ヴィキラックス配合錠
に関する資料

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アッヴィ合同会社

1.5 起原又は発見の経緯及び開発の経緯

1.5.1 起原又は発見の経緯

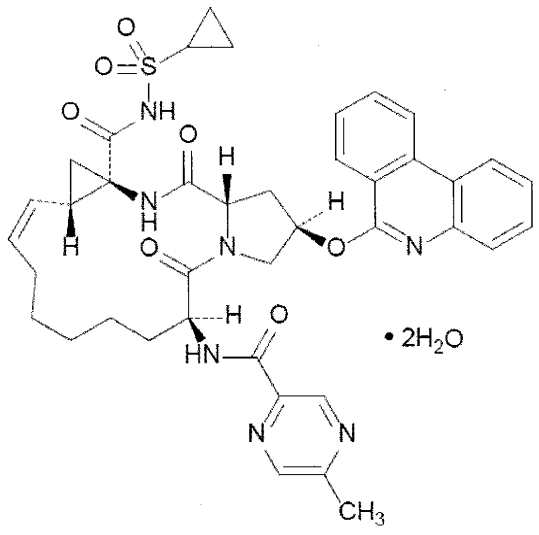
パリタプレビル及びオムビタスビルは，米国 Abbott Laboratories（現 AbbVie Inc.）が開発した C 型肝炎ウイルス（以下「HCV」）非構造たん白質 3/4A（以下「NS3/4A」）プロテアーゼ阻害剤及び HCV 非構造たん白質 5A（以下「NS5A」）阻害剤である。ヴィキラックス配合錠は，オムビタスビル，パリタプレビル及びパリタプレビルの薬物動態学的エンハンサーであるリトナビルを配合し，インターフェロン（以下「IFN」）を使用しない C 型慢性肝炎治療薬として AbbVie Inc.が開発した薬剤である。

(1) パリタプレビル

パリタプレビルは，HCV NS3/4A プロテアーゼ阻害剤で，ジェノタイプ 1a，1b 及び 2a サブジェノミックレプリコン細胞の複製をそれぞれ 1.0，0.21 及び 5.3 nmol/L（EC_{50} 値）の濃度で阻害する。また，パリタプレビルはジェノタイプ 3a，4a 及び 6a 由来 NS3/4A 領域を含むレプリコン細胞においてもそれぞれ 19，0.09 及び 0.68 nmol/L（EC_{50} 値）の濃度で複製阻害作用を示す。パリタプレビルは主としてチトクロム P450 3A4（以下「CYP3A4」）により代謝される。許容できる投与頻度で有効な曝露量を得るために，パリタプレビルは CYP3A4 の強力な阻害剤であるリトナビルと併用（以下「パリタプレビル/リトナビル」）される。

パリタプレビルの抗ウイルス作用は，リトナビルを併用したとき，パリタプレビル のサブジェノミックレプリコン細胞の複製阻害に影響を及ぼさず，リバビリン（以下「RBV」）を併用したときも同様に複製阻害に影響を及ぼさなかった。パリタプレビルの構造式を図 1.5-1 に示す。

図 1.5-1. パリタプレビル構造式

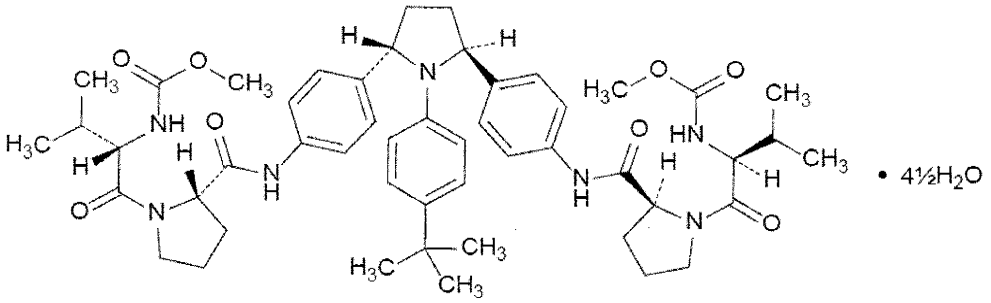


(2) オムビタスビル

オムビタスビルは，HCV NS5A 阻害剤で，ジェノタイプ 1a，1b，2a 及び 2b サブジェノミックレプリコン細胞の複製をそれぞれ 14.1，5.0，12.4 及び 4.3 pmol/L（EC_{50} 値）の濃度で阻害する。また，ジェノタイプ 3a，4a，5a 及び 6a 由来 NS5A 領域を含むレプリコン細胞においてもそれぞれ 19.3，1.7，3.2 及び 366 pmol/L（EC_{50} 値）の濃度で複製阻害作用を示す。オムビタスビルは，パリタプレビル又は RBV との併用において，短期レプリコンアッセイで HCV の複製に対して相加的から相乗的な複製阻害作用を示した。

オムビタスビルの構造式を図 1.5-2 に示す。

図 1.5-2.　　オムビタスビル構造式



(3) パリタプレビル/リトナビル/オムビタスビル配合製剤

米国 AbbVie Inc.では，C 型慢性肝炎治療薬として，HCV の複製を様々な段階で阻害する直接作用型抗ウイルス剤（以下「DAA」）の臨床開発を進めてきた。IFN を使用しない DAA 併用療法の種々の臨床試験から，併用投与で良好な抗ウイルス活性を示すことが報告されている。HCV ジェノタイプの分布は地域によって異なるため，各ジェノタイプの分布に沿って最適な IFN 非併用の治療法を開発する必要があると考えた。本邦においては，ジェノタイプ 1b 及びジェノタイプ 2 が多く占めることから，アッヴィ合同会社（以下「アッヴィ社」）がこれらのジェノタイプに対して特に効果が認められた DAA であるオムビタスビル並びにパリタプレビル及びリトナビルの併用療法の開発について進めることとした。

個々の DAA の試験結果より，DAA を単剤で投与することにより，HCV 耐性株が早期に出現することが確認されている。そのため，HCV に対して異なる作用機序を持ち，かつ耐性プロファイルの異なるパリタプレビルとオムビタスビルを併用することにより，それぞれの薬剤に対して治療抵抗性を生じる耐性変異による治療不成功例を軽減させることが期待される。また，強力な CYP3A4 阻害剤であるリトナビルを併用することにより，CYP3A4 の基質となるパリタプレビルの代謝が阻害されることから，パリタプレビルの血漿中濃度が増加し，半減期が延長する。パリタプレビルの非存在下でオムビタスビルとリトナビルを併用投与すると，リトナビルによる CYP3A 及び/又は排出系トランスポーター阻害により，オムビタスビルの曝露量が 60–

70%増加する。リトナビル 100 mg との併用下では，パリタプレビル 200 mg 及び 250 mg 投与時の曝露量は，オムビタスビル 25mg の同時投与によりわずかに影響を受ける程度であった（5–27%）。

IFN 非併用下におけるこれらの DAA 2 剤と薬物動態学的エンハンサーであるリトナビルの併用療法については，国内外の臨床試験において，有効性及び安全性のプロファイルが好ましいことを確認している。更に，パリタプレビル，オムビタスビル及びリトナビルを服薬が簡便な 1 つの錠剤に配合したことにより，HCV に対して異なる作用機序を有するパリタプレビルとオムビタスビルの 2 剤が確実に併用投与され，単剤の場合での併用服薬不順守などによる曝露量の減少で引き起こされるウイルス耐性変異の出現リスクを抑制できることが期待される。

1.5.2 本剤の対象疾患及び臨床上の位置づけ

1.5.2.1 C 型慢性肝炎の概要

C 型慢性肝炎は，公衆衛生上の問題となっており，その感染者数は，全世界で約 1 億 7000 万人，本邦では 150–200 万人と推定されている[1]。C 型慢性肝炎は，本邦では 1930 年代及び 1940 年代に拡大し，C 型慢性肝炎患者は欧米に比べて高齢であることから，今後数年から数十年で HCV 感染による健康保険負担が増大すると予測されている。HCV 感染後，約 70%の患者で HCV 感染が持続し，慢性肝炎へと移行する[1]。C 型慢性肝炎患者では，ウイルスの自然排除は年率 0.2%と稀であり，HCV 感染による炎症の持続により肝線維化が惹起され，肝硬変や肝細胞癌へと進展する[2]。肝硬変は，C 型慢性肝炎患者の約 20%に認められる[3]。肝硬変に伴う合併症には肝代償不全があり，腹水，脳症，静脈瘤出血，肝腎症候群又は肝合成機能障害などが生じる。また，肝細胞癌は 1 年あたり約 3 %の患者に発症する[4, 5, 6, 7]。肝移植を行わない場合，非代償性肝硬変患者の 50%が 5 年以内に死に至る[8]。HCV 感染及び HCV 感染から続発した合併症の有病率が高いため，HCV 感染は肝細胞癌の発生率上昇の主な要因になっており[9]，発展途上国では肝移植の適応疾患となっている[10, 11]。肝硬変が代償性であり，持続性ウイルス学的著効（以下「SVR」）が認められ，非代償性化する危険性を本質的に取り除かれた患者では，組織学的な寛解がもたらされ，肝細胞癌に至る危険性を 1/3 に軽減することができる[12, 13, 14]。

HCV は，7 種の主なジェノタイプ（ジェノタイプ 1 からジェノタイプ 7）に分類され，更に異なるサブジェノタイプに分けられる[15]。本邦においては 60%–70%がサブジェノタイプ 1b，25%–30%がサブジェノタイプ 2a 又は 2b に感染していると推定される[16]。米国及び欧州の多くの国と比較して，日本人 C 型慢性肝炎患者ではサブジェノタイプ 1a の感染は非常に稀である（HCV ジェノタイプ 1 患者の 1.2%–2.5%）[17]。

1.5.2.2 C 型慢性肝炎の治療の現状

C 型慢性肝炎治療の目標は，HCV 持続感染によって惹起される慢性肝疾患の長期予後の改善，即ち，肝癌並びに肝疾患関連死を抑止することにある。そのための効果的な治療として，ウイ

ルス排除が重要と考えられており，高齢者や肝硬変を含む高発癌リスク群では，早期に抗ウイルス療法が考慮されるべきとされている[1]。

本邦では，1992 年に IFN 製剤が C 型慢性肝炎治療として承認され，その後 RBV との併用療法やペグインターフェロン（以下「pegIFN」製剤が開発され，ジェノタイプ型に応じて投与期間が最適化された。しかしながら，pegIFN 及び RBV の併用療法では，難治性のジェノタイプ 1 型かつ高ウイルス量の C 型慢性肝炎患者における投与終了 24 週後の持続性ウイルス学的著効（以下「SVR24」）達成率は 60%程度であった[18]。また，pegIFN 及び RBV の併用による著しい副作用（発熱，倦怠感，頭痛等のインフルエンザ様症状，うつ病，発疹を含む重篤な皮膚反応，貧血等）により，多くの患者が減量，休薬に至り，12%–15%の患者が治療を中止した[18]。そのため，治療効果の向上，安全性及び忍容性の改善が課題であった。

2011 年に NS3/4A プロテアーゼ阻害作用を有する DAA のテラプレビルが本邦で承認され，pegIFN 及び RBV の 24 週間 3 剤併用療法が導入された。この 3 剤併用療法により，ジェノタイプ 1 型かつ高ウイルス量の C 型慢性肝炎患者における SVR24 達成率は，未治療及び IFN 製剤による前治療再燃例において 73%及び 88%と向上し，治療期間は pegIFN 及び RBV の併用療法の 48 週間–72 週間から 24 週間に短縮したが，IFN 製剤による前治療無効例における SVR24 達成率は 34%であった[19, 20]。また，テラプレビル，pegIFN 及び RBV の 3 剤併用療法では，pegIFN 及び RBV による副作用に加えて，中毒性表皮壊死融解症や皮膚粘膜眼症候群（スティーブンス・ジョンソン症候群）等を含む皮膚障害の発現が倍増し（テラプレビル，pegIFN 及び RBV：46%，pegIFN 及び RBV：23%）[21]，更に pegIFN 及び RBV の 2 剤併用療法に比べて貧血の悪化が強く，既存の腎疾患を悪化させることが報告されている。なお，テラプレビル，pegIFN 及び RBV の 3 剤併用療法は，代償性肝硬変患者に対する適応は得られていない。

2013 年に NS3/4A プロテアーゼ阻害作用を有する DAA のシメプレビルと pegIFN 及び RBV との 3 剤併用療法が承認された。この 3 剤併用療法のジェノタイプ 1 型かつ高ウイルス量の C 型慢性肝炎患者における SVR24 達成率は，未治療例及び IFN 製剤による前治療再燃例において 89%–92%及び 90%–97%を示し，安全性プロファイルはビリルビン値上昇及び光線過敏症の発現率が高かったが，pegIFN 及び RBV の 2 剤併用療法と同様であった[22, 23, 24]。しかし，IFN 製剤による前治療無効例における SVR24 達成率は 38%–51%であり，テラプレビルと同様に IFN 製剤による前治療無効例における治療効果は不十分であった。また，シメプレビルと pegIFN 及び RBV との 3 剤併用療法では，pegIFN 及び RBV による副作用及びシメプレビルによる光線過敏症の発現に加えて，市販後においては，ビリルビン値が著しく上昇し，肝機能障害を発現し死亡に至った症例が報告されている[25]。なお，シメプレビル，pegIFN 及び RBV の 3 剤併用療法はテラプレビルと同様に代償性肝硬変患者に対する有効性及び安全性は検討されていないため，代償性肝硬変患者に対しては pegIFN 及び RBV の 2 剤併用療法が標準治療とされていた。

2014 年にバニプレビル，pegIFN 及び RBV の 12 週間又は 24 週間 3 剤併用療法が肝硬変の認められないジェノタイプ 1 型かつ高ウイルス量の C 型慢性肝炎患者の未治療例，IFN 製剤による前治療無効例又は再燃例に対して承認され，ジェノタイプ 1 型かつ高ウイルス量の C 型慢性肝炎患者における SVR24 達成率は，未治療例，IFN 製剤による前治療再燃例及び無効例におい

てそれぞれ 84%，92%及び 62%を示した。しかし，バニプレビルはテラプレビルやシメプレビルと同様に pegIFN 及び RBV との併用が必要であるため，pegIFN 及び RBV による副作用が発現し，好中球減少，血小板減少，貧血及びうつ病がそれぞれ 51%，32%，22%及び 2.1%に認められている[26]。

