b; 94% for treatment-naive patients vs 95% for null responders; and 95% for patients with or without cirrhosis. Among the subset of 25 patients who were prior null responders with cirrhosis, 12 weeks of treatment with or without ribavirin yielded an SVR12 rate of 92%. Seven serious AEs were reported, but 6 were considered unrelated to the study treatment. All treatment-emergent AEs were mild to moderate. The most common events were fatigue (26%), headache (23%), and asthenia (14%).

Presentations in IBD

Low Rates of Infection With Vedolizumab Alone or With Corticosteroids and/or Immunosuppressants in Ulcerative Colitis and Crohn's Disease Patients

The GEMINI 1 and 2 studies examined the efficacy and safety of vedolizumab for ulcerative colitis and Crohn's disease, respectively. In both studies, rates of some infections were higher with vedolizumab therapy than with placebo. At the ACG meeting, Edward Loftus, MD, of the Mayo Clinic in Rochester, Minnesota presented results from an analysis of infection rates in patients treated with vedolizumab alone or with concomitant corticosteroids and/or immunosuppressants vs placebo in GEMINI 1 and 2 (Abstract 16).

Data from the 2 studies were pooled from the 6-week induction phase, in which patients received vedolizumab (300 mg) or placebo at weeks 0 and 2, and from the 46-week maintenance phase, in which patients received vedolizumab (300 mg) or placebo every 4 or 8 weeks. The proportions of patients with AEs and serious AEs were determined for those who received the antibody or placebo continuously through the induction and maintenance portions of the study.

For the 1434 pooled GEMINI 1 and 2 patients who received vedolizumab, the rates of infection considered AEs or serious AEs were similar among the subgroups, regardless of the use of concomitant corticosteroids or immunosuppressants. In general, rates of infection-related AEs were similar between the placebo and vedolizumab subgroups, with rates of any infectious AE ranging from 32% to 44% for the 4 placebo subgroups vs 42% to 45% for the 4 vedolizumab subgroups. Nasopharyngitis was more common with vedolizumab, occurring in 10% to 14% of the subgroups (vs 4% to 12% of the subgroups receiving placebo). Rates of infections considered serious AEs were also similar or nominally lower for the placebo subgroups vs the vedolizumab subgroups, but the infrequency of these events limited interpretation of the data.

Meta-Analysis of Cyclosporine Vs Infliximab for Patients With Acute Severe Corticosteroid-Refractory Ulcerative Colitis

Treatment with intravenous corticosteroids fails in up to 40% of patients who present with acute severe ulcerative colitis. The prognosis for these patients is poor. Cyclosporine and infliximab can be used as salvage therapies for these corticosteroid-refractory patients. At the ACG meeting, Edward Loftus, Jr, MD, of the Mount Sinai Hospital in New York, New York, presented results from a systematic review and meta-analysis conducted to assess cyclosporine and infliximab as rescue agents in patients with corticosteroid-refractory ulcerative colitis (Abstract 15).

A literature search identified studies that investigated cyclosporine and infliximab in corticosteroid-refractory ulcerative colitis patients. The primary outcome was short-term response to treatment. Secondary outcomes included the rates of colectomy at 3 months and 12 months, adverse drug reactions, postoperative complications in those who received rescue therapy but subsequently underwent colectomy, and mortality.

Eleven studies with 988 participants were eligible for inclusion. For the 2 randomized controlled trials with 145 patients, no significant difference was seen for infliximab vs cyclosporine based on treatment response, colectomy at 3 months, or colectomy at 12 months. For the 9 nonrandomized studies with 843 eligible participants, infliximab treatment was associated with significantly higher rates of treatment response (OR, 2.99; 95% CI, 2.99-4.30) and lower rates of colectomy at 12 months (OR, 0.38; 95% CI, 0.17-0.85). There was no significant difference between infliximab and cyclosporine in the rates of colectomy at 3 months (OR, 0.71; 95% CI, 0.26-1.89). No significant differences emerged between cyclosporine and infliximab in terms of drug-related AEs, postoperative complications, or mortality.