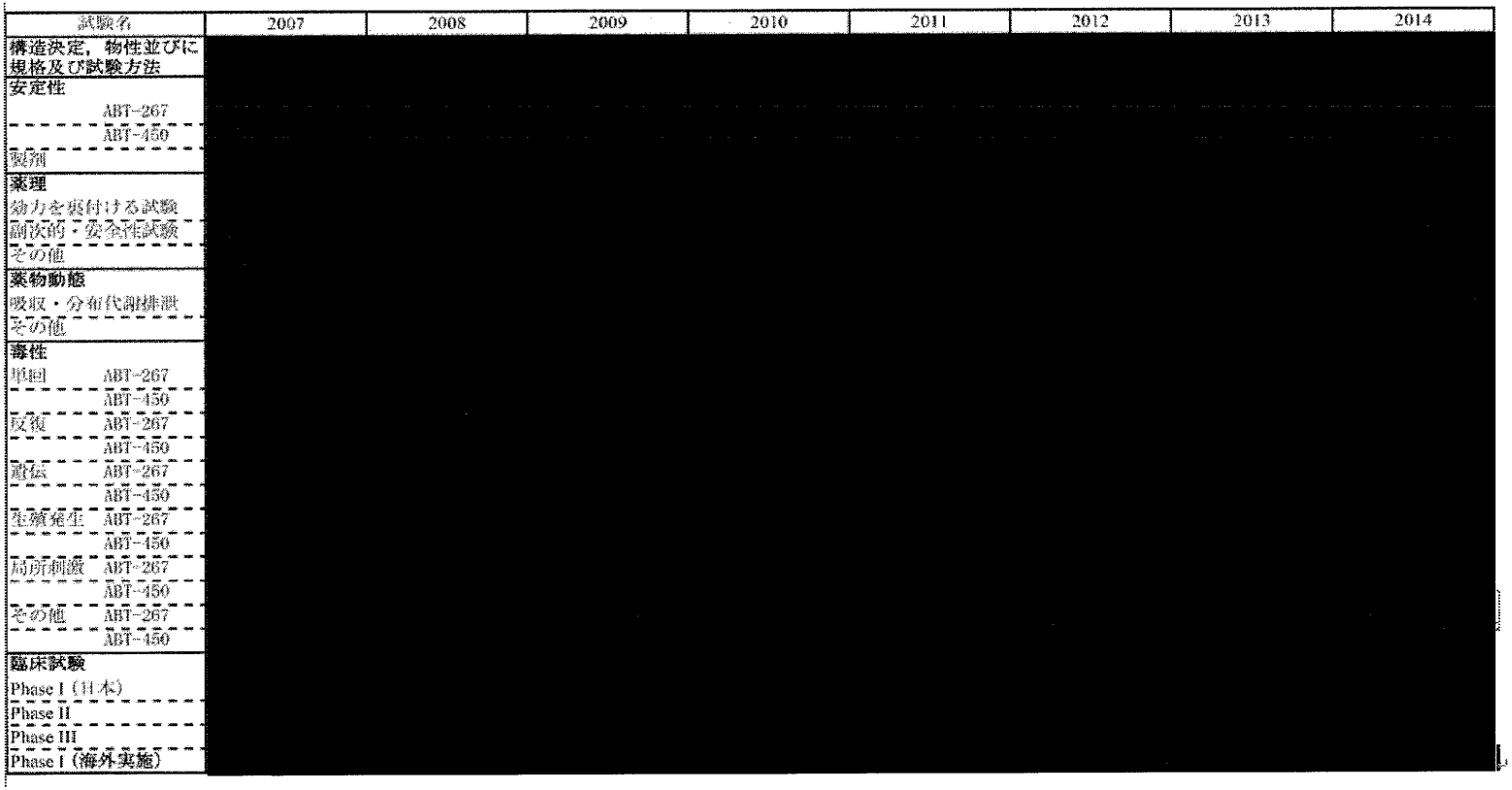
2014 年 7 月に，NS3/4A プロテアーゼ阻害剤であるアスナプレビルと NS5A 阻害剤であるダクラタスビルが IFN，RBV を使用しない DAA 2 剤併用療法として承認された。この DAA 2 剤併用療法の SVR24 達成率は，IFN 製剤による治療に不適格の未治療例又は不耐容例において 87%であり，IFN 製剤による治療で無反応例又は部分反応例において 80%を示した。また，代償性肝硬変患者に対しても 91%の SVR24 達成率を示した[27]。治療期間は 24 週間で，3 剤併用療法では IFN の皮下投与のため毎週通院する必要があったのに対して，アスナプレビルは 1 日 2 回，ダクラタスビルは 1 日 1 回の経口投与が可能となった。しかし，この DAA 2 剤併用療法で IFN による副作用は回避できる一方で，グレード 3（基準値上限の 5 倍超 10 倍以下）又はグレード 4（基準値上限の 10 倍超）のアラニンアミノトランスフェラーゼ（以下「ALT」）上昇やアスパラギン酸アミノトランスフェラーゼ（以下「AST」）上昇がそれぞれ 7.2%及び 5.4%に発現し，投与中止に至る重大な肝機能障害の発現が 4.5%に認められている[27]。更に，この DAA 2 剤併用療法開始前に NS5A 領域に Y93H 又は L31M/V の耐性変異を認める患者における SVR24 達成率は，それぞれ 43.3%及び 25%と低いことが報告されている。

以上より，本邦におけるジェノタイプ 1 型 C 型慢性肝炎患者の治療においては，高発癌リスク群（高齢かつ線維化進展例）を含む，未治療の IFN 製剤による治療に適格及び不適格患者，IFN 製剤による前治療で再燃，無効及び不耐容患者並びに代償性肝硬変患者のいずれにおいても有効性及び安全性が高く，簡便な 1 日 1 回の経口投与で，投与期間が短縮した（12 週間）治療法が求められている。

1.5.3 開発の経緯

本剤の開発経緯図を図 1.5- 3 に示す。

図 1.5- 3.　　開発経緯図



注：ABT-450：パリタプレビル
　　ABT-267：オムビタスビル

1.5.3.1 品質に関する試験の概要

(1)原薬

アッヴィ社では，オムビタスビル水和物及びパリタプレビル水和物の構造及び物理化学的特性を評価した。オムビタスビル水和物及びパリタプレビル水和物の規格はアッヴィ社にて ICH ガイドラインに従って設定した。

ICH ガイドラインに従ってオムビタスビル水和物及びパリタプレビル水和物の安定性試験（長期保存試験，加速試験及び苛酷試験）を実施した。24 ヵ月間長期安定性試験のデータに基づき，リテスト期間を[redacted]ヵ月間に設定した。長期安定性試験は[redacted]ヵ月まで継続する。

(2)製剤

原薬は 3 種類とも溶解性が極めて低いことから，製剤の製造工程に[redacted]工程を適用している。

製剤の規格はアッヴィ社にて ICH ガイドラインに従って設定した。

ICH ガイドラインに従って製剤の安定性試験（長期保存試験，加速試験及び苛酷試験）を実施した。ブリスター包装を用いた 24 ヵ月間長期安定性試験のデータに基づき，有効期間を 36 ヵ月間に設定した。長期安定性試験は[redacted]ヵ月まで継続する。

(3)新添加物

基剤として配合しているコポリビドンは，医薬品医療機器総合機構（PMDA）の簡易相談にてその含有量が使用前例を超えていることが確認された。そのため，コポリビドンを新医薬品添加物として新医薬品添加物委員会に提出する。

1.5.3.2 非臨床試験の概略

1.5.3.2.1 薬理試験

効力を裏付ける試験として，HCV NS3/4A プロテアーゼ阻害剤であるパリタプレビルについてはプロテアーゼ酵素阻害活性と HCV サブジェノミックレプリコン細胞を用いた複製阻害活性を評価し，パリタプレビルはナノモル以下の濃度で阻害作用を示すことが確認された。HCV NS5A 阻害剤であるオムビタスビルについては，HCV サブジェノミックレプリコン細胞を用いた複製阻害活性を評価し，ピコモル濃度で阻害作用を示すことが確認された。パリタプレビルとオムビタスビルの併用投与では，サブジェノミックレプリコン細胞アッセイにおいて評価したほとんどの濃度で相乗的な阻害作用がみられた。パリタプレビルの HCV ジェノタイプ 1 及び 2 の *in vitro* 試験又は臨床試験で認められた NS3 の耐性関連変異は，アミノ酸位置 56，155，156 及び 168 位であった。オムビタスビルの HCV ジェノタイプ 1 及び 2 の *in vitro* 試験又は臨床試験で認められた主要な耐性関連変異は，アミノ酸位置 24（ジェノタイプ 2a のみ），28，30，31，58 及び 93 位であった。

副次的薬理試験及び安全性薬理試験として，一連の安全性コアバッテリー試験及び受容体結合性を評価した。パリタプレビル及びオムビタスビルの非臨床安全性薬理試験では，特に問題となる所見はみられなかった。

1.5.3.2.2 薬物動態試験

オムビタスビル並びにパリタプレビル（リトナビル併用及び非併用）の薬物動態は，マウス（CD-1，TgHras），ラット（Sprague-Dawley，Long Evans）New Zealand white ウサギ，カニクイザル，ビーグル犬及びヒトにおいて評価された。パリタプレビルは主に CYP3A4 で代謝され各種水酸化体を生成する。高い初回通過効果又は肝における消失を軽減するために，パリタプレビルは強力な CYP 及び排出トランスポーター阻害剤であるリトナビルと同時投与することにより，非臨床試験における動物種及びヒトにおいて，バイオアベイラビリティの相当な増加をもたらされる。オムビタスビルはアミド加水分解及びそれに続く酸化的代謝を受ける。定常状態における循環血漿中の代謝物のプロファイルを検討することにより， 不活性なヒト特有のオムビタスビルの代謝物（M29 及び M36）が同定された。ヒトにおいてリトナビルとの併用時にパリタプレビルの主な代謝物（血漿中の薬物関連物質全体に占める割合が 10%を超える）は認められなかった。放射性標識物質を用いた試験によって，主な毒性評価動物種及びヒトにおける放射能の排泄パターン並びに雄ラット及び妊娠ラットにおける組織内分布の概要が示された。いずれの種においてもパリタプレビル及びオムビタスビルの蛋白結合は極めて高く 99%以上であった。パリタプレビル，リトナビル及びオムビタスビルの CYP 他薬物代謝酵素各分子種及び各種トランスポーターに対する基質特異性及び阻害特性が明らかにされた。パリタプレビル，リトナビル及びオムビタスビルの CYP，トランスポーター及び UGT1A1 を介する薬物相互作用を受ける側及び与える側としての可能性は非臨床試験で検討され，さらに DAA 2 剤療法と併用薬を同時投与した時の薬物相互作用は臨床試験においても評価された。

1.5.3.2.3 毒性試験

パリタプレビル/リトナビル及びオムビタスビルの反復投与毒性試験における最長投与期間は，ラットでは 3 ヵ月間，マウスでは 6 ヵ月間及びイヌではオムビタスビルは 6 ヵ月間，パリタプレビル/リトナビルは 9 ヵ月間とした。オムビタスビルをパリタプレビル/リトナビルと併用した場合及び臨床曝露量の 4 倍量まで単剤で投与した臨床試験においてもオムビタスビルに起因する重篤な副作用はみられていない。反復投与毒性試験に加え，遺伝毒性試験，生殖発生毒性試験及びトランスジェニックマウスを用いた 6 ヵ月間がん原性試験を実施し，パリタプレビル及びオムビタスビルの毒性を評価した。オムビタスビルについてはヘアレスマウスを用いた光毒性試験を実施した。一方、パリタプレビルについては，これまでに実施した臨床試験において光毒性を示唆する副作用がみられていないことから光毒性試験を実施しなかった。ラットの 2 年間がん原性試験についても実施した。不純物又は分解物の毒性試験については，オムビタスビルではマウスの 1 ヵ月間反復投与毒性試験，パリタプレビルではラットの 1 ヵ月間反復投与

毒性試験を実施した。ヒトにおけるDAA併用療法の一部としてオムビタスビル 25 mgを投与したところ，定常状態においてヒト特有に存在する 2 種類のオムビタスビルの循環血中代謝物（M29及びM36）が同定された。これらの代謝物については， *in vitro* 遺伝毒性（復帰突然変異試験，染色体異常試験），マウスの 1 ヵ月間反復投与毒性試験及び胚・胎児発生に関する試験を実施した。代謝物を用いた 1 ヵ月間反復投与毒性試験には，遺伝毒性評価項目（小核試験）を含めた。主要なトキシコキネティクス及び毒性試験は，医薬品の安全性に関する非臨床試験の実施の基準（以下「GLP」）に準拠して実施した。なお，一部の試験は非 GLP 試験として実施したが，GLP と同程度の高い科学水準で実施した。

1.5.3.3 臨床開発の概略

1.5.3.3.1 第 I 相試験

日本人健康被験者を対象としたパリタプレビル/リトナビル及びオムビタスビル各々の単剤又は併用投与時の安全性，忍容性及び薬物動態を検討する試験（M[redacted]-384 試験，M[redacted]-181 試験，M[redacted]-221 試験及び M[redacted]-688 試験，M[redacted]-505 試験，M[redacted]-771 試験，M[redacted]-247 試験）を実施した。これらの試験は，国内又は海外在住の日本人被験者を対象とした。これらの試験で使用したパリタプレビル/リトナビル又はオムビタスビルの用法・用量は以下のとおりである。

- パリタプレビル/リトナビル単剤による 50/100 mg，100/100 mg 又は 200/100 mg の単回投与，50/100 mg，200/100 mg 又は 250/100 mg の 1 日 1 回 14 日間反復投与；
- オムビタスビル単剤による 25 mg 及び 200 mg の 1 日 1 回 7 日間反復投与；
- パリタプレビル/リトナビル 100/100 mg 又は 150/100 mg とオムビタスビル 25 mg の単回投与；
- パリタプレビル/リトナビル 150/100 mg，200/100 mg 又は 250/100 mg とオムビタスビル 25 mg の 1 日 1 回 7 日間又は 14 日間の併用投与；
- パリタプレビル/リトナビル 150/100 mg，オムビタスビル 25 mg 及び dasabuvir* [redacted] mg の 1 日 1 回（dasabuvir* は 1 日 2 回）21 日間反復投与。

これらの用法・用量における忍容性は，良好であった。日本人被験者にパリタプレビル/リトナビルとオムビタスビル 25 mg を併用投与したときのオムビタスビルの曝露量は外国人被験者と同程度だったが，パリタプレビルの曝露量は外国人被験者に比べて高かった。

また，国内第 II 相試験で使用した製剤と，申請製剤である国内第 III 相試験で使用したパリタプレビル/リトナビル/オムビタスビル配合剤の薬物動態を検討した（M[redacted]-505 試験）。その結果，パリタプレビル/リトナビル/オムビタスビル配合錠（150/100/25 mg）におけるオムビタスビル及びリトナビルの曝露量は，国内第 II 相試験で使用した製剤と同程度であったが，パリタプレビルの曝露量（AUC）は 53%増加した。

その他，日本人被験者を対象としたパリタプレビル/リトナビル/オムビタスビル配合剤の第 I 相試験として，食事の影響試験（M[redacted]-771 試験），薬物相互作用試験（M[redacted]-247 試験）を実施した。また海外試験として，QT/QTc 評価試験（M[redacted]-680 試験），バイオアベイラビリティ，食事の影響の試験（10 試験），薬物動態試験（6 試験），併用投与を検討する試験（2 試験），薬物

*新薬承認情報提供時に置き換え

相互作用試験（25 試験），絶対的バイオアベイラビリティ試験（1 試験），特殊な患者（肝機能障害患者及び腎機能障害患者）の薬物動態を検討する試験（2 試験），パリタプレビル及び dasabuvir*（海外第Ⅲ相試験で使用した非ヌクレオシド系 NS5B 阻害剤）の相互作用を検討する試験を実施した。

1.5.3.3.2 国内第 II 相試験

M[redacted]-536 試験は，pegIFN 及び RBV 既治療（無反応例，部分反応例及び再燃例）の肝硬変の認められない日本人 HCV ジェノタイプ 1b 又はジェノタイプ 2 感染患者を対象に，パリタプレビル/リトナビル及びオムビタスビルの安全性，忍容性，抗ウイルス活性，薬物動態，用量及び投与期間を評価する第 II 相，無作為化，並行群間，非盲検試験である。日本人及び外国人健康被験者並びに外国人 HCV 感染患者の薬物動態及び抗ウイルス活性の結果に基づいて，オムビタスビルは至適用量として 25 mg 1 日 1 回投与，パリタプレビル/リトナビルは外国人被験者において 100 mg，150 mg 及び 200 mg の用量範囲内である 100/100 mg 及び 150/100 mg を選択し，投与期間はジェノタイプ 1b では 12 週間又は 24 週間，ジェノタイプ 2 では 12 週間と設定した。主要評価項目は，SVR24 が認められた被験者の割合とした。

その結果，HCV ジェノタイプ 1b 感染被験者では，12 週間投与群での SVR24 達成率はパリタプレビル/リトナビル 100/100 mg とオムビタスビル 25 mg 併用群が 100%，パリタプレビル/リトナビル 150/100 mg とオムビタスビル 25 mg 併用群が 88.9%であり，24 週間投与群での SVR24 達成率はパリタプレビル/リトナビル 100/100 mg とオムビタスビル 25 mg 併用群及びパリタプレビル/リトナビル 150/100 mg とオムビタスビル 25 mg 併用群がいずれにおいても 100%であった。いずれの群においても SVR24 達成率と投与終了 12 週後の持続性ウイルス学的著効（以下「SVR12」）達成率は変わらなかった。また，パリタプレビル/リトナビルとオムビタスビル併用時の安全性及び忍容性は良好で，パリタプレビル/リトナビル 100/100 mg とオムビタスビル 25 mg 又はパリタプレビル/リトナビル 150/100 mg とオムビタスビル 25 mg を 12 週間又は 24 週間併用投与において類似していた。第 II 相試験の結果及び日本人被験者におけるパリタプレビル/リトナビル/オムビタスビル配合錠 150/100/25 mg 投与時のパリタプレビル曝露量は，海外の第 I 相試験においてパリタプレビル/リトナビル/オムビタスビル及び dasabuvir* を併用投与したときのパリタプレビルの曝露量と同程度であったことから，第 III 相試験ではパリタプレビル/リトナビル/オムビタスビル配合錠を使用し，耐性関連変異の出現を抑制して有効性を最適化するとともに安全性を最大限確保する目的で，本剤の用量は 150/100/25 mg，投与期間は 12 週間投与を選択した。

1.5.3.3.3 国内第 III 相試験

M13-004 試験は，日本人 HCV ジェノタイプ 1b 感染患者の未治療例及び既治療例（代償性肝硬変を含む）を対象として，パリタプレビル/リトナビル/オムビタスビルの有効性及び安全性を評価する第 III 相，多施設共同試験である。肝硬変の認められない被験者に対しては，無作為化，

*新薬承認情報提供時に置き換え

二重盲検，プラセボ対照試験（サブ試験 1），また代償性肝硬変の認められる被験者に対しては，非盲検試験（サブ試験 2）で実施した。肝硬変の認められない被験者において，既治療例では IFN 製剤による前治療無効例，再燃例及び不耐容例を層別因子とし，未治療例では高ウイルス量及び低ウイルス量を層別因子とし，高ウイルス量では更に IFN 製剤による治療適格例及び不適格例を層別因子とした。二重盲検期間ではパリタプレビル/リトナビル/オムビタスビル（投与群 A）又はプラセボ（投与群 B）を 2：1 の割合で無作為に割付けし，プラセボに割付けられた被験者には，その後非盲検下でパリタプレビル/リトナビル/オムビタスビルを投与した。肝硬変の認められる被験者には非盲検下でパリタプレビル/リトナビル/オムビタスビル（投与群 C）を投与した。パリタプレビル/リトナビル/オムビタスビルは 75/50/12.5 mg 配合錠 2 錠を 1 日 1 回 12 週間投与した。主要評価項目は，肝硬変の認められない未治療例のうち，高ウイルス量で IFN 製剤による治療適格例における SVR12 達成率の 95%信頼区間の下限と，テラプレビルと pegIFN 及び RBV のヒストリカル SVR 達成率に基づいて，臨床的に適切な閾値（63%）を比較することにより，本剤の優越性を検証することとした。

その結果，主要評価項目において，肝硬変の認められない未治療の高ウイルス量で IFN 製剤による治療適格例における SVR12 達成率は 94.6%（95%信頼区間：90.5%–98.8%）であり，95%信頼区間の下限が 63%を上回ったことから，パリタプレビル/リトナビル/オムビタスビルの優越性が検証された。また，各部分集団における SVR12 達成率は，既治療例では IFN 製剤による前治療無効例，再燃例及び不耐容例がそれぞれ 100%，95.5%及び 92.3%，未治療例では IFN 製剤による治療不適格例及び低ウイルス量例がそれぞれ 91.3%及び 100%，また代償性肝硬変例では 90.5%であり，いずれも肝硬変の認められない未治療の高ウイルス量で IFN 製剤による治療適格例における SVR12 達成率と類似した高い達成率（90%超）を示した。有効性の主要解析対象集団（投与群 A の ITT 集団のうち，肝硬変の認められない被験者において未治療の高ウイルス量で IFN 製剤による治療適格例）での SVR24 達成率は 93.8%であった。サブ試験 1 で DB 治療期にプラセボを投与した後，OL 治療期に実薬を投与した肝硬変の認められない被験者（投与群 B の非盲検集団［以下「OL 集団」］）において，SVR12 達成率は 98.1%であった。これらの被験者のうち未治療の高ウイルス量で IFN 製剤による治療適格例（有効性の主要解析対象集団に相当）での SVR12 達成率は 100%であった。DB 治療期の安全性において，パリタプレビル/リトナビル/オムビタスビル投与による有害事象の発現率（68.8%）及びパリタプレビル/リトナビル/オムビタスビルとの因果関係「関連あり」と判断された有害事象の発現率（30.7%）は，プラセボのそれぞれ 56.6%及び 14.2%と比べて統計学的に有意に高かったが，個々の有害事象においてプラセボに比べて統計学的に有意に高かったのは末梢性浮腫のみであった（パリタプレビル/リトナビル/オムビタスビル：5.1%，プラセボ：0%）。また，末梢性浮腫を発現したすべての被験者で Ca 拮抗薬が併用されていた。末梢性浮腫は Ca 拮抗薬との関連性がある有害事象であり，また Ca 拮抗薬はリトナビルとの薬物相互作用が認められている。追加解析の結果から，肝硬変の認められない被験者における浮腫関連事象の発現率は，低用量の Ca 拮抗薬を併用した被験者（添付文書（案）に記載）の方が，低用量以外の Ca 拮抗薬を併用した被験者に比べて低いことが示された。一方，重篤な有害事象の発現率，投与中止に至った有害事象の発現率は両群間に

統計学的な有意差はなかった。サブ試験 1 において OL 治療期での投与群 B の安全性プロファイルは，DB 治療期での投与群 A と同様であった。また，投与群 B の OL 集団では非盲検でパリタプレビル/リトナビル/オムビタスビルの投与中止又は投与中断に至った有害事象はなかった。パリタプレビル/リトナビル/オムビタスビルの忍容性は良好で，既存の DAA で報告されている血液障害や皮膚障害は認められなかった。

1.5.3.3.4 海外試験

M[redacted]-393 試験は，未治療又は既治療の代償性肝硬変を含む HCV ジェノタイプ 1 及びジェノタイプ 4 感染患者を対象として，パリタプレビル/リトナビル及びオムビタスビルの安全性，有効性及び薬物動態を評価した第 II 相，無作為化，非盲検試験である。肝硬変の認められない HCV ジェノタイプ 1b 感染被験者は pegIFN 及び RBV による前治療無反応例であり，肝硬変の認められる HCV ジェノタイプ 1b 感染被験者及び肝硬変の認められない HCV ジェノタイプ 4 感染被験者は pegIFN 及び RBV による前治療無反応例，部分反応例又は再燃例であった。肝硬変の認められない被験者にはパリタプレビル/リトナビル 150/100 mg 及びオムビタスビル 25 mg を 1 日 1 回 12 週間投与し，肝硬変の認められる被験者には，パリタプレビル/リトナビル 150/100 mg 及びオムビタスビル 25 mg を 1 日 1 回 24 週間投与した。その結果，M[redacted]-393 試験におけるパリタプレビル/リトナビル及びオムビタスビルの安全性プロファイルは，本邦で行われた結果とおおむね一致していた。

M[redacted]-998 試験は，未治療の肝硬変の認められない HCV ジェノタイプ 1a 及び 1b，2 又は 3 感染患者を対象として，RBV 併用又は非併用下にパリタプレビル/リトナビル 200/100 mg 及びオムビタスビル 25 mg を 1 日 1 回 12 週間併用したときの抗ウイルス活性，安全性及び薬物動態を検討した非盲検，多施設共同試験である。HCV ジェノタイプ 1a 感染被験者に RBV 非併用でパリタプレビル/リトナビル及びオムビタスビルを評価した海外試験は，本試験のみである。HCV ジェノタイプ 1a 感染被験者及び HCV ジェノタイプ 1b 感染被験者において，RBV 非併用下でのパリタプレビル/リトナビル及びオムビタスビルの併用投与による SVR24 達成率は，それぞれ 62.5%（5/8 例）及び 50.0%（1/2 例）であった。M[redacted]-393 試験におけるパリタプレビル/リトナビル及びオムビタスビルの安全性プロファイルは，本邦で行われた結果とおおむね一致していた。

1.5.3.4 対面助言

各臨床試験実施に先立ち医薬品医療機器総合機構と以下の対面助言行った。

1.5.3.4.1 [redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

以上の見解が得られたが，[redacted]を検討することとした。

1.5.3.4.2 [redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
  - [redacted]

- [redacted]
- [redacted]

- [redacted]
- [redacted]

1.5.3.4.3 [redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]。
- [redacted]。

1.5.3.4.4 [redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
- [redacted]
- [redacted]

なお，[redacted]については，[redacted]相談を行った。また，[redacted]相談についても実施した。

1.5.4 その他の海外での臨床開発状況

米国においては肝硬変を含むジェノタイプ 1 型（主にジェノタイプ 1a）C 型慢性肝炎に対する IFN 非併用の DAA 3 剤併用療法として，パリタプレビル/リトナビル/オムビタスビル配合錠

及びNS5Bポリメラーゼ阻害剤であるdasabuvir* の組合せ製剤として承認申請を2014年4月に行い，同年 12 月に承認を得た。一方，欧州においてはパリタプレビル/リトナビル/オムビタスビル配合錠及びdasabuvir* 製剤の承認申請を2014年5月に行い，2015年1月に承認を得た。また，欧州では，ジェノタイプ4型C型慢性肝炎に対してDAA 2剤併用療法として，パリタプレビル/リトナビル/オムビタスビル配合錠の申請を2014年5月に行い，2015年1月に承認を得ている。

1.5.5 本剤の予測される治療上の位置づけ

IFN を使用しない本剤（パリタプレビル/リトナビル/オムビタスビル）による治療は，国内臨床試験において，HCV ジェノタイプ 1b 感染患者に対し，未治療例（高ウイルス量で IFN 製剤による治療適格例，IFN 製剤による治療不適格例及び低ウイルス量例），既治療例（IFN 製剤による前治療再燃例，無効例及び不耐容例）及び代償性肝硬変例のいずれに対しても高い SVR12 達成率を示すとともに，忍容性は良好であることが確認された。各部分集団における再燃率は，IFN 製剤による治療が困難と考えられる集団を含め 0%-5.0%と低く，SVR12 達成率は各部分集団において 90.5%-100%であり，主要評価項目の未治療の高ウイルス量で IFN 製剤による治療適格例においては，投与期間中のウイルス学的治療不成功以外の投与中止例及び SVR12 のデータ欠測例を除いた SVR12 達成率は 97.2%を示したことから，本剤の抗ウイルス活性は高いことが示された。また，既存の治療薬では HCV ジェノタイプ 1b 感染患者に対して 24 週間-48 週間の投与が必要であったが，本剤は 12 週間の経口投与で高い SVR12 達成率を示した。更に，本剤は，[redacted]成法（[redacted]）の技術を用いてパリタプレビル，オムビタスビル及びリトナビルを服薬が簡便な 1 つの錠剤に配合したことにより，HCV に対して異なる作用機序を有するパリタプレビルとオムビタスビルの 2 剤が確実に併用投与され，単剤の場合での併用服薬不順守などによる曝露量の減少で引き起こされるウイルス耐性変異の出現リスクを抑制することが期待される。

国内第 II 相試験（M[redacted]-536 試験）及び第 III 相試験（M13-004 試験）の結果より，代償性肝硬変を含む日本人 C 型慢性肝炎患者に対する本剤の高い有効性及び安全性が確認された。これらの結果は，医療上の必要性が高い C 型慢性肝炎患者に対して，IFN を使用しない本剤は高い SVR 達成率及び安全性を示し，簡便な 1 日 1 回の経口投与及び短縮した投与期間（12 週間）で使用する新しい治療を提供するものと考え，以下の効能・効果，用法・用量において本剤の製造販売承認申請を行った。なお，[redacted]である。

*新薬承認情報提供時に置き換え

【効能又は効果】
セログループ 1（ジェノタイプ 1）の C 型慢性肝炎又は C 型代償性肝硬変におけるウイルス血症の改善

【用法及び用量】
通常，成人には 1 日 1 回 2 錠（オムビタスビルとして 25 mg，パリタプレビルとして 150 mg 及びリトナビルとして 100 mg）を食後に経口投与し，投与期間は 12 週間とする．

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1.6 外国における使用状況等に関する資料

1.6.1 外国における使用状況

海外においては，本剤と dasabuvir（HCV NS5B）錠の組合せ製剤もしくは本剤と dasabuvir 錠の両剤の製造販売承認申請を行っている。承認取得済みの主要国は表 1.6-1 のとおり。

表 1.6-1. 外国の承認状況

国・地域 申請年月/ 承認年月	販売名，承認製剤	効能効果
米国 2014 年 4 月/ 2014 年 12 月	VIEKIRA PAK ABT-450/リトナビル/ABT-267 固定用量の配合錠及び dasabuvir 錠との組み合わせ製剤 - 配合錠(ABT-450/リトナビル/ABT-267：75mg/50mg/12.5mg) - dasabuvir 錠(250mg)	VIEKIRA PAK 及びリバビリン併用もしくは非併用による，ジェノタイプ 1 型の代償性肝硬変を含む C 型慢性肝炎の治療 使用制限： 非代償性の肝疾患患者への資料は推奨されない。
カナダ 2014 年 5 月/ 2014 年 12 月	HOLKIRA PAK ABT-450/リトナビル/ABT-267 固定用量の配合錠及び dasabuvir 錠との組み合わせ製剤 -配合錠(ABT-450/リトナビル/ABT-267：75mg/50mg/12.5mg) - dasabuvir 錠(250mg)	成人のジェノタイプ 1 型の代償性肝硬変を含む C 型慢性肝炎の治療 リバビリン併用：肝硬変のないジェノタイプ 1a 型 リバビリン非併用；肝硬変のないジェノタイプ 1b 型 リバビリン併用：代償性肝硬変
EU 2014 年 5 月/ 2015 年 1 月	VIEKIRAX ABT-450/リトナビル/ABT-267 フィルムコーティング錠（75mg/50mg/12.5mg) EXVIERA dasabuvir フィルムコーティング錠 (ナトリウム 1 水和物として 250mg)	VIEKIRAX： 他剤との併用による成人の C 型慢性肝炎の治療 EXVIERA： 他剤との併用による成人の C 型慢性肝炎の治療
スイス 2014 年 5 月 2014 年 11 月	VIEKIRAX ABT-450/リトナビル(薬物動態学的エンハンサー)/ABT-267 フィルムコーティング錠（75mg/50mg/12.5mg) EXVIERA dasabuvir フィルムコーティング錠 (ナトリウム 1 水和物として 250mg)	VIEKIRAX： EXVIERA 又は EXVIERA とリバビリンの併用による成人のジェノタイプ 1 型の C 型慢性肝炎の治療 ジェノタイプに特化した作用については注意事項参照 EXVIERA： 他剤との併用による成人の C 型慢性肝炎の治療 ジェノタイプに特化した作用については注意事項参照

1

1.6.2 海外における添付文書

1.6.2.1 米国における添付文書

VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use （原文）

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIEKIRA PAK safely and effectively. See full prescribing information for VIEKIRA PAK.

VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Dosage and Administration, Recommended Dosage in Adults (2.1) 3/2015

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. VIEKIRA PAK includes ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor. (1)

Limitation of Use: VIEKIRA PAK is not recommended for use in patients with decompensated liver disease. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. (2.1)

Treatment Regimen and Duration by Patient Population

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[See Clinical Studies (14.3)]*.

- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above. (2.1)
- Liver Transplant Recipients: In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets:
- Ombitasvir, paritaprevir, ritonavir: 12.5/75/50 mg (3)
- Dasabuvir: 250 mg (3)

CONTRAINDICATIONS

- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. (4)
- Patients with severe hepatic impairment. (4, 8.6, 12.3)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; strong inducers of CYP3A and CYP2C8; and strong inhibitors of CYP2C8. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

WARNINGS AND PRECAUTIONS

- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting VIEKIRA PAK (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on VIEKIRA PAK, monitor closely and follow recommendations in full prescribing information. (5.1)
- Risks Associated With Ribavirin Combination Treatment: If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. (5.2)
- 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. (5.3)

ADVERSE REACTIONS

In subjects receiving VIEKIRA PAK with ribavirin, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving VIEKIRA PAK without ribavirin, the most commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of VIEKIRA PAK can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of VIEKIRA PAK. The potential for drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.3, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2015

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 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 (8.6), and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

The recommended oral dosage of VIEKIRA PAK is two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). Take VIEKIRA PAK with a meal without regard to fat or calorie content *[see Clinical Pharmacology (12.3)]*.

VIEKIRA PAK is used in combination with ribavirin (RBV) in certain patient populations (see Table 1). When administered with VIEKIRA PAK, the recommended dosage of RBV is based on weight: 1000 mg for subjects <75 kg and 1200 mg/day for those ≥75 kg, divided and administered twice-daily with food. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

Monitor liver chemistry tests before initiating and during therapy *[see Warnings and Precautions (5.1)]*.

Table 1 shows the recommended VIEKIRA PAK treatment regimen and duration based on patient population.

Table 1. Treatment Regimen and Duration by Patient Population (Treatment-Naïve or Interferon-Experienced)

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**

Patient Population	Treatment*	Duration
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection. **VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[see Clinical Studies (14.3)]*.		

2.2 Use in Liver Transplant Recipients

In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks, irrespective of HCV genotype 1 subtype *[see Clinical Studies (14.6)]*. When VIEKIRA PAK is administered with calcineurin inhibitors in liver transplant recipients, dosage adjustment of calcineurin inhibitors is needed *[see Drug Interactions (7)]*.

2.3 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 patients with moderate hepatic impairment (Child-Pugh B). VIEKIRA PAK is contraindicated in patients with severe hepatic impairment (Child-Pugh C) *[see Contraindications (4), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

- Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with "AV1" on one side.
- Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with "AV2" on one side. Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

4 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 (8.6) and Clinical Pharmacology (12.3)]*.
- 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 2 lists drugs that are contraindicated with VIEKIRA PAK *[see Drug Interactions (7)]*.