Increased Vedolizumab Dosing Frequency in Ulcerative Colitis and Crohn's Disease Patients Who Have Lost Response

The GEMINI 1 and 2 trials demonstrated the efficacy and safety of vedolizumab in patients with ulcerative colitis and Crohn's disease, respectively. At the 2014 Advances in Inflammatory Bowel Diseases conference, Bruce Sands, MD, of the Icahn School of Medicine at Mount Sinai in New York, New York presented results of GEMINI-LTS, an open-label, long-term extension study evaluating an increased frequency of vedolizumab in patients who lost response to the drug during the maintenance phase of GEMINI 1 or 2 (Abstract P098).

The current extension study included patients from GEMINI 1 and 2 who responded to vedolizumab during the 6-week induction phase (300 mg at weeks 0 and 2) but subsequently lost response during the 46-week maintenance phase (300 mg every 8 weeks) and discontinued treatment. These patients accounted for 26% of the population in GEMINI 1 and 37% in GEMINI 2.

For the extension study, the frequency of vedolizumab

dosing was increased to 300 mg every 4 weeks. This dosage improved the mean disease activity scores for both ulcerative colitis and Crohn's disease patients. Rates of clinical remission and response also improved. For the GEMINI 1 cohort, the proportion of patients in clinical remission was 6.3% at baseline, 25% at week 28, and 25% at week 52. The rate of clinical response increased from 18.8% at baseline to 53.1% at week 28, but then decreased to 37.5% at week 52. For the GEMINI 2 cohort, clinical remission rates were 3.5% at baseline, 22.8% at week 28, and 31.6% at week 52. The clinical response rates were 38.6% at baseline, 54.4% at week 28, and 47.4% at week 52. AE profiles were similar for vedolizumab dosed at 300 mg every 8 weeks vs every 4 weeks.

Immunosuppressant Treatment Does Not Increase Cancer Incidence in IBD Patients With a History of Cancer

Nearly 30% of inflammatory bowel disease (IBD) patients with a history of cancer develop a secondary or recurrent cancer. At the 2014 Advances in Inflammatory Bowel Diseases conference, Jordan Axelrad, MD, of the Icahn School of Medicine at Mount Sinai in New York, New York described findings from a retrospective analysis showing no correlation between exposure to IBD treatments and the likelihood of developing cancer (Abstract O005).

The retrospective study included 185 patients with IBD and a history of cancer from 3 different institutions. Among these patients, 65 (35%) had received antitumor necrosis factor α (TNFα) therapy, 46 (25%) had received antimetabolites, including thiopurines or methotrexate, and 74 (40%) had not received immunosuppressants. The primary outcome was the development of new or recurrent cancer.

No significant differences emerged in the development of cancer for the 3 cohorts. Approximately 14% of patients developed a new cancer, 12% developed a recurrent cancer, and 3% developed both a new and a recurrent cancer. More skin cancers were observed in the anti-TNFα group and more GI cancers occurred in the control group, but neither difference was statistically significant. Incident cancer rates were 3.9 with 361 person-years of follow-up for the control group; 6.6 with 181 person-years of follow-up for the antimetabolites group; and 8.8 with 306 person-years of follow-up for the anti-TNFα group. After 5 years of follow-up, there were no significant differences in cancer-free survival rates among the 3 treatment groups. The study was limited by the population size and the lack of data on dose-related effects and periods of cancer remission.

Baseline 5-Aminosalicylic Acid Use Is Compatible With Budesonide Foam Treatment

Budesonide foam is a rectally administered, second-generation corticosteroid. It was developed to treat distal forms of ulcerative colitis with optimal drug retention and uniform drug delivery. At the ACG meeting, William Sandborn, MD, of the University of California San Diego in La Jolla, California described results from 2 phase 3 studies that evaluated the impact of baseline oral 5-aminosalicylic acid (5-ASA) on the safety and efficacy of budesonide foam (Abstract P470).