Table 2. 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 (5.1)]*.
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	Lovastatin,	Potential for myopathy including

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Inhibitors	simvastatin	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.

5 WARNINGS AND PRECAUTIONS

5.1 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 (6.1)]*. 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 (4)]*. 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 (6.1)]*.

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.

5.2 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.

5.3 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 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. 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 (4) and Drug Interactions (7)]*.

5.4 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.

6 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 (5.1)]*

6.1 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) *[see Clinical Studies (14.1, 14.2)]*. 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 3). 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 3. 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, 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) *[see Clinical Studies (14.1, 14.2)]*. 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 4). 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 4. 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) *[see Clinical Studies (14.1, 14.3)]*. 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 (4) and Warnings and Precautions (5.1)]*. 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 (5.1)]*.

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 (5.4), Adverse Reactions (6.1) and Clinical Studies (14.6)]*. 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 *[see Clinical Studies (14.5)]*.

7 DRUG INTERACTIONS

See also Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3).

7.1 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.

7.2 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.

7.3 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 5 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 (4)* for drugs that are contraindicated with VIEKIRA PAK. Refer to the ritonavir prescribing information for other potentially significant drug interactions with ritonavir.

Table 5. 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

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
		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.
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 $1/5^{th}$ 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

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
		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.
See Clinical Pharmacology, Tables 6 and 7. 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%).*		

7.4 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.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.3 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).

8.4 Pediatric Use

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

8.5 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.

8.6 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 (4) and Clinical Pharmacology (12.3)]*.

8.7 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 *[see Clinical Pharmacology (12.3)]*.

8.8 Other HCV Genotypes

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

10 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.

11 DESCRIPTION

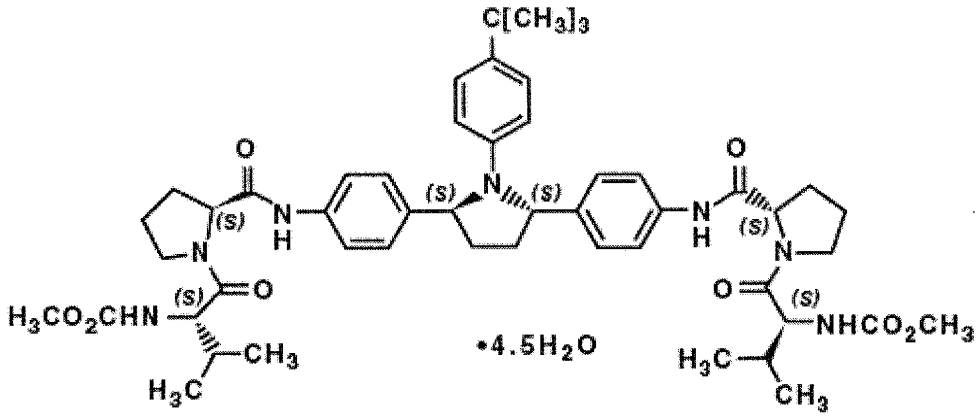
VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a

CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir. Dasabuvir is a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, which is supplied as separate tablets in the copackage. Both tablets are for oral administration.

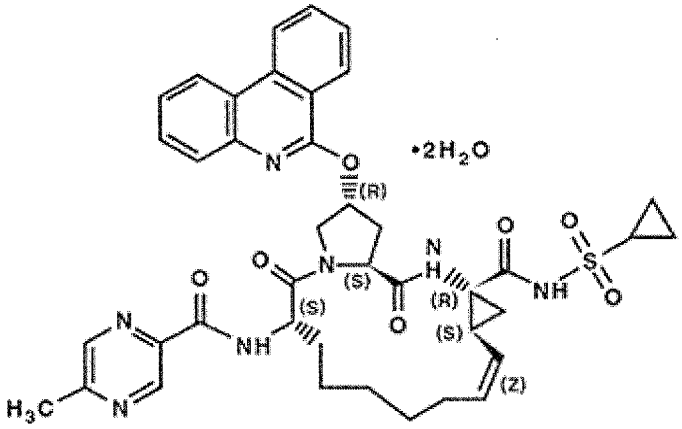
Ombitasvir

The chemical name of ombitasvir is Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate. The molecular formula is $C_{50}H_{67}N_7O_8 \cdot 4.5H_2O$ (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). The drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir has the following molecular structure:



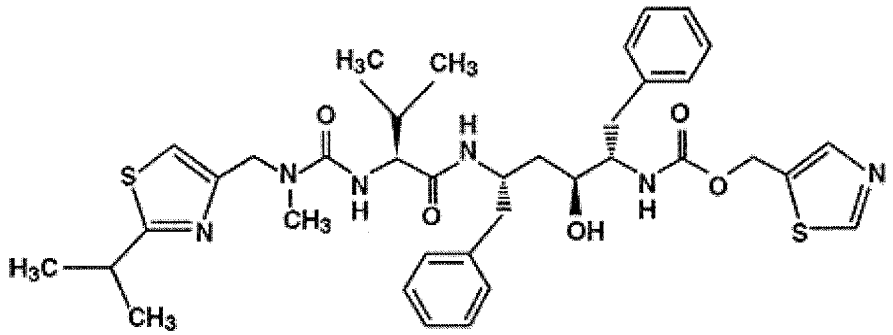
Paritaprevir

The chemical name of paritaprevir is (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate. The molecular formula is $C_{40}H_{43}N_7O_7S \cdot 2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). The drug substance is white to off-white powder with very low water solubility. Paritaprevir has the following molecular structure:



Ritonavir

The chemical name of ritonavir is [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester. The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight for the drug substance is 720.95. The drug substance is white to off white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has the following molecular structure:



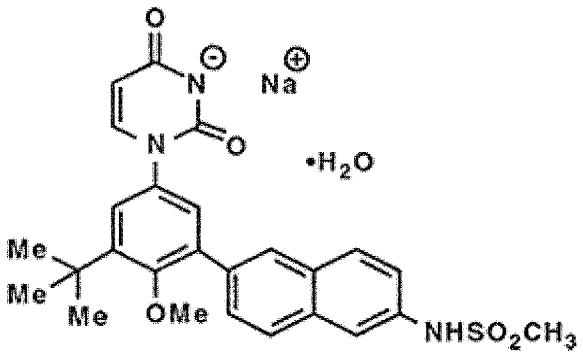
Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination Tablets

Ombitasvir, paritaprevir, and ritonavir film-coated tablets are co-formulated immediate release tablets. The tablet contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. The strength for the tablet is 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir.

Dasabuvir

The chemical name of dasabuvir is Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1). The molecular formula is $C_{26}H_{26}N_3O_5S{\bullet}Na{\bullet}H_2O$ (salt, hydrate) and the molecular weight of the drug substance is 533.57 (salt, hydrate). The drug substance is white to

pale yellow to pink powder, slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol. Dasabuvir has the following molecular structure:



Dasabuvir is formulated as a 250 mg film-coated, immediate release tablet containing microcrystalline cellulose (D50-100 um), microcrystalline cellulose (D50-50 um), lactose monohydrate, copovidone, croscarmellose sodium, colloidal silicon dioxide/anhydrous colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350/macrogol 3350, talc, and iron oxide yellow, iron oxide red and iron oxide black. Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIEKIRA PAK combines three direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action *[see Microbiology (12.4)]*.

Ritonavir is not active against HCV. Ritonavir is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e., area under the curve).

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of a combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir on QTc interval was evaluated in a randomized, double blind, placebo and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 60 healthy subjects. At concentrations approximately 6, 1.8 and 2 times the therapeutic concentrations of paritaprevir, ombitasvir, and dasabuvir, the combination did not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Ombitasvir, paritaprevir, ritonavir and dasabuvir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. While ombitasvir and dasabuvir exposures increased in a dose proportional manner, paritaprevir and ritonavir exposures increased in a more than dose

proportional manner. Accumulation is minimal for ombitasvir and dasabuvir and approximately 1.5- to 2-fold for ritonavir and paritaprevir. Steady state exposures are achieved after approximately 12 days of dosing.

The absolute bioavailability of dasabuvir estimated to be approximately 70%. The absolute bioavailability of ombitasvir, paritaprevir, and ritonavir was not evaluated.

Based on the population pharmacokinetic analysis, the median steady-state AUC_{0-24} for ombitasvir, paritaprevir and ritonavir were 1000, 2220 and 6180 ng•hr/mL, respectively, and the median steady-state AUC_{0-12} for dasabuvir was 3240 ng•hr/mL when VIEKIRA PAK was administered to HCV-infected subjects. Median steady-state C_{max} for ombitasvir, paritaprevir, ritonavir and dasabuvir were 68, 262, 682 and 667 ng/mL, respectively, when VIEKIRA PAK was administered to HCV-infected subjects.

Effects of Food on Oral Absorption

Relative to fasting conditions, administration of ombitasvir, paritaprevir, ritonavir, and dasabuvir with a moderate fat meal (approximately 600 Kcal, 20-30% calories from fat) increased the mean AUC by 82%, 211%, 49%, and 30%, respectively.

Relative to fasting conditions, administration of ombitasvir, paritaprevir, ritonavir, and dasabuvir with a high fat meal (approximately 900 Kcal, 60% calories from fat) increased the mean AUC by 76%, 180%, 44%, and 22%, respectively.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir should always be administered with a meal.

Distribution

Ombitasvir: Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 µg per mL. The mean blood-to-plasma concentration ratio was 0.49. The apparent volume of distribution (V/F) was 50.1 L.

Paritaprevir: Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 µg per mL. The mean blood-to-plasma concentration ratio was 0.7. The apparent volume of distribution (V/F) was 16.7 L.

Ritonavir: Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 µg per mL. The mean blood-to-plasma concentration ratio was 0.6. The apparent volume of distribution (V/F) was 21.5 L.

Dasabuvir: Dasabuvir was greater than 99.5% bound to human plasma proteins over a concentration range of 0.05 to 5 µg per mL. The mean blood-to-plasma concentration ratio was 0.7. The apparent volume of distribution (V/F) was 396 L.

Metabolism

Ombitasvir: Ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism.

Paritaprevir: Paritaprevir is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

Ritonavir: Ritonavir is predominantly metabolized by CYP3A, and to a lesser extent, by CYP2D6.

Dasabuvir: Dasabuvir is predominantly metabolized by CYP2C8, and to a lesser extent by CYP3A.

Elimination

Ombitasvir: Following a single dose administration of ^{14}C-ombitasvir, approximately 90.2% of the radioactivity was recovered in feces with limited radioactivity (1.91%) in urine; unchanged ombitasvir accounted for 87.8% of the radioactivity in the feces and 0.03% in the urine. The mean elimination half-life of ombitasvir was approximately 21 to 25 hours.

Paritaprevir: Following a single dose administration of ^{14}C-paritaprevir co-dosed with 100 mg of ritonavir, approximately 88% of the radioactivity was recovered in feces with limited radioactivity (8.8%) in urine; unchanged paritaprevir accounted for 1.1% of the radioactivity in the feces and 0.05% in the urine. The mean plasma half-life of paritaprevir was approximately 5.5 hours.

Ritonavir: Following dosing of ritonavir with ombitasvir and paritaprevir, mean plasma half-life of ritonavir was approximately 4 hours. Following a single 600 mg dose of ^{14}C-ritonavir oral solution, 86.4% of the radioactivity was recovered in the feces and 11.3% of the dose was excreted in the urine.

Dasabuvir: Following a single dose administration of ^{14}C-dasabuvir, approximately 94.4% of the radioactivity was recovered in feces with limited radioactivity (approximately 2%) in urine; unchanged dasabuvir accounted for 26% of the radioactivity in the feces and 0.03% in the urine. The mean plasma half-life of dasabuvir was approximately 5.5 to 6 hours.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir do not inhibit organic anion transporter (OAT1) *in vivo* and based on *in vitro* data, are not expected to inhibit organic cation transporter (OCT2), organic anion transporter (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Specific Populations

Hepatic Impairment

The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir were evaluated in non-HCV infected subjects with mild hepatic impairment (Child-Pugh Category A; score of 5-6), moderate hepatic impairment (Child-Pugh Category B, score of 7-9) and severe hepatic impairment (Child-Pugh Category C, score of 10-15).

Relative to subjects with normal hepatic function, ombitasvir, paritaprevir and ritonavir AUC values decreased by 8%, 29% and 34%, respectively, and dasabuvir AUC values increased by 17% in subjects with mild hepatic impairment.

Relative to subjects with normal hepatic function, ombitasvir, ritonavir and dasabuvir AUC values decreased by 30%, 30% and 16%, respectively, and paritaprevir AUC values increased by 62% in subjects with moderate hepatic impairment.

Relative to subjects with normal hepatic function, paritaprevir, ritonavir and dasabuvir AUC values increased by 945%, 13%, and 325% respectively, and ombitasvir AUC values decreased by 54% in subjects with severe 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 hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.3), Contraindications (4) and Use in Specific Populations (8.6)]*.

Renal Impairment

The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir were evaluated in non-HCV infected subjects with mild (CL_{cr}: 60 to 89 mL/min), moderate (CL_{cr}: 30 to 59 mL/min), and severe (CL_{cr}: 15 to 29 mL/min) renal impairment.

Overall, changes in exposure of ombitasvir, paritaprevir, ritonavir and dasabuvir in non-HCV infected subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant. Pharmacokinetic data are not available on the use of VIEKIRA PAK in non-HCV infected subjects with End Stage Renal Disease (ESRD).

Relative to subjects with normal renal function, paritaprevir, ritonavir and dasabuvir AUC values increased by 19%, 42% and 21%, respectively, while ombitasvir AUC values were unchanged in subjects with mild renal impairment.

Relative to subjects with normal renal function, paritaprevir, ritonavir and dasabuvir AUC values increased by 33%, 80% and 37%, respectively, while ombitasvir AUC values were unchanged in subjects with moderate renal impairment.

Relative to subjects with normal renal function, paritaprevir, ritonavir and dasabuvir AUC values increased by 45%, 114% and 50%, respectively, while ombitasvir AUC values were unchanged in subjects with severe renal impairment *[see Use in Specific Populations (8.7)]*.

Pediatric Population

The pharmacokinetics of VIEKIRA PAK in pediatric patients less than 18 years of age has not been established *[see Use in Specific Populations (8.4)]*.

Sex

No dose adjustment is recommended based on sex or body weight.

Race/Ethnicity

No dose adjustment is recommended based on race or ethnicity.

Age

No dose adjustment is recommended in geriatric patients *[see Use in Specific Populations (8.5)]*.

Drug Interaction Studies

See also Contraindications (4), Warnings and Precautions (5.3), Drug Interactions (7)

The effects of drugs discussed in Table 5 on the exposures of the individual components of VIEKIRA PAK are shown in Table 6. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 6. Drug Interactions: Change in Pharmacokinetic Parameters of the Individual Components of VIEKIRA PAK in the Presence of Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Alprazolam	0.5 single dose	12	ombitasvir	0.98 (0.93, 1.04)	1.00 (0.96, 1.04)	0.98 (0.93, 1.04)
			paritaprevir	0.91 (0.64, 1.31)	0.96 (0.73, 1.27)	1.12 (1.02, 1.23)
			ritonavir	0.92 (0.84, 1.02)	0.96 (0.89, 1.03)	1.01 (0.94, 1.09)
			dasabuvir	0.93 (0.83, 1.04)	0.98 (0.87, 1.11)	1.00 (0.87, 1.15)
Amlodipine	5 single dose	14	ombitasvir	1.00 (0.95, 1.06)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
			paritaprevir	0.77 (0.64, 0.94)	0.78 (0.68, 0.88)	0.88 (0.80, 0.95)
			ritonavir	0.96 (0.87, 1.06)	0.93 (0.89, 0.98)	0.95 (0.89, 1.01)
			dasabuvir	1.05 (0.97, 1.14)	1.01 (0.96, 1.06)	0.95 (0.89, 1.01)
Atazanavir/ ritonavir[a]	Atazanavir 300 and ritonavir 100 once daily in the evening	11	ombitasvir	0.83 (0.72, 0.96)	0.90 (0.78, 1.02)	1.00 (0.89, 1.13)
			paritaprevir	2.19 (1.61, 2.98)	3.16 (2.40, 4.17)	11.95 (8.94, 15.98)
			ritonavir	1.60 (1.38, 1.86)	3.18 (2.74, 3.69)	24.65 (18.64, 32.60)
			dasabuvir	0.81 (0.73, 0.91)	0.81 (0.71, 0.92)	0.80 (0.65, 0.98)
Carbamazepine	200 once daily followed by 200 twice daily	12	ombitasvir	0.69 (0.61, 0.78)	0.69 (0.64, 0.74)	NA
			paritaprevir	0.34 (0.25, 0.48)	0.30 (0.23, 0.38)	NA
			ritonavir	0.17 (0.12, 0.24)	0.13 (0.09, 0.17)	NA
			dasabuvir	0.45 (0.41, 0.50)	0.30 (0.28, 0.33)	NA
Cyclosporine	30 single dose[b]	10	ombitasvir	0.99 (0.92, 1.07)	1.08 (1.05, 1.11)	1.15 (1.08, 1.23)
			paritaprevir	1.44 (1.16, 1.78)	1.72 (1.49, 1.99)	1.85 (1.58, 2.18)
			ritonavir	0.90	1.11	1.49

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
				(0.78, 1.04)	(1.04, 1.19)	(1.28, 1.74)
			dasabuvir	0.66 (0.58, 0.75)	0.70 (0.65, 0.76)	0.76 (0.71, 0.82)
Darunavir[c]	800 once daily	9	ombitasvir	0.86 (0.77, 0.95)	0.86 (0.79, 0.94)	0.87 (0.82, 0.92)
			paritaprevir	1.54 (1.14, 2.09)	1.29 (1.04, 1.61)	1.30 (1.09, 1.54)
			ritonavir	0.84 (0.72, 0.98)	0.85 (0.78, 0.93)	1.07 (0.93, 1.23)
			dasabuvir	1.10 (0.88, 1.37)	0.94 (0.78, 1.14)	0.90 (0.76, 1.06)
Darunavir/ ritonavir[d]	Darunavir 600 twice daily and ritonavir 100 once daily in the evening	7	ombitasvir	0.76 (0.65, 0.88)	0.73 (0.66, 0.80)	0.73 (0.64, 0.83)
			paritaprevir	0.70 (0.43, 1.12)	0.59 (0.44, 0.79)	0.83 (0.69, 1.01)
			ritonavir	1.61 (1.30, 2.00)	1.28 (1.12, 1.45)	0.88 (0.79, 0.99)
			dasabuvir	0.84 (0.67, 1.05)	0.73 (0.62, 0.86)	0.54 (0.49, 0.61)
Darunavir/ ritonavir[e]	Darunavir 800 and ritonavir 100 once daily in the evening	12	ombitasvir	0.87 (0.82, 0.93)	0.87 (0.81, 0.93)	0.87 (0.80, 0.95)
			paritaprevir	0.70 (0.50, 0.99)	0.81 (0.60, 1.09)	1.59 (1.23, 2.05)
			ritonavir	1.19 (1.06, 1.33)	1.70 (1.54, 1.88)	14.15 (11.66, 17.18)
			dasabuvir	0.75 (0.64, 0.88)	0.72 (0.64, 0.82)	0.65 (0.58, 0.72)
Ethinyl estradiol/ Norgestimate	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	7[f]	ombitasvir	1.05 (0.81, 1.35)	0.97 (0.81, 1.15)	1.00 (0.88, 1.12)
			paritaprevir	0.70 (0.40, 1.21)	0.66 (0.42, 1.04)	0.87 (0.67, 1.14)
			ritonavir	0.80 (0.53, 1.21)	0.71 (0.54, 0.94)	0.79 (0.68, 0.93)
			dasabuvir	0.51 (0.22, 1.18)	0.48 (0.23, 1.02)	0.53 (0.30, 0.95)
Furosemide	20 single dose	12	ombitasvir	1.14 (1.03, 1.26)	1.07 (1.01, 1.12)	1.12 (1.08, 1.16)
			paritaprevir	0.93 (0.63, 1.36)	0.92 (0.70, 1.21)	1.26 (1.16, 1.38)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	1.10 (0.96, 1.27)	1.04 (0.92, 1.18)	1.07 (0.99, 1.17)
			dasabuvir	1.12 (0.96, 1.31)	1.09 (0.96, 1.23)	1.06 (0.98, 1.14)
Gemfibrozil[g]	600 twice daily	11	ombitasvir	NA	NA	NA
			paritaprevir	1.21 (0.94, 1.57)	1.38 (1.18, 1.61)	NA
			ritonavir	0.84 (0.69, 1.03)	0.90 (0.78, 1.04)	NA
			dasabuvir	2.01 (1.71, 2.38)	11.25 (9.05, 13.99)	NA
Ketoconazole	400 once daily	12	ombitasvir	0.98 (0.90, 1.06)	1.17 (1.11, 1.24)	NA
			paritaprevir	1.37 (1.11, 1.69)	1.98 (1.63, 2.42)	NA
			ritonavir	1.27 (1.04, 1.56)	1.57 (1.36, 1.81)	NA
			dasabuvir	1.16 (1.03, 1.32)	1.42 (1.26, 1.59)	NA
Lopinavir/ ritonavir	400/100 twice daily	6	ombitasvir	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
			paritaprevir	2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
			ritonavir	1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)
			dasabuvir	0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
Lopinavir/ ritonavir[h]	800/200 once daily	12	ombitasvir	0.87 (0.83, 0.92)	0.97 (0.94, 1.02)	1.11 (1.06, 1.16)
			paritaprevir	0.99 (0.79, 1.25)	1.87 (1.40, 2.52)	8.23 (5.18, 13.07)
			ritonavir	1.57 (1.34, 1.83)	2.62 (2.32, 2.97)	19.46 (15.93, 23.77)
			dasabuvir	0.56 (0.47, 0.66)	0.54 (0.46, 0.65)	0.47 (0.39, 0.58)
Omeprazole	40 once daily	11	ombitasvir	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	1.04 (0.98, 1.11)
			paritaprevir	1.19 (1.04, 1.36)	1.18 (1.03, 1.37)	0.92 (0.76, 1.12)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	1.04 (0.96, 1.12)	1.02 (0.97, 1.08)	0.97 (0.89, 1.05)
			dasabuvir	1.13 (1.03, 1.25)	1.08 (0.98, 1.20)	1.05 (0.93, 1.19)
Pravastatin	10 once daily	12	ombitasvir	0.95 (0.89, 1.02)	0.94 (0.89, 0.99)	0.94 (0.89, 0.99)
			paritaprevir	0.96 (0.69, 1.32)	1.13 (0.92, 1.38)	1.39 (1.21, 1.59)
			ritonavir	0.89 (0.73, 1.09)	0.95 (0.86, 1.05)	1.08 (0.98, 1.19)
			dasabuvir	1.00 (0.87, 1.14)	0.96 (0.85, 1.09)	1.03 (0.91, 1.15)
Rosuvastatin	5 once daily	11	ombitasvir	0.92 (0.82, 1.04)	0.89 (0.83, 0.95)	0.88 (0.83, 0.94)
			paritaprevir	1.59 (1.13, 2.23)	1.52 (1.23, 1.90)	1.43 (1.22, 1.68)
			ritonavir	0.98 (0.84, 1.15)	1.02 (0.93, 1.12)	1.00 (0.90, 1.12)
			dasabuvir	1.07 (0.92, 1.24)	1.08 (0.92, 1.26)	1.15 (1.05, 1.25)
Rilpivirine	25 once daily (morning)[i]	10	ombitasvir	1.11 (1.02, 1.20)	1.09 (1.04, 1.14)	1.05 (1.01, 1.08)
			paritaprevir	1.30 (0.94, 1.81)	1.23 (0.93, 1.64)	0.95 (0.84, 1.07)
			ritonavir	1.10 (0.98, 1.24)	1.08 (0.93, 1.27)	0.97 (0.91, 1.04)
			dasabuvir	1.18 (1.02, 1.37)	1.17 (0.99, 1.38)	1.10 (0.89, 1.37)
Tacrolimus	2 single dose	12	ombitasvir	0.93 (0.88, 0.99)	0.94 (0.89, 0.98)	0.94 (0.91, 0.96)
			paritaprevir	0.57 (0.42, 0.78)	0.66 (0.54, 0.81)	0.73 (0.66, 0.80)
			ritonavir	0.76 (0.63, 0.91)	0.87 (0.79, 0.97)	1.03 (0.89, 1.19)
			dasabuvir	0.85 (0.73, 0.98)	0.90 (0.80, 1.02)	1.01 (0.91, 1.11)

a. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of VIEKIRA PAK.
b. 30 mg cyclosporine was administered with VIEKIRA PAK and 100 mg in the reference arm

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}

without VIEKIRA PAK.

c. Darunavir administered with VIEKIRA PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.
d. Darunavir administered with VIEKIRA PAK in the morning and with 100 mg ritonavir in the evening was compared to darunavir administered with 100 mg ritonavir in the morning and evening.
e. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after the morning dose of VIEKIRA PAK compared to darunavir administered with 100 mg ritonavir in the evening.
f. N=3 for dasabuvir.
g. Study was conducted with paritaprevir, ritonavir and dasabuvir.
h. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of VIEKIRA PAK.
i. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.

NA: not available/not applicable; DAA: Direct-acting antiviral agent; CI: Confidence interval
Doses of ombitasvir, paritaprevir, and ritonavir were 25 mg, 150 mg and 100 mg. Doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures).
Ombitasvir, paritaprevir and ritonavir were dosed once daily and dasabuvir was dosed twice daily in all the above studies except studies with gemfibrozil, ketoconazole and carbamazepine that used single doses.

Table 7 summarizes the effects of VIEKIRA PAK on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 7. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of VIEKIRA PAK

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
Alprazolam	0.5 single dose	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
Amlodipine	5 single dose	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
Atazanavir/ritonavir[a]	Atazanavir 300 and ritonavir 100 once daily in the evening	12	1.02 (0.92, 1.13)[b]	1.19 (1.11, 1.28)[b]	1.68 (1.44, 1.95)[b]

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
Buprenorphine	Buprenorphine: 4 to 24 once daily and Naloxone 1 to 6 once daily	10	2.18 (1.78, 2.68)[c]	2.07 (1.78, 2.40)[c]	3.12 (2.29, 4.27)[c]
Norbuprenorphine			2.07 (1.42, 3.01)[c]	1.84 (1.30, 2.60)[c]	2.10 (1.49, 2.97)[c]
Naloxone			1.18 (0.81, 1.73)	1.28 (0.92, 1.79)[c]	NA
Carbamazepine	200 once daily followed by 200 twice daily	12	1.10 (1.07, 1.14)	1.17 (1.13, 1.22)	1.35 (1.27, 1.45)
Carbamazepine's metabolite, carbamazepine-10,11-epoxide (CBZE)			0.84 (0.82, 0.87)	0.75 (0.73, 0.77)	0.57 (0.54, 0.61)
Cyclosporine	30 single dose[d]	10	1.01 (0.85, 1.20)[c]	5.82 (4.73, 7.14)[c]	15.80 (13.81, 18.09)[c]
Darunavir[e]	800 once daily	8	0.92 (0.87, 0.98)[b]	0.76 (0.71, 0.82)[b]	0.52 (0.47, 0.58)[b]
Darunavir/ritonavir[f]	Darunavir 600 twice daily and ritonavir 100 once daily in the evening	7	0.87 (0.79, 0.96)[b]	0.80 (0.74, 0.86)[b]	0.57 (0.48, 0.67)[b]
Darunavir/ritonavir[g]	Darunavir 800 and ritonavir 100 once daily in the evening	10	0.79 (0.70, 0.90)[b]	1.34 (1.25, 1.43)[b]	0.54 (0.48, 0.62)[b]
Ethinyl Estradiol	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	8	1.16 (0.90, 1.50)	1.06 (0.96, 1.17)	1.12 (0.94, 1.33)
Norelgestromin		9	2.01 (1.77, 2.29)	2.60 (2.30, 2.95)	3.11 (2.51, 3.85)
Norgestrel		9	2.26 (1.91, 2.67)	2.54 (2.09, 3.09)	2.93 (2.39, 3.57)
Furosemide	20 single dose	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
Ketoconazole	400 once daily	12	1.15	2.17	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
			(1.09, 1.21)	(2.05, 2.29)	
Lopinavir/ritonavir	400/100 twice daily	6	0.87 (0.76, 0.99)[b]	0.94 (0.81, 1.10)[b]	1.15 (0.93, 1.42)[b]
Lopinavir/ritonavir[h]	800/200 once daily	12	0.86 (0.80, 0.93)[b]	0.94 (0.87, 1.01)[b]	3.18 (2.49, 4.06)[b]
Omeprazole	40 once daily	11	0.62 (0.48, 0.80)	0.62 (0.51, 0.75)	NA
Pravastatin	10 once daily	12	1.37 (1.11, 1.69)	1.82 (1.60, 2.08)	NA
Rosuvastatin	5 once daily	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)
Rilpivirine	25 once daily (morning)[i]	8	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
Tacrolimus	2 single dose	12	3.99 (3.21, 4.97)[c]	57.13 (45.53, 71.69)[c]	16.56 (12.97, 21.16)[c]

a. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of VIEKIRA PAK.
b. Atazanavir or darunavir or lopinavir parameters are reported.
c. Dose normalized parameters reported.
d. 30 mg cyclosporine was administered with VIEKIRA PAK in the test arm and 100 mg cyclosporine was administered in the reference arm without VIEKIRA PAK.
e. Darunavir administered with VIEKIRA PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.
f. Darunavir administered with VIEKIRA PAK in the morning and with 100 mg ritonavir in the evening was compared to darunavir administered with 100 mg ritonavir in the morning and evening.
g. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of VIEKIRA PAK compared to darunavir administered with 100 mg ritonavir in the evening.
h. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of VIEKIRA PAK.
i. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.

NA: not available/not applicable; CI: Confidence interval
Doses of ombitasvir, paritaprevir, and ritonavir were 25 mg, 150 mg and 100 mg. Doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures).
Ombitasvir, paritaprevir and ritonavir were dosed once daily and dasabuvir was dosed twice

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
daily in all the above studies except studies with ketoconazole and carbamazepine that used single doses.					

12.4 Microbiology

Mechanism of Action

VIEKIRA PAK combines three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of ombitasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Paritaprevir

Paritaprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, paritaprevir inhibited the proteolytic activity of recombinant HCV genotype 1a and 1b NS3/4A protease enzymes with IC_{50} values of 0.18 nM and 0.43 nM, respectively. Paritaprevir inhibited the activity of NS3/4A enzymes from single isolates of genotypes 2a, 2b, 3a, and 4a with IC_{50} values of 2.4 nM, 6.3 nM, 14.5 nM, and 0.16 nM, respectively.

Dasabuvir

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. In a biochemical assay, dasabuvir inhibited a panel of genotype 1a and 1b NS5B polymerases with median IC_{50} values of 2.8 nM (range 2.4 nM to 4.2 nM; n = 3) and 3.7 nM (range 2.2 nM to 10.7 nM; n = 4), respectively. Based on drug resistance mapping studies of HCV genotypes 1a and 1b, dasabuvir targets the palm domain of the NS5B polymerase, and is therefore referred to as a non-nucleoside NS5B-palm polymerase inhibitor. Dasabuvir had reduced activity in biochemical assays against NS5B polymerases from HCV genotypes 2a, 2b, 3a and 4a (IC_{50} values ranging from 900 nM to >20 μM).

Antiviral Activity

Ombitasvir

The EC_{50} values of ombitasvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays were 14.1 pM and 5 pM, respectively. The median EC_{50} values of ombitasvir against HCV replicons containing NS5A genes from a panel of genotype 1a and 1b isolates from treatment-naïve subjects were 0.68 pM (range 0.35 to 0.88 pM; n = 11) and 0.94 pM (range 0.74

to 1.5 pM; n = 11), respectively. Ombitasvir had EC_{50} values of 12 pM, 4.3 pM, 19 pM, 1.7 pM, 3.2 pM, and 366 pM against chimeric replicons constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 5a, and 6a, respectively.

Paritaprevir

The EC_{50} values of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay were 1.0 nM and 0.21 nM, respectively. The median EC_{50} values of paritaprevir against HCV replicons containing NS3 genes from a panel of genotype 1a and 1b isolates from treatment-naïve subjects were 0.68 nM (range 0.43 nM to 1.87 nM; n = 11) and 0.06 nM (range 0.03 nM to 0.09 nM; n = 9), respectively. Paritaprevir had an EC_{50} value of 5.3 nM against the HCV genotype 2a-JFH-1 replicon cell line, and EC_{50} values of 19 nM, 0.09 nM, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, and 6a, respectively.

In HCV replicon cell culture assays, ritonavir did not exhibit a direct antiviral effect and the presence of ritonavir did not affect the antiviral activity of paritaprevir.