Data were pooled from 2 identical multicenter, double-blind, placebo-controlled, phase 3 studies. Both studies included patients with mild-to-moderate active ulcerative proctitis or ulcerative proctosigmoiditis. Patients were randomized to receive budesonide foam or placebo. The dose of budesonide foam was 2 mg in 25 mL; it was given twice daily for 2 weeks followed by once daily for 4 weeks. Patients could receive concomitant treatment with oral 5-ASA (up to 4.8 g daily). Use of rectal 5-ASA was not permitted.

Efficacy was evaluated at week 6. The pooled studies yielded 267 patients in the budesonide foam treatment group and 279 patients in the placebo group. Baseline use of 5-ASA was reported in 147 patients (55.1%) receiving budesonide foam and 154 patients (55.2%) receiving placebo. The percentages of patients achieving remission and a rectal bleed score of 0 were significantly higher with budesonide foam as compared with placebo, regardless of the use of 5-ASA (Table 3). No significant differences in AEs emerged for patients who did or did not report 5-ASA use at baseline.

Table 3. Efficacy of Budesonide Foam in a Pooled Analysis of Phase 3 Trials

Efficacy Endpoints	Subgroup	Budesonide Foam, n (%)	Placebo, n (%)	Treatment Difference (%)	*P* Value
Remission at week 6	5-ASA No 5-ASA	62 (42.2) 48 (40.0)	49 (31.8) 18 (14.4)	10.4 25.6	.0265 <.0001
Rectal bleeding score of 0 at week 6	5-ASA No 5-ASA	74 (50.3) 55 (45.8)	55 (35.7) 24 (19.2)	14.6 26.6	.0031 <.0001
Endoscopy score ≤1 at week 6	5-ASA No 5-ASA	82 (55.8) 67 (55.8)	72 (46.8) 39 (31.2)	9.0 24.6	.0761 .0004

5-ASA, 5-aminosalicylic acid.

Data from Sandborn W et al. ACG abstract P470. Presented at: ACG 2014 Annual Scientific Meeting; October 17-22, 2014; Philadelphia, PA.

Presentations in Endoscopy

Retroflexion Vs Forward View for Detecting Adenomas in the Right Colon

Colonoscopy is effectively used to screen for distal colon cancers; however, its ability to detect right-sided colon cancers is unclear. Some studies have suggested that retroflexion in the right colon may improve adenoma detection. At the ACG meeting, Vladimir Kushnir, MD, of the Washington University School of Medicine in St. Louis, Missouri presented results from a study evaluating whether a second withdrawal from the right colon in retroflexion vs a forward view can improve detection of colonic adenomas (Abstract 8).

The randomized controlled trial enrolled patients at 2 centers. All patients underwent cecal intubation; the colonoscope was then withdrawn to the hepatic flexure, and all visible polyps were removed. Endoscopist confidence in the quality of the first examination of the right colon was recorded on a 5-point Likert scale. After reintubation of the cecum, patients underwent a second examination of the proximal colon and were randomized to either forward or retroflexion view. The primary outcome was the rate of adenoma detection per patient.

The 850 patients had a mean age of 59.1±8.3 years, and 59% were female. Randomization assigned 400 patients (47%) to forward view and 450 (53%) to retroflexion view. Retroflexion was successfully performed in 421 patients (93.5%) in the latter arm. In both groups, 46% to 47% of patients had at least 1 adenoma (*P*=.69), and the mean number of adenomas per patient was 1 (*P*=.69). The proportion of patients with at least 1 additional adenoma detected on the second withdrawal from the proximal colon was also similar in the forward view and retroflexion view groups (10.5% and 7.5%, respectively; *P*=.13). Logistic regression analysis revealed the following significant predictors that adenomas would be identified on the second withdrawal from the right colon: older age (OR, 1.04; 95% CI, 1.01-1.08), adenomas seen on initial withdrawal (OR, 2.8; 95% CI, 1.7-4.7), and low endoscopist confidence in quality of the first examination of the right colon (OR, 4.8; 95% CI, 1.9-12.1). No AEs were observed.

Optimal Timing of Endoscopy After Acute Caustic Ingestion

At the ACG meeting, Munish Ashat, MD, of the Postgraduate Institute of Medical Education and Research in Panchkula, Haryana, India presented results from a study assessing the utility of upper GI endoscopy on day 1 vs day 5 in predicting cicatrization and other outcomes after caustic ingestion (Abstract 20). The study included consecutive patients admitted for ingesting a caustic substance. Upper GI mucosal changes were graded according to the Zargar classification, and these changes were classified as mild for grade IIa or less and severe for grade IIb or higher. Endoscopy changes on day 1 vs day 5 were evaluated for the development of cicatrization and complications.

Among the 63 consecutive patients who presented within 24 hours of caustic ingestion, 51 underwent upper GI endoscopy on both day 1 and day 5 and were included in the study (Table 4). Patients had a mean age of 32±13.3 years, and 61% were male. The caustic substance was acid in 43 patients (84.3%), alkali in 6 (11.8%), and unknown in 2 (3.9%). Antropyloric stricture developed in 18 patients (35.3%), and esophageal stricture developed in 12 (23.5%). One patient (2%) died, 1 (2%) required emergency surgery, and 7 (13.7%) required definitive surgery for cicatrization. Conservative management consisting of only dilatation in those with cicatrization led to recovery in 42 patients (82.3%).

Esophageal grading on day 1 overestimated severity by 23.5% compared with day 5 (*P*=.008), and stomach grading on day 1 overestimated severity by 29.4% compared with day 5 (*P*=.006). Stricture formation correlated

Table 4. Endoscopic Assessment After Caustic Ingestion on Day 1 Vs Day 5

	Mild Changes Grade ≤IIA, n (%)	Severe Changes Grade ≥IIB, n (%)	Day 1 Vs Day 5 *P* Value
Esophagus day 1 (n=51)	19 (37.3)	32 (62.7)	
Esophagus day 5 (n=51)	31 (60.8)	20 (39.2)	.008
Stomach day 1 (n=51)	11 (21.6)	40 (78.4)	
Stomach day 5 (n=49)	25 (51.0)	24 (49.0)	.006

Data from Ashat M et al. ACG abstract 20. Presented at: ACG 2014 Annual Scientific Meeting; October 17-22, 2014; Philadelphia, PA.

with endoscopic grading of esophageal injury on day 5 (P=.019) but not day 1 (P=.287). Gastric cicatrization correlated with endoscopic grading on both day 1 and day 5 (P=.005 and P=.000, respectively). Day 5 endoscopic grading correlated with the need for surgery and recovery (P<.05).

Improving Endoscopic Techniques for Complete Resection of Subepithelial Tumors

Medical centers in Asia have pioneered the development of 2 natural orifice endoscopic techniques that achieve R0 en bloc resection of subepithelial tumors originating in the muscularis propria. Submucosal tunnel endoscopic resection uses the submucosal tunnel method to ensure secure closure of the full-thickness defect in the wall of the GI tract. Endoscopic full-thickness resection involves direct resection with closure of the defect by clips or sutures. At the ACG meeting, Stavros Stavropoulos, MD, of the Winthrop University Hospital in Mineola, New York described results using these 2 techniques as an alternative to laparoscopic wedge resection for subepithelial tumors originating in the muscularis propria (Abstract 22).

Procedures were performed between April 2012 and June 2014 at Winthrop University Hospital. This report is the first to describe use of these procedures in the United States. Data were retrieved from a prospectively maintained database. Among the study group, there were 26 endoscopic full-thickness resection procedures and 7 submucosal tunnel endoscopic resection procedures, all performed by a gastroenterologist with extensive experience in similar procedures.