Dasabuvir

The EC_{50} values of dasabuvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays were 7.7 nM and 1.8 nM, respectively. The median EC_{50} values of dasabuvir against HCV replicons containing NS5B genes from a panel of genotype 1a and 1b isolates from treatment-naïve subjects were 0.6 nM (range 0.4 nM to 2.1 nM; n = 11) and 0.3 nM (range 0.2 nM to 2 nM; n = 10), respectively.

Combination Antiviral Activity

Evaluation of pairwise combinations of ombitasvir, paritaprevir, dasabuvir and ribavirin in HCV genotype 1 replicon cell culture assays showed no evidence of antagonism in antiviral activity.

Resistance

In Cell Culture

Exposure of HCV genotype 1a and 1b replicons to ombitasvir, paritaprevir or dasabuvir resulted in the emergence of drug resistant replicons carrying amino acid substitutions in NS5A, NS3, or NS5B, respectively. Amino acid substitutions in NS5A, NS3, or NS5B selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in genotype 1a or 1b replicons.

For ombitasvir, in HCV genotype 1a replicons single NS5A substitutions M28T/V, Q30E/R, L31V, H58D, and Y93C/H/L/N reduced ombitasvir antiviral activity by 58- to 67,000-fold. In genotype 1b replicons, single NS5A substitutions L28T, L31F/V, and Y93H reduced ombitasvir antiviral activity by 8- to 661-fold. In general, combinations of ombitasvir resistance-associated substitutions in HCV genotype 1a or 1b replicons further reduced ombitasvir antiviral activity.

For paritaprevir, in HCV genotype 1a replicons single NS3 substitutions F43L, R155G/K/S, A156T, and D168A/E/F/H/N/V/Y reduced paritaprevir antiviral activity by 7- to 219-fold. An NS3 Q80K substitution in a genotype 1a replicon reduced paritaprevir antiviral activity by 3-fold. Combinations of V36M, Y56H, or E357K with R155K or D168 substitutions reduced the activity of paritaprevir by an additional 2- to 7-fold relative to the single R155K or D168

substitutions in genotype 1a replicons. In genotype 1b replicons single NS3 substitutions A156T and D168A/H/V reduced paritaprevir antiviral activity by 7- to 159-fold. The combination of Y56H with D168 substitutions reduced the activity of paritaprevir by an additional 16- to 26-fold relative to the single D168 substitutions in genotype 1b replicons.

For dasabuvir, in HCV genotype 1a replicons single NS5B substitutions C316Y, M414I/T, E446K/Q, Y448C/H, A553T, G554S, S556G/R, and Y561H reduced dasabuvir antiviral activity by 8- to 1,472-fold. In genotype 1b replicons, single NS5B substitutions C316H/N/Y, S368T, N411S, M414I/T, Y448C/H, A553V, S556G and D559G reduced dasabuvir antiviral activity by 5- to 1,569-fold.

In Clinical Studies

In a pooled analysis of subjects treated with regimens containing ombitasvir, paritaprevir, and dasabuvir with or without ribavirin (for 12 or 24 weeks) in Phase 2b and Phase 3 clinical trials, resistance analyses were conducted for 64 subjects who experienced virologic failure (20 with on-treatment virologic failure, 44 with post-treatment relapse). Treatment-emergent substitutions observed in the viral populations of these subjects are shown in Table 8. Treatment-emergent substitutions were detected in all 3 HCV drug targets in 30/57 (53%) HCV genotype 1a infected subjects, and 1/6 (17%) HCV genotype 1b infected subjects.

Table 8. Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of VIEKIRA PAK with and without Ribavirin Regimens (12- or 24-week durations) in Phase 2b and Phase 3 Clinical Trials

Target	Emergent Amino Acid Substitutions	Genotype 1a N = 58[a] % (n)	Genotype 1b N = 6 % (n)
NS3	Any of the following NS3 substitutions: V36A/M/T, F43L, V55I, Y56H, Q80L, I132V, R155K, A156G, D168(any), P334S, S342P, E357K, V406A/I, T449I, P470S, V23A (NS4A)	88 (51)	67 (4)
	V36A/M/T[b]	7 (4)	--
	V55I[b]	7 (4)	--
	Y56H[b]	10 (6)	50 (3)
	I132V[b]	7 (4)	--
	R155K	16 (9)	--
	D168 (any)[d]	72 (42)	67 (4)
	D168V	59 (34)	50 (3)
	P334S[b,c]	7 (4)	--
	E357K[b,c]	5 (3)	17 (1)
	V406A/I[b,c]	5 (3)	--
	T449I[b,c]	5 (3)	--
	P470S[b,c]	5 (3)	--
	NS4A V23A[b]	--	17 (1)

Target	Emergent Amino Acid Substitutions	Genotype 1a N = 58[a] % (n)	Genotype 1b N = 6 % (n)
	F43L[b], Q80L[b], A156G, S342P[b,c]	<5%	--
NS5A	Any of the following NS5A substitutions: K24R, M28A/T/V, Q30E/K/R, H/Q54Y, H58D/P/R, Y93C/H/N	78 (45)	33 (2)
	K24R	5 (3)	--
	M28A/T/V	33 (19)	--
	Q30E/K/R	47 (27)	--
	H/Q54Y	--	17(1)
	H58D/P/R	7 (4)	--
	Y93C/N	5 (3)	--
	Y93H	--	33 (2)
NS5B	Any of the following NS5B substitutions: G307R, C316Y, M414I/T, E446K/Q, A450V, A553I/T/V, G554S, S556G/R, G558R, D559G/I/N/V, Y561H	67 (38)	33 (2)
	C316Y	4(2)	17 (1)
	M414I	--	17 (1)
	M414T	5 (3)	17 (1)
	A553I/T/V	7 (4)	--
	S556G/R	39 (22)	17 (1)
	D559G/I/N/V	7 (4)	--
	Y561H	5 (3)	--
	G307R, E446K/Q, A450V, G554S, G558R	<5%	--

a. N = 57 for the NS5B target.
b. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.
c. Position located in NS3 helicase domain.
d. D168A/F/H/I/L/N/T/V/Y.

Persistence of Resistance-Associated Substitutions

The persistence of ombitasvir, paritaprevir, and dasabuvir treatment-emergent amino acid substitutions in NS5A, NS3, and NS5B, respectively, was assessed in HCV genotype 1a-infected subjects in Phase 2 trials whose virus had at least 1 treatment-emergent resistance-associated substitution in the drug target, and with available data through at least 24 weeks post-treatment. Population and clonal nucleotide sequence analyses (assay sensitivity approximately 5-10%) were conducted to detect the persistence of viral populations with treatment-emergent substitutions.

For ombitasvir, viral populations with 1 or more resistance-associated treatment-emergent substitutions in NS5A persisted at detectable levels through at least Post-Treatment Week 24 in

24/24 (100%) subjects, and through Post-Treatment Week 48 in 18/18 (100%) subjects with available data.

For paritaprevir, viral populations with 1 or more treatment-emergent substitutions in NS3 persisted at detectable levels through at least Post-Treatment Week 24 in 17/29 (59%) subjects, and through Post-Treatment Week 48 in 5/22 (23%) subjects with available data. Resistance-associated variant R155K remained detectable in 5/8 (63%) subjects through Post-Treatment Week 24, and in 1/5 (20%) subjects through Post-Treatment Week 48. Resistance-associated D168 substitutions remained detectable in 6/22 (27%) subjects through Post-Treatment Week 24, and were no longer detectable through Post-Treatment Week 48.

For dasabuvir, viral populations with 1 or more treatment-emergent substitutions in NS5B persisted at detectable levels through at least Post-Treatment Week 24 in 11/16 (69%) subjects, and through Post-Treatment Week 48 in 8/15 (53%) subjects with available data. Treatment-emergent S556G persisted through Post-Treatment Week 48 in 6/9 (67%) subjects.

Due to virologic failure rates in clinical trials of less than 1% for subjects infected with HCV genotype 1b, trends in persistence of treatment-emergent substitutions in this genotype could not be established.

The lack of detection of virus containing a resistance-associated substitution does not indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the emergence or persistence of virus containing VIEKIRA PAK-resistance-associated substitutions is unknown.

Effect of Baseline HCV Polymorphisms on Treatment Response

A pooled analysis of subjects in the Phase 3 clinical trials of ombitasvir, paritaprevir, and dasabuvir with or without ribavirin was conducted to explore the association between baseline HCV NS5A, NS3, or NS5B resistance-associated polymorphisms and treatment outcome. Baseline samples from HCV genotype 1a infected subjects who experienced virologic failure (n=47), as well as samples from a subset of demographically matched subjects who achieved SVR (n=94), were analyzed to compare the frequencies of resistance-associated polymorphisms in these two populations. The NS3 Q80K polymorphism was detected in approximately 38% of subjects in this analysis and was enriched approximately 2-fold in virologic failure subjects compared to SVR-achieving subjects. Ombitasvir resistance-associated polymorphisms in NS5A (pooling data from all resistance-associated amino acid positions) were detected in approximately 22% of subjects in this analysis and similarly were enriched approximately 2-fold in virologic failure subjects. Dasabuvir resistance-associated polymorphisms in NS5B were detected in approximately 5% of subjects in this analysis and were not enriched in virologic failure subjects.

In contrast to the Phase 3 subset analysis, no association of NS3 or NS5A polymorphisms and treatment outcome was seen in an analysis of noncirrhotic HCV genotype 1a-infected subjects (n=174 for NS3 and n=183 for NS5A) who received ombitasvir, paritaprevir, and dasabuvir with or without ribavirin (for 12 or 24 weeks) in a Phase 2b trial.

Baseline HCV polymorphisms are not expected to have a substantial impact on the likelihood of achieving SVR when VIEKIRA PAK is used as recommended for HCV genotype 1a and 1b infected patients, based on the low virologic failure rates observed in clinical trials.

Cross-resistance

Cross-resistance is expected among NS5A inhibitors, NS3/4A protease inhibitors, and non-nucleoside NS5B-palm inhibitors by class. Dasabuvir retained full activity against HCV replicons containing a single NS5B S282T substitution, which is associated with resistance to nucleos(t)ide analogue NS5B polymerase inhibitors. In clinical trials of VIEKIRA PAK, no subjects who experienced virologic failure had treatment-emergent substitutions potentially associated with resistance to nucleot(s)ide analogue NS5B polymerase inhibitors.

The impact of prior ombitasvir, paritaprevir, or dasabuvir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied. Similarly, the efficacy of VIEKIRA PAK has not been studied in subjects who have failed prior treatment with another NS5A inhibitor, NS3/4A protease inhibitor, or NS5B inhibitor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Ombitasvir

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (150 mg per kg per day).

The carcinogenicity study of ombitasvir in rats is ongoing.

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Paritaprevir, ritonavir

Paritaprevir, ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (300/30 mg per kg per day). Similarly, paritaprevir, ritonavir was not carcinogenic in a 2-year rat study up to the highest dose tested (300/30 mg per kg per day), resulting in paritaprevir exposures approximately 9-fold higher than those in humans at 150 mg.

Paritaprevir was positive in an *in vitro* chromosome aberration test using human lymphocytes. Paritaprevir was negative in a bacterial mutation assay, and in two *in vivo* genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

Dasabuvir

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (2000 mg per kg per day).

The carcinogenicity study of dasabuvir in rats is ongoing.

Dasabuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

If VIEKIRA PAK is administered with ribavirin, refer to the prescribing information for ribavirin for information on carcinogenesis, and mutagenesis.

Impairment of Fertility

Ombitasvir

Ombitasvir had no effects on embryo-fetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg per kg per day. Ombitasvir exposures at this dose were approximately 25-fold the exposure in humans at the recommended clinical dose.

Paritaprevir, ritonavir

Paritaprevir, ritonavir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg per kg per day. Paritaprevir exposures at this dose were approximately 2- to 5-fold the exposure in humans at the recommended clinical dose.

Dasabuvir

Dasabuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 800 mg per kg per day. Dasabuvir exposures at this dose were approximately 33-fold the exposure in humans at the recommended clinical dose.

If VIEKIRA PAK is administered with ribavirin, refer to the prescribing information for ribavirin for information on Impairment of Fertility.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of VIEKIRA PAK was evaluated in six randomized, multicenter, clinical trials in 2,308 subjects with genotype 1 (GT1) chronic hepatitis C virus (HCV) infection, including one trial exclusively in subjects with cirrhosis with mild hepatic impairment (Child-Pugh A), as summarized in Table 9.

Table 9. Randomized, Multicenter Trials Conducted with VIEKIRA PAK With or Without Ribavirin (RBV) in Subjects with Chronic HCV GT1 Infection

Trial	Population	Study Arms (Number of Subjects Treated)
SAPPHIRE-I (double-blind)	GT1 (a and b) TN[a] without cirrhosis	• VIEKIRA PAK + RBV (473) • Placebo (158)
SAPPHIRE-II (double-blind)	GT1 (a and b) TE[b] without cirrhosis	• VIEKIRA PAK + RBV (297) • Placebo (97)
PEARL-II (open-label)	GT1b TE without cirrhosis	• VIEKIRA PAK + RBV (88) • VIEKIRA PAK (91)
PEARL-III (double-blind)	GT1b TN without cirrhosis	• VIEKIRA PAK + RBV (210) • VIEKIRA PAK (209)

Trial	Population	Study Arms (Number of Subjects Treated)
PEARL-IV (double-blind)	GT1a TN without cirrhosis	• VIEKIRA PAK + RBV (100) • VIEKIRA PAK (205)
TURQUOISE-II (open-label)	GT1 (a and b) TN & TE with cirrhosis	• VIEKIRA PAK + RBV (12 weeks) (208) • VIEKIRA PAK + RBV (24 weeks) (172)
a. TN, treatment-naïve was defined as not having received any prior therapy for HCV infection. b. TE, treatment-experienced subjects were defined as either: prior relapsers, prior partial responders, or prior null responders to pegIFN/RBV treatment.		

- In SAPPHIRE-I and -II, subjects without cirrhosis were randomized to VIEKIRA PAK in combination with ribavirin for 12 weeks or to placebo. Subjects in the placebo arm received placebo for 12 weeks, after which they received open-label VIEKIRA PAK in combination with RBV for 12 weeks *[see Clinical Studies (14.2)]*.
- In PEARL-II, -III and -IV, subjects without cirrhosis were randomized to receive VIEKIRA PAK with or without RBV for 12 weeks of treatment *[see Clinical Studies (14.2)]*.
- In the open-label TURQUOISE-II trial, subjects with compensated cirrhosis (Child-Pugh A) who were either treatment-naïve or pegylated interferon/RBV (pegIFN/RBV) treatment-experienced were randomized to receive VIEKIRA PAK in combination with RBV for either 12 or 24 weeks of treatment. Subjects who previously failed therapy with a treatment regimen that included VIEKIRA PAK or other direct-acting antiviral agents were excluded *[see Clinical Studies (14.3)]*.

In these six clinical trials, the ombitasvir, paritaprevir, ritonavir dose was 25/150/100 mg once daily and the dasabuvir dose was 250 mg twice daily. Doses of drugs in VIEKIRA PAK were not adjusted. For subjects who received RBV, the RBV dose was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg. RBV dose adjustments were performed according to the RBV labeling.

VIEKIRA PAK with RBV was also evaluated in the following two studies:

- HCV GT1-infected liver transplant recipients (CORAL-I) *[see Clinical Studies (14.5)]*.
- Subjects with HCV GT1 co-infected with HIV-1 (TURQUOISE-I) *[see Clinical Studies (14.6)]*.

In all eight clinical studies, sustained virologic response was defined as HCV RNA below the lower limit of quantification (<LLOQ) 12 weeks after the end of treatment (SVR12). Plasma HCV RNA levels were measured using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System, which has an LLOQ of 25 IU per mL. Outcomes for subjects not achieving an SVR12 were recorded as on-treatment virologic failure (VF), post-treatment virologic relapse through post-treatment Week 12 or failure due to other non-virologic reasons (e.g., premature discontinuation, adverse event, lost to follow-up, consent withdrawn).

14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis

Subjects with Chronic HCV GT1a Infection without Cirrhosis

Subjects with HCV GT1a infection without cirrhosis treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV *[see Clinical Studies (14.1)]* had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 19% had a body mass index of at least 30 kg per m^2; 55% of patients were enrolled in US sites; 72% had IL28B non-CC genotype; 85% had baseline HCV RNA levels of at least 800,000 IU per mL.

Table 10 presents treatment outcomes for HCV GT1a treatment-naïve and treatment-experienced subjects treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I, PEARL-IV and SAPPHIRE-II.

Treatment-naïve, HCV GT1a-infected subjects without cirrhosis treated with VIEKIRA PAK in combination with RBV for 12 weeks in PEARL-IV had a significantly higher SVR12 rate than subjects treated with VIEKIRA PAK alone (97% and 90% respectively; difference +7% with 95% confidence interval, +1% to +12%). VIEKIRA PAK alone was not studied in treatment-experienced subjects with GT1a infection.