Patients had a mean age of 58 years (range, 18-84 years). According to criteria from the American Society of Anesthesiologists, 12% were class I, 70% were class II, and 18% were class III. The 33 subepithelial tumors were located in the esophagus (6), stomach (22), colon (2), and rectum (3) and included 17 GI stromal tumors, 8 leiomyomas, 2 pancreatic rests, 1 schwannoma, and 1 leiomyosarcoma. Tumors had a mean size of 22 mm (range, 10-55 mm).

Mean resection time was 72 minutes (range, 21-220 minutes). Means of closure included endoclips (30%), endoscopic suturing (49%), and both (21%). Complete en bloc resection was achieved in 91% of procedures. Piecemeal resection was required in 3 patients, 2 with pancreatic rests and 1 with a GI stromal tumor of 5 cm. Notable AEs included 2 cases of needle decompression of the capnoperitoneum and 3 cases of bleeding requiring prolonged endoscopic hemostasis, with 2 of the 3 patients requiring blood transfusion. The mean length of the hospital stay was 1.5 days (range, 1 to 3 days).

The Role of Esophageal Biopsy in Screening At-Risk Patients for Eosinophilic Esophagitis

Eosinophilic esophagitis patients commonly present with dysphagia and food impaction. However, variation in clinical symptoms and endoscopic findings can confound the diagnosis. At the ACG meeting, Kristina Ross, MD, of the University of Colorado Anschutz Medical Campus in Denver, Colorado presented findings from a study that examined the role of esophageal biopsies in screening patients for eosinophilic esophagitis (Abstract P616).

A retrospective chart review from 2001 to 2012 was conducted in a tertiary care, university-affiliated hospital. Included patients were referred for esophagogastroduodenoscopy for either food impaction or dysphagia with documented stricture. Patients with esophageal malignancy, a history of radiation therapy, or esophageal dysmotility disorders were excluded. The study calculated the proportion of patients with esophageal biopsies taken at the time of the initial endoscopy or on subsequent esophagogastroduodenoscopy, and the number of patients with follow-up esophagogastroduodenoscopies.

Ninety-one patients with food impaction were included. Thirteen patients (14%) underwent initial biopsy, and 54 (58%) did not have a follow-up esophagogastroduodenoscopy. Among the 85 patients with esophageal stricture, 33 (39%) underwent an initial biopsy; 29 patients (34%) did not undergo subsequent biopsy. Eosinophilic esophagitis was diagnosed in 13 of the food impaction patients (14%) and 17 of the stricture patients (20%). This rate of eosinophilic esophagitis diagnosis is considerably higher compared with that in the general population, in which prevalence estimates range from 0.05% to 6.5%. These results suggest that esophageal biopsies are currently underutilized, and that consistent use of esophageal biopsy in at-risk populations could improve diagnosis of this condition.

Endoscopic Management of Esophageal Anastomotic Leaks Following Surgery for Cancer

Esophageal anastomotic leaks constitute a major cause of morbidity and mortality after surgery for gastric or esophageal cancer. Endoscopic interventions such as stenting, clipping, and percutaneous endoscopic jejunostomy have been increasingly used to limit the risk of anastomotic leaks in these patients. At the ACG meeting, Eugene Licht, MD, of the Memorial Sloan Kettering Cancer Center in New York, New York presented results of a study that evaluated the efficacy of endoscopic management of esophageal leaks following cancer surgery (Abstract P636).

The study identified 107 patients with anastomotic leaks, and 51 underwent endoscopic management. Patients had a mean age of 61 years, and 78% were male. Procedures included 42 (82%) esophagectomies, 6 (12%) partial or total gastrectomies, and 3 (6%) esophagogastrectomies. Fully covered esophageal stents were placed in 32 patients. The stents remained in place for a mean of 59 days (range, 12-170 days). Stent migration was reported in 17 patients (53%) and was managed with endoscopic revision. Twenty-six patients (81%) treated with stents healed.

Direct percutaneous endoscopic jejunostomy tubes were placed in 41 patients, for a mean duration of 106 days (range, 18-358 days). No complications from percutaneous endoscopic jejunostomy tube placement were observed. The tube placement wound healed in 39 patients (95%). Three patients who received stents also received endoscopic clips. No complications related to clip placement were observed, and all 3 patients healed. Among the 22 patients who received both a stent and a percutaneous endoscopic jejunostomy tube, 21 (95%) healed, by a mean of 105 days (range, 31-337 days).

Among the 51 patients who underwent endoscopic management, 44 (86%) achieved documented anastomotic healing, with a mean healing time of 92 days (range, 3-337 days). Of the remaining 7 patients, 3 required anastomotic revision, 1 required esophageal exclusion, 2 died of multiple surgical complications, and 1 died at another facility with a stent in place.

An Ultrathin Endoscope for Diagnosing Barrett Esophagus

The GIF-XP290N is a new, ultrathin endoscope that supplies a resolving power similar to that of the GIF-H260 at a distance of 3 mm. At the ACG meeting, Takashi Kawai, MD, of the Endoscopy Center, Tokyo Medical University Hospital in Japan described findings from a study that evaluated patients with Barrett esophagus using the ultrathin endoscope (Abstract P1221).

Diagnosis of Barrett esophagus was made according to Japanese guidelines. The lower margin of the lower esophageal palisade vessels was defined as the gastroesophageal junction when the diaphragm was lowered in deep inspiration. A diagnosis of Barrett esophagus was made if the columnar epithelium was present on the oral side of the gastroesophageal junction.

Upper GI screening using an ultrathin endoscope was performed in 135 patients. The patients' mean age was 63.5±9.7 years, and most patients were male. Both white light and narrow band imaging were used for all examinations. Barrett esophagus was classified as long (>30 mm), short (10-30 mm), or ultrashort (<10 mm). The Goda classification system was used to categorize the mucosal pattern.

Barrett esophagus was confirmed in 116 of 135 patients (86%) and included 17 cases (15%) of short segments and 99 cases (85%) of ultrashort segments. Narrow band imaging to assess the mucosal structural pattern revealed cases that were villous (41%), oval or round (25%), long straight (25%), cerebriform (7%), and irregular (5%). Histologic examination showed that 8 patients (7%) had intestinal metaplasia. Analysis of the relationship between mucosal patterns and background factors revealed a significant correlation between the presence of intestinal metaplasia and the combined "open type" cohort of villous, cerebriform, and irregular patterns.

Comparison of Cold Biopsy and Other Techniques for Removal of Diminutive Colonic Polyps

Colonoscopic polypectomy is an effective technique for preventing colon cancer. Cold biopsy is the current standard practice for removal of diminutive polyps, the type most often found during colonoscopy. At the ACG meeting, Priyam Tripathi, MD, of Case Western Reserve University in Cleveland, Ohio performed a systematic review and meta-analysis to evaluate the efficacy of cold biopsy vs other techniques for eradicating diminutive polyps (Abstract 24).

The study identified published reports of randomized controlled trials available through MEDLINE, Web of Science, and EMBASE and through abstracts presented at meetings of the ACG, the American Gastroenterological Association, and Digestive Disease Week. The primary outcome was the complete eradication rate of diminutive polyps, and the secondary outcome was procedural time.