In SAPPHIRE-I and SAPPHIRE-II, no placebo subject achieved a HCV RNA <25 IU/mL during treatment.

Table 10. SVR12 for HCV Genotype 1a-Infected Subjects without Cirrhosis Who Were Treatment-Naïve or Previously Treated with PegIFN/RBV

	VIEKIRA PAK with RBV for 12 Weeks % (n/N)
GT1a treatment-naïve	
SAPPHIRE-I SVR12	96% (308/322)
Outcome for subjects without SVR12	
On-treatment VF	<1% (1/322)
Relapse	2% (6/314)
Other	2% (7/322)
PEARL-IV SVR12	97% (97/100)
Outcome for subjects without SVR12	
On-treatment VF	1% (1/100)
Relapse	1% (1/98)
Other	1% (1/100)
GT1a treatment-experienced	
SAPPHIRE-II SVR12	96% (166/173)
Outcome for subjects without SVR12	
On-treatment VF	0% (0/173)

	VIEKIRA PAK with RBV for 12 Weeks % (n/N)
Relapse	3% (5/172)
Other	1% (2/173)
SVR12 by Prior pegIFN Experience	
Null Responder	95% (83/87)
Partial Responder	100% (36/36)
Relapser	94% (47/50)

Subjects with Chronic HCV GT1b Infection without Cirrhosis

Subjects with HCV GT1b infection without cirrhosis were treated with VIEKIRA PAK with or without RBV for 12 weeks in PEARL-II and -III *[see Clinical Studies (14.1)]*. Subjects had a median age of 52 years (range: 22 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were Hispanic or Latino; 21% had a body mass index of at least 30 kg per m^2; 21% of patients were enrolled in US sites; 83% had IL28B non-CC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per mL.

The SVR rate for HCV GT1b-infected subjects without cirrhosis treated with VIEKIRA PAK without RBV for 12 weeks in PEARL-II (treatment-experienced: null responder, n=32; partial responder, n=26; relapser, n=33) and PEARL-III (treatment-naïve, n=209) was 100%.

14.3 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection and Compensated Cirrhosis

TURQUOISE-II was an open-label trial that enrolled 380 HCV GT1a and 1b-infected subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Subjects were randomized to receive VIEKIRA PAK in combination with RBV for either 12 or 24 weeks of treatment.

Treated subjects had a median age of 58 years (range: 21 to 71); 70% of the subjects were male; 95% were White; 3% were Black/African American; 12% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m^2; 43% of patients were enrolled in US sites; 82% had IL28B non-CC genotype; 86% had baseline HCV RNA levels of at least 800,000 IU per mL; 69% had HCV GT1a infection, 31% had HCV GT1b infection; 42% were treatment-naïve, 36% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 14% were prior pegIFN/RBV relapsers; 15% had platelet counts of less than 90 x 10^9 per L; 50% had albumin less than 4.0 mg per dL.

Table 11 presents treatment outcomes for GT1 treatment-naïve and treatment-experienced subjects with cirrhosis treated with VIEKIRA PAK with RBV for 12 or 24 weeks in TURQUOISE-II. In GT1a infected subjects, the overall SVR12 rate difference between 24 and 12 weeks of treatment with VIEKIRA PAK with RBV was +6% with 95% confidence interval, -0.1% to +13% with differences varying by pretreatment history.

Table 11. TURQUOISE-II: SVR12 for Chronic HCV Genotype 1-Infected Subjects with Cirrhosis Who Were Treatment-Naïve or Previously Treated with pegIFN/RBV

	GT1a		GT1b
	VIEKIRA PAK with RBV for 24 Weeks % (n/N)	**VIEKIRA PAK with RBV for 12 Weeks % (n/N)**	**VIEKIRA PAK with RBV for 12 Weeks % (n/N)**
SVR12	95% (115/121)	89% (124/140)	99% (67/68)
Outcome for subjects without SVR12			
On-treatment VF	2% (3/121)	<1% (1/140)	0% (0/68)
Relapse	1% (1/116)	8% (11/135)	1% (1/68)
Other	2% (2/121)	3% (4/140)	0% (0/68)
SVR12 for Naïve	95% (53/56)	92% (59/64)	100% (22/22)
SVR12 by Prior pegIFN Experience			
Null Responder	93% (39/42)	80% (40/50)	100% (25/25)
Partial Responder	100% (10/10)	100% (11/11)	86% (6/7)
Relapser	100% (13/13)	93% (14/15)	100% (14/14)

14.4 Effect of Ribavirin Dose Reductions on SVR12

Seven percent of subjects (101/1551) treated with VIEKIRA PAK with RBV had a RBV dose adjustment due to a decrease in hemoglobin level; of these, 98% (98/100) achieved an SVR12.

14.5 Clinical Trial of Selected Liver Transplant Recipients (CORAL-I)

VIEKIRA PAK with RBV was administered for 24 weeks to 34 HCV GT1-infected liver transplant recipients who were at least 12 months post transplantation at enrollment with normal hepatic function and mild fibrosis (Metavir fibrosis score F2 or lower). The initial dose of RBV was left to the discretion of the investigator with 600 to 800 mg per day being the most frequently selected dose range at initiation of VIEKIRA PAK and at the end of treatment.

Of the 34 subjects (29 with HCV GT1a infection and 5 with HCV GT1b infection) enrolled, (97%) achieved SVR12 (97% in subjects with GT1a infection and 100% of subjects with GT1b infection). One subject with HCV GT1a infection relapsed post-treatment.

14.6 Clinical Trial in Subjects with HCV/HIV-1 Co-infection (TURQUOISE-I)

In an open-label clinical trial 63 subjects with HCV GT1 infection co-infected with HIV-1 were treated for 12 or 24 weeks with VIEKIRA PAK in combination with RBV. Subjects were on a stable HIV-1 antiretroviral therapy (ART) regimen that included tenofovir disoproxil fumarate plus emtricitabine or lamivudine, administered with ritonavir boosted atazanavir or raltegravir. Subjects on atazanavir stopped the ritonavir component of their HIV-1 ART regimen upon initiating treatment with VIEKIRA PAK in combination with RBV. Atazanavir was taken with the morning dose of VIEKIRA PAK. The ritonavir component of the HIV-1 ART regimen was restarted after completion of treatment with VIEKIRA PAK and RBV.

Treated subjects had a median age of 51 years (range: 31 to 69); 24% of subjects were black; 81% of subjects had IL28B non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection.

The SVR12 rates were 91% (51/56) for subjects with HCV GT1a infection and 100% (7/7) for those with HCV GT1b infection. Of the 5 subjects who were non-responders, 1 experienced virologic breakthrough, 1 discontinued treatment, 1 experienced relapse and 2 subjects had evidence of HCV re-infection post-treatment.

One subject had confirmed HIV-1 RNA >400 copies/mL during the post-treatment period. This subject had no evidence of resistance to the ART regimen. No subjects switched their ART regimen due to loss of plasma HIV-1 RNA suppression.

14.7 Durability of Response

In an open-label clinical trial, 92% of subjects (526/571) who received various combinations of the direct acting antivirals included in VIEKIRA PAK with or without RBV achieved SVR12, and 99% of those who achieved SVR12 maintained their response through 48 weeks post-treatment (SVR48).

16 HOW SUPPLIED/STORAGE AND HANDLING

VIEKIRA PAK is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each child resistant daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening. The NDC number is NDC 0074-3093-28.

Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with "AV1" on one side. Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with "AV2" on one side.

Store at or below 30°C (86°F).

17 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 (5.2)]*.

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 (5.1) and Adverse Reactions (6)]*.

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 (8.1)]*.

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 (4), Warnings and Precautions (5.3) and Drug Interactions (7)]*.

Inform patients that contraceptives containing ethinyl estradiol are contraindicated with VIEKIRA PAK *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

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.

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03-B151

MEDICATION GUIDE

VIEKIRA PAK (vee-KEE-rah-pak)

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

co-packaged for oral use

Read this Medication Guide before you start taking VIEKIRA PAK and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about your treatment with VIEKIRA PAK before you start taking it and at regular check-ups. You should stay under your healthcare provider's care when taking VIEKIRA PAK.

When taking VIEKIRA PAK in combination with ribavirin, you should also read the Medication Guide that comes with ribavirin.

What is the most important information I should know about VIEKIRA PAK?

VIEKIRA PAK can cause increases in your liver function blood test results, especially if you use ethinyl estradiol-containing medicines (such as some birth control products).

- You must stop using ethinyl estradiol-containing medicines before you start treatment with VIEKIRA PAK. See the section **"Who should not take VIEKIRA PAK?"** for a list of these medicines.
- If you use these medicines as a method of birth control, you must use another method of birth control during treatment with VIEKIRA PAK, and for about **2** weeks after you finish treatment with VIEKIRA PAK. Your healthcare provider will tell you when you may begin taking ethinyl estradiol-containing medicines.
- Your healthcare provider should do blood tests to check your liver function during the first 4 weeks and then as needed, during treatment with VIEKIRA PAK.
- Your healthcare provider may tell you to stop taking VIEKIRA PAK if you develop signs or symptoms of liver problems.
- Tell your healthcare provider right away if you develop any of the following symptoms, or if they worsen during treatment with VIEKIRA PAK:
  - tiredness
  - weakness
  - loss of appetite
  - nausea and vomiting
  - yellowing of your skin or eyes

- color changes in your stools

What is VIEKIRA PAK?

VIEKIRA PAK is a prescription medicine used with or without ribavirin to treat people with genotype 1 chronic (lasting a long time) hepatitis C virus (HCV) infection, including people who have a certain type of cirrhosis (compensated).

VIEKIRA PAK is not for people with advanced cirrhosis (decompensated). If you have cirrhosis, talk to your healthcare provider before taking VIEKIRA PAK.

VIEKIRA PAK contains 2 different types of tablets. **You must take both types of tablets** exactly as prescribed, to treat your chronic hepatitis C virus (HCV) infection.

- the pink tablet contains: the medicines ombitasvir, paritaprevir, and ritonavir
- the beige tablet contains: the medicine dasabuvir

If you take VIEKIRA PAK with ribavirin, you should also read the Medication Guide for ribavirin.

It is not known if VIEKIRA PAK is safe and effective in children under 18 years of age.

Who should not take VIEKIRA PAK?

Do not take VIEKIRA PAK if you:

- **have severe liver problems**
- **take any of the following medicines:**
  - alfuzosin hydrochloride (Uroxatral®)
  - carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
  - efavirenz (Atripla®, Sustiva®)
  - ergot containing medicines including:
    - ergotamine tartrate (Cafergot®, Ergomar®, Ergostat®, Medihaler®, Migergot®, Wigraine®, Wigrettes®)
    - dihydroergotamine mesylate (D.H.E. 45®, Migranal®)
    - methylergonovine (Ergotrate®, Methergine®)
  - ethinyl estradiol-containing medicines:
    - combination birth control pills or patches, such as Lo Loestrin® FE, Norinyl®, Ortho Tri-Cyclen Lo®, Ortho Evra®
    - hormonal vaginal rings such as NuvaRing®
    - the hormone replacement therapy medicine, Fem HRT®
  - gemfibrozil (Lopid®)
  - lovastatin (Advicor®, Altoprev®, Mevacor®)

- midazolam, when taken by mouth
- phenytoin, (Dilantin®, Phenytek®)
- phenobarbital (Luminal®)
- pimozide (Orap®)
- rifampin (Rifadin®, Rifamate®, Rifater® Rimactane®)
- sildenafil citrate (Revatio®), when taken for pulmonary artery hypertension (PAH)
- simvastatin (Simcor®, Vytorin®, Zocor®)
- St. John's wort (Hypericum perforatum) or a product that contains St. John's wort
- triazolam (Halcion®)

- **have had a severe skin rash after taking ritonavir (Norvir®).**

What should I tell my healthcare provider before taking VIEKIRA PAK?

Tell your healthcare provider about all your medical conditions, including if you:

- have liver problems other than hepatitis C infection. **See "Who should not take VIEKIRA PAK?"**
- have HIV infection
- have had a liver transplant. If you take the medicines tacrolimus (Prograf®) or cyclosporine (Gengraf®, Neoral®, Sandimmune®) to help prevent rejection of your transplanted liver, the amount of these medicines in your blood may increase during treatment with VIEKIRA PAK.
  - Your healthcare provider should check the level of tacrolimus or cyclosporine in your blood, and if needed may change your dose of these medicines or how often you take them.
  - When you finish taking VIEKIRA PAK or if you have to stop VIEKIRA PAK for any reason, your healthcare provider should tell you what dose of tacrolimus or cyclosporine you should take and how often you should take it.
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if VIEKIRA PAK will harm your unborn baby. **When taking VIEKIRA PAK in combination with ribavirin you should also read the ribavirin Medication Guide for important pregnancy information.**
  Pregnancy Registry: There is a registry for females who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of the pregnant mother and her baby. If you are a pregnant female and have both HCV and HIV infection, talk with your healthcare provider about enrolling in this registry.

- are breastfeeding or plan to breastfeed. It is not known if VIEKIRA PAK passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take VIEKIRA PAK.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with VIEKIRA PAK. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with VIEKIRA PAK.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take VIEKIRA PAK with other medicines.
- When you finish treatment with VIEKIRA PAK:
  - If your doctor changed the dose of any of your usual medicines during treatment with VIEKIRA PAK: Ask your doctor about when you should change back to your original dose after you finish treatment with VIEKIRA PAK.
  - If your doctor told you to stop taking any of your usual medicines during treatment with VIEKIRA PAK: Ask your doctor if you should start taking these medicines again after you finish treatment with VIEKIRA PAK.

How should I take VIEKIRA PAK?

- Take VIEKIRA PAK exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking VIEKIRA PAK without first talking with your healthcare provider.
- When you receive your VIEKIRA PAK prescription, you will get a **monthly carton that contains enough medicine for 28 days**.
- Each monthly carton of VIEKIRA PAK contains **4 smaller cartons**.
- Each of the 4 smaller cartons contains enough child resistant **daily dose packs** of medicine to last for **7 days** (1 week).
- Each **daily dose pack** contains all of your VIEKIRA PAK medicine for **1 day** (4 tablets). Follow the instructions on each daily dose pack about how to remove the tablets.
- Take VIEKIRA PAK tablets with a meal as follows:
  - take the **2** pink tablets (ombitasvir, paritaprevir, and ritonavir), with **1** of the beige tablets (dasabuvir), at about the same time every morning.
  - take the **second** beige tablet (dasabuvir), at about the same time every evening.

- If you miss a dose of the pink tablets, and it is **less than 12 hours** from the time you usually take your dose, **take the missed dose** with a meal as soon as possible. Then take your next dose at your usual time with a meal.
- If you miss a dose of the pink tablets, and it is **more than 12 hours** from the time you usually take your dose, **do not take the missed dose**. Take your next dose at your usual time with a meal.
- If you miss a dose of the beige tablet, and it is **less than 6 hours** from the time you usually take your dose, **take the missed dose** with a meal as soon as possible. Then take your next dose at your usual time with a meal.
- If you miss a dose of the beige tablet, and it is **more than 6 hours** from the time you usually take your dose, **do not take the missed dose**. Take your next dose at your usual time with a meal.
- Do not take more than your prescribed dose of VIEKIRA PAK to make up for a missed dose.
- If you take too much VIEKIRA PAK, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of VIEKIRA PAK?

See **"What is the most important information I should know about VIEKIRA PAK?"**

Common side effects of VIEKIRA PAK when used with ribavirin include:

- tiredness
- nausea
- itching
- skin reactions such as redness or rash
- sleep problems
- feeling weak

Common side effects of VIEKIRA PAK when used without ribavirin include:

- nausea
- itching
- sleep problems

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of VIEKIRA PAK. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIEKIRA PAK?

- Store VIEKIRA PAK at or below 86°F (30°C).

Keep VIEKIRA PAK and all medicines out of the reach of children.

General information about the safe and effective use of VIEKIRA PAK

It is not known if treatment with VIEKIRA PAK will prevent you from infecting another person with the hepatitis C virus during your treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIEKIRA PAK for a condition for which it was not prescribed. Do not give VIEKIRA PAK to other people, even if they have the same condition you have. It may harm them.

If you would like more information about VIEKIRA PAK, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VIEKIRA PAK that is written for health professionals.

For more information, call 1-800-633-9110 or go to www.viekira.com.

What are the ingredients in VIEKIRA PAK?

Ombitasvir, paritaprevir, and ritonavir tablets:

Active ingredients: ombitasvir, paritaprevir, and ritonavir

Inactive ingredients: copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and red iron oxide.