The analysis included 5 randomized controlled trials (N=610). Mean polyp size was 4.5 mm (range, 2-10 mm). Removal techniques included cold biopsy, jumbo forceps biopsy, and cold snare polypectomy. The rate of incomplete polyp eradication was significantly lower with cold snare or jumbo forceps biopsy compared with cold biopsy (relative risk, 0.48; 95% CI, 0.30-0.77), with little heterogeneity (I2, 9%). The procedure time for the cold snare or jumbo forceps biopsy was on average 4.1 minutes shorter compared with that of cold biopsy (95% CI, -8 to -2). The authors concluded that randomized controlled trials comparing the efficacy of cold snare, jumbo biopsy, and cold biopsy techniques in the eradication of diminutive polyps are warranted.

Brief Summary about BreathTek UBT

Intended Use
The BreathTek® UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients and pediatric patients 3 to 17 years old. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples, in clinical laboratories or point-of-care settings. The Pediatric Urea Hydrolysis Rate Calculation Application (*p*UHR-CA), provided as a web-based calculation program, is required to obtain pediatric test results.

The BreathTek UBT Kit is for administration by a health care professional, as ordered by a licensed health care practitioner.

Warnings and Precautions
- For in vitro diagnostic use only. The Pranactin®-Citric solution is taken orally as part of the diagnostic procedure and contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit, and should be used with caution in diabetic patients. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
- A negative result does not rule out the possibility of *H. pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternate method.
- False negative test results may be caused by:
  - — Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false-negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon.
  - — Ingestion of antimicrobials, or bismuth preparations within 2 weeks prior to performing the BreathTek UBT
  - — Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
  - — Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of *H. pylori*.
- False positive test results may be caused by urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii* or achlorhydria.
- If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.
- Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients. Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.
- No information is available on use of the Pranactin-Citric solution during pregnancy.
- For pediatric test results, the Urea Hydrolysis Rate (UHR) results must be calculated. The Delta over Baseline (DOB) results are only used to calculate the UHR metrics to determine *H. pylori* infection in pediatric patients. DOB results **cannot** be used to determine the infection status of pediatric patients. Use the web-based *p*UHR-CA (https://BreathTekKids.com) to calculate the UHR.
- Safety and effectiveness has not been established in children below the age of 3 years.

Adverse Events
During post-approval use of the BreathTek UBT in adults, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

In two clinical studies conducted in 176 (analyzed) pediatric patients ages 3 to 17 years to determine the initial diagnosis and post treatment monitoring of *H. pylori*, the following adverse events experienced by ≥1% of these patients were: vomiting (5.1%), oropharyngeal pain (4.5% to include throat irritation, sore throat, throat burning), nausea (2.3%), restlessness (2.3%), stomach ache/belly pain (1.1%), and diarrhea (1.1%). Most of the adverse events were experienced by patients within minutes to hours of ingestion of the Pranactin-Citric solution.

In another clinical study comparing the UBiT®-IR300 and POCone® in pediatric patients ages 3 to 17 years, the following adverse events were observed among the 99 subjects enrolled: 2 incidences of headache, and 1 incidence each of cough, dry mouth and acute upper respiratory infection.

May 2014 05US14EBP1200

References: 1. Vakil N, Megraud F. Eradication therapy for Helicobacter pylori. *Gastroenterology*. 2007;133(3):985-1001. **2.** Vakil N, Fendrick AM. How to test for Helicobacter pylori in 2005. *Cleve Clin J Med*. 2005;72(suppl 2):S8-S13. **3.** Chu Y-T, Wang Y-H, Wu J-J, Lei H-Y. Invasion and multiplication of Helicobacter pylori in gastric epithelial cells and implications for antibiotic resistance. *Infect Immun*. 2010;78(10):4157-4165. **4.** Chey WD, Wong BCY; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol*. 2007;102(8):1808-1825. **5.** Package Insert for BreathTek UBT. Otsuka America Pharmaceutical, Inc; 2014.

Otsuka
Medical Device Division of
Otsuka America Pharmaceutical, Inc.

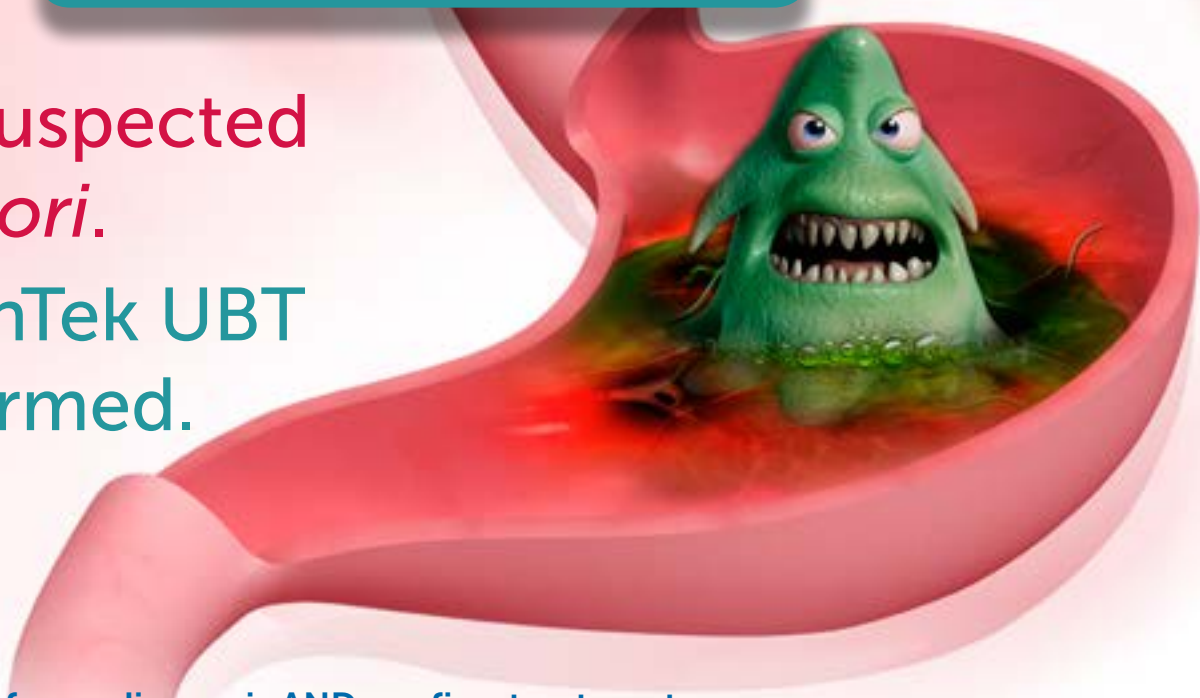
Urea Breath Test for H. pylori
BreathTek®

November 2014 05US14EBP1391

BREATHTEK® UBT FOR *H. PYLORI*

You Suspected *H. pylori*.

BreathTek UBT Confirmed.



To be sure of your diagnosis AND confirm treatment success, choose BreathTek UBT

- Antibiotic resistance is approaching 25%, increasing the need for eradication confirmation[1-3]
- ACG* calls the UBT method "the most reliable nonendoscopic test…" to confirm *H. pylori* eradication[4]
- BreathTek UBT offers excellent sensitivity (96%) and specificity (96%) to confirm eradication in adult patients[5]
- False negative test results may be caused by:
  - Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false-negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon
  - Ingestion of antimicrobials or bismuth preparations within 2 weeks prior to performing the BreathTek UBT
  - Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
  - Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of *H. pylori*
- False positive test results may be caused by urease associated with other gastric spiral organisms observed in humans, such as *Helicobacter heilmannii* or achlorhydria.

H. pylori can't hide from BreathTek UBT…

Approved as an aid for the detection and post-treatment monitoring of *H. pylori* infection in adults and children ages 3 to 17 years

Please see BRIEF SUMMARY on adjacent page or visit BreathTek.com.

Scan to learn more or visit BreathTek.com.

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*ACG, American College of Gastroenterology.

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