Dasabuvir tablets:

Active ingredients: dasabuvir

Inactive ingredients: microcrystalline cellulose (D50-100 um), microcrystalline cellulose (D50-50 um), lactose monohydrate, copovidone, croscarmellose sodium, colloidal silicon dioxide/anhydrous colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350/macrogol 3350, talc and iron oxide yellow, iron oxide red and iron oxide black.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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

Revised: March 2015

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03-B151

VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use （和文）

添付文書の重要点

以下の重要点には，VIEKIRA PAK の安全かつ有効な使用に必要なすべての情報は含まれていない。VIEKIRA PAK に関する添付文書（全文）を参照のこと。

VIEKIRA PAK（オムビタスビル，パリタプレビル及びリトナビル配合錠，ダサブビル錠），経口投与用同梱製品

米国内初回承認：2014 年

----------主な変更----------

用法・用量，成人の推奨用量(2.1) 3/2015

----------効能・効果----------

VIEKIRA PAK は，リバビリンとの併用又は非併用により，ジェノタイプ 1 型の慢性 C 型肝炎ウイルス（HCV）感染患者（代償性肝硬変患者を含む）の治療に用いる。VIEKIRA PAK には，オムビタスビル（C 型肝炎ウイルス NS5A 阻害薬），パリタプレビル（C 型肝炎ウイルス NS3/4A プロテアーゼ阻害薬），リトナビル（CYP3A 阻害薬）及びダサブビル（C 型肝炎ウイルス非ヌクレオシド NS5B palm 領域ポリメラーゼ阻害薬）が含まれる（1）。

使用制限：非代償性肝疾患患者に対する VIEKIRA PAK の使用は推奨されない。

----------用法・用量----------

推奨用量：オムビタスビル，パリタプレビル，リトナビル 12.5/75/50 mg 配合錠 2 錠 1 日 1 回（朝）及びダサブビル 250 mg 錠 1 錠 1 日 2 回（朝夕）を脂肪又はカロリー含有量にかかわらず食事とともに服用する（2.1）。

各患者集団の治療レジメン及び投与期間

患者集団	治療*	投与期間
肝硬変を伴わないジェノタイプ 1a	VIEKIRA PAK＋リバビリン	12 週間
肝硬変を伴うジェノタイプ 1a	VIEKIRA PAK＋リバビリン	24 週間**
肝硬変を伴わないジェノタイプ 1b	VIEKIRA PAK	12 週間
肝硬変を伴うジェノタイプ 1b	VIEKIRA PAK＋リバビリン	12 週間
*注：ジェノタイプ 1 のサブタイプが不明，又はジェノタイプ 1 混合感染の場合は，ジェノタイプ 1a の推奨用量に従うこと。 **前治療歴に基づき，一部の患者については VIEKIRA PAK とリバビリンの併用を 12 週間とすることも考慮する［臨床試験（14.3）を参照］		

HCV/HIV-1 重複感染患者：HCV/HIV-1 重複感染患者については，表 1 の用法に関する推奨事項に従うこと。

肝移植患者：

肝機能が正常，かつ線維症が軽度（Metavir 線維症スコア 2 以下）の肝移植患者の場合，VIEKIRA PAK の推奨投与期間は，リバビリンとの併用で 24 週間である。(2.2)

錠剤：

- オムビタスビル，パリタプレビル，リトナビル：12.5/75/50 mg（3）
- ダサブビル：250 mg（3）

----------禁忌----------

- VIEKIRA PAK とリバビリンを併用投与する場合，リバビリンに対する禁忌も本併用レジメンに適用される（4）。
- 重度の肝障害を有する患者（4，8.6，12.3）

- 以下の薬剤との同時投与：クリアランスが CYP3A に大きく依存する薬剤，CYP3A 及び CYP2C8 の強力な誘導剤，CYP2C8 の強力な阻害剤（4）
- リトナビルに対する過敏症（例：中毒性表皮壊死融解症，スティーブンス・ジョンソン症候群）の既往歴のある患者（4）

----------警告及び使用上の注意----------

- ALT 増加：VIEKIRA PAK の投与を開始する前に，エチニルエストラジオールを含有する薬剤を中止すること（別の避妊法が推奨される）。投与開始から 4 週間以内に肝機能に関する臨床検査を実施すること。VIEKIRA PAK 投与中に ALT 増加が認められた場合は，慎重にモニタリングを行い，添付文書全文に記載された推奨事項に従うこと（5.1）。
- リバビリン併用投与に関連するリスク：VIEKIRA PAK とリバビリンを併用投与する場合は，リバビリンに対する警告及び使用上の注意も本併用レジメンに適用される（5.2）。
- 薬物相互作用：VIEKIRA PAK と特定の他剤との併用により，既知又は潜在的に重大な薬物相互作用が生じる可能性がある。薬物相互作用によっては VIEKIRA PAK の治療効果が消失することもある（5.3）。

----------副作用----------

VIEKIRA PAK とリバビリンの併用投与群で，最も高頻度で報告された副作用（被験者の 10%超）は，疲労，悪心，そう痒症，その他の皮膚反応，不眠症及び無力症であった。リバビリンを併用しない VIEKIRA PAK 群では最も一般的に報告された副作用（被験者の 5%以上）は悪心，そう痒症及び不眠症であった。

副作用の疑いがある場合には，AbbVie 社（1-800-633-9110）又は FDA（1-800-FDA-1088 又は www.fda.gov/medwatch）に連絡されたい。

----------薬物相互作用----------

VIEKIRA PAK との同時投与は一部の薬剤の血漿中濃度を変化させる可能性があり，また，一部の薬剤が VIEKIRA PAK の血漿中濃度を変化させる可能性もある。投与前及び投与中は薬物相互作用が生じる可能性を考慮すること。潜在的な薬物相互作用については，投与前及び投与中に添付文書全文を参照のこと（4，5.3，7，12.3）。

患者に伝えるべき情報及び患者向け医薬品ガイド（Medication Guide）については，17 項を参照のこと。

改訂日：2014 年 12 月

添付文書（全文）：目次*

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14 臨床試験

14.1 臨床試験の概要

14.2 肝硬変を認めない成人の慢性 HCV ジェノタイプ 1a 及び 1b 感染患者を対象とした臨床試験の結果

14.3 代償性肝硬変を有する成人の慢性 HCV ジェノタイプ 1a 及び 1b 感染患者を対象とした臨床試験の結果

14.4 リバビリン減量が SVR12 に及ぼす影響

14.5 選択された肝移植患者を対象とした臨床試験（CORAL-I 試験）待機的

14.6 HCV/HIV-1 重複感染患者を対象とした臨床試験

14.7 奏効期間

16 包装／保存及び取り扱い

17 患者に伝えるべき情報

*添付文書（全文）から削除された項目は記載されていません。

添付文書（全文）

1 効能・効果

VIEKIRA PAK は，リバビリンとの併用又は非併用により，ジェノタイプ 1 型の慢性 C 型肝炎ウイルス（HCV）感染患者（代償性肝硬変患者を含む）の治療に用いる。

使用制限：

非代償性肝疾患患者に対する VIEKIRA PAK の使用は推奨されない［特別な患者集団への投与（*8.6*）及び臨床薬理（*12.3*）を参照］。

2 用法・用量

2.1 成人の推奨用量

VIEKIRA PAK は，オムビタスビル，パリタプレビル，リトナビル配合錠とダサブビル錠を同梱したものである。

VIEKIRA PAK の経口投与における推奨用量は，オムビタスビル，パリタプレビル，リトナビル配合錠 2 錠 1 日 1 回（朝）及びダサブビル錠 1 錠 1 日 2 回（朝夕）である。

VIEKIRA PAK は，脂肪又はカロリー含有量にかかわらず食事とともに服用すること［臨床薬理（*12.3*）を参照］。

特定の患者集団には VIEKIRA PAK とリバビリン（RBV）を併用する（表 1 を参照）。VIEKIRA PAK と併用する際の RBV の推奨用量は被験者の体重に基づき，体重 75 kg 未満の場合には 1,000 mg/日，75 kg 以上の場合には 1,200 mg/日であり，これを 2 回に分けて食事とともに投与する。リバビリンの用量変更については，リバビリンの添付文書を参照のこと。

HCV/HIV-1 重複感染患者については，表 1 の用法に関する推奨事項に従うこと。併用する HIV-1 抗ウイルス薬の推奨事項については，薬物相互作用（7）を参照のこと。

治療開始前及び治療中は肝臓に関連する生化学的検査値のモニタリングを行うこと［警告及び使用上の注意（*5.1*）を参照］。

各患者集団に推奨される VIEKIRA PAK の治療レジメン及び投与期間を表 1 に示す。

表 1　　各患者集団（未治療又はインターフェロン治療歴あり）の治療レジメン及び投与期間

患者集団	治療*	投与期間
肝硬変を伴わないジェノタイプ 1a	VIEKIRA PAK＋リバビリン	12 週間
肝硬変を伴うジェノタイプ 1a	VIEKIRA PAK＋リバビリン	24 週間**
肝硬変を伴わないジェノタイプ 1b	VIEKIRA PAK	12 週間
肝硬変を伴うジェノタイプ 1b	VIEKIRA PAK＋リバビリン	12 週間
*注：ジェノタイプ 1 のサブタイプが不明，又はジェノタイプ 1 混合感染の場合は，ジェノタイプ 1a の推奨用量に従うこと。 **前治療歴に基づき，一部の患者については VIEKIRA PAK とリバビリンの併用を 12 週間とすることも考慮する［臨床試験（*14.3*）を参照］。		

2.2 肝移植患者における使用

肝機能が正常，かつ線維症が軽度（Metavir 線維症スコア 2 以下）の肝移植患者の場合，VIEKIRA PAK の推奨投与期間は，HCV ジェノタイプ 1 型のサブタイプにかかわらずリバビリンとの併用で 24 週間である［臨床試験（*14.6*）を参照］。肝移植患者に対して VIEKIRA PAK とカルシニューリン阻害薬を併用投与する場合は，カルシニューリン阻害薬の用量を調節する必要がある［薬物相互作用（7）を参照］。

2.3 肝障害

軽度の肝障害（Child-Pugh A）を有する患者の場合，VIEKIRA PAK の用量調節は不要である。中等度の肝障害（Child-Pugh B）を有する患者には，VIEKIRA PAK は推奨されない。重度の肝障害（Child-Pugh C）を有する患者には，VIEKIRA PAK は禁忌である［禁忌（*4*），特別な患者集団への投与（*8.6*）及び臨床薬理（*12.3*）を参照］。

3 剤形及び含量

VIEKIRA PAK は，オムビタスビル，パリタプレビル，リトナビル配合錠とダサブビル錠を同梱したものである。

- オムビタスビル，パリタプレビル，リトナビル 12.5/75/50 mg 錠は，桃色の両凸長楕円形のフィルムコーティング錠であり，片面に「AV1」の刻印がある。
- ダサブビル 250 mg 錠は，淡黄赤色の楕円形のフィルムコーティング錠であり，片面には「AV2」の刻印がある。1 錠中にダサブビル sodium monohydrate 270.3 mg（ダサブビルとして 250 mg）を含有する。

4 禁忌

- VIEKIRA PAK とリバビリンを併用投与する場合，リバビリンに対する禁忌も本併用レジメンに適用される。リバビリンの禁忌一覧については，リバビリンの添付文書を参照のこと。
- 重度の肝障害を有する患者では，毒性が発現するおそれがあるため，VIEKIRA PAK は禁忌である［特別な患者集団における使用（*8.6*）及び臨床薬理（*12.3*）を参照］。
- VIEKIRA PAK と以下の薬剤との併用は禁忌である。
  - クリアランスが CYP3A に大きく依存し，血漿中濃度の上昇が重篤及び／又は生命を脅かす事象を伴う薬剤
  - CYP3A 及び CYP2C8 の強力な誘導剤であり，VIEKIRA PAK の効果を減弱させる可能性のある薬剤
  - CYP2C8 の強力な阻害剤であり，血漿中ダサブビル濃度が増加し，QT 延長リスクが増大する可能性のある薬剤

VIEKIRA PAK で禁忌とされる薬剤を表 2 に示す［薬物相互作用（*7*）を参照］。

表 2　　VIEKIRA PAK で禁忌とされる薬剤

薬剤クラス	禁忌とされるクラス内の薬剤	臨床的見解
α1 アドレナリン受容体拮抗薬	アルフゾシン塩酸塩	低血圧の可能性がある。
抗痙攣薬	カルバマゼピン，フェニトイン，フェノバルビタール	オムビタスビル，パリタプレビル，リトナビル及びダサブビルの曝露量が減少し，VIEKIRA PAK の治療活性欠如に至る可能性がある。
高脂血症治療薬	ゲムフィブロジル	ダサブビルの曝露量が 10 倍に増加し，QT 延長リスクが増大するおそれがある。
抗マイコバクテリア薬	リファンピシン	オムビタスビル，パリタプレビル，リトナビル及びダサブビルの曝露量が減少し，VIEKIRA PAK の治療活性欠如に至る可能性がある。
麦角誘導体	エルゴタミン，ジヒドロエルゴタミン，エルゴメトリン，メチルエルゴメトリン	リトナビルとエルゴメトリン，エルゴタミン，ジヒドロエルゴタミン又はメチルエルゴメトリンとの併用と，血管痙攣及び組織虚血を特徴とする急性麦角中毒との関連性が認められている。
エチニルエストラジオール含有製剤	経口避妊薬合剤などのエチニルエストラジオール含有薬	ALT 増加の可能性がある［警告及び使用上の注意（5.1）を参照］。
漢方製品	セント・ジョーンズ・ワート（セイヨウオトギリソウ）	オムビタスビル，パリタプレビル，リトナビル及びダサブビルの曝露量が減少し，VIEKIRA PAK の治療活性欠如に至る可能性がある。
HMG-CoA 還元酵素阻害薬	ロバスタチン，シンバスタチン	横紋筋融解症を含むミオパチーの可能性がある。
神経遮断薬	ピモジド	不整脈の可能性がある。
非ヌクレオシド系逆転写酵素阻害薬	エファビレンツ	エファビレンツをベースとするレジメンとパリタプレビル，リトナビル＋ダサブビルとの併用投与は忍容性不良であり，肝酵素上昇に至る。
ホスホジエステラーゼ 5（PDE5）阻害薬	肺動脈性肺高血圧症（PAH）治療薬レバチオとして投与する場合のシルデナフィル	視覚障害，低血圧，持続勃起症，失神などのシルデナフィル関連の有害事象の可能性が増加する。
鎮静薬／睡眠薬	トリアゾラム 経口投与によるミダゾラム	トリアゾラム及び経口投与によるミダゾラムはそのほとんどが CYP3A4 によって代謝される。トリアゾラム又は経口投与によるミダゾラムと VIEKIRA PAK との併用投与により，これらベンゾジアゼピン系薬剤の濃度が大きく増加する可能性がある。鎮静作用の延長又は増大，呼吸抑制などの重篤及び／又は生命を脅かす事象が発現する可能性がある。

- VIEKIRA PAK は，リトナビルに対する過敏症［中毒性表皮壊死融解症（TEN），スティーブンス・ジョンソン症候群等］の既往歴のある患者には禁忌である。

5 警告及び使用上の注意

5.1 ALT 増加のリスク増大

リバビリンとの併用か非併用かを問わず，VIEKIRA PAK を用いた臨床試験において，正常値上限（ULN）の 5 倍を超える ALT 増加が全被験者の約 1%に認められた［副作用（*6.1*）を参照］。通常，ALT 増加は無症候性で，投与開始から 4 週間以内に発現し，リバビリンとの併用又は非併用で VIEKIRA PAK の投与を継続したところ，発現から 2～8 週間以内に減少した。

このような ALT 増加は，経口避妊薬合剤，避妊パッチ，避妊膣リングなどのエチニルエストラジオールを含有する薬剤を使用している女性で有意に発現頻度が高かった。VIEKIRA PAK による治療を開始する前に，エチニルエストラジオールを含有する薬剤の使用を中止すること［禁忌（*4*）を参照］。VIEKIRA PAK 投与中は別の避妊法（例：プロゲスチンのみの避妊法，ホルモンを使用しない方法）が推奨される。VIEKIRA PAK による治療が完了してから約 2 週間後より，エチニルエストラジオールを含有する薬剤の使用を再開することができる。

ホルモン補充療法で使用されるエストラジオールや結合型エストロゲンなど，エチニルエストラジオール以外のエストロゲン製剤を使用している女性患者では，ALT 増加の発現率はエストロゲンの投与を受けていない患者と同程度であった。しかし，他のエストロゲン製剤を服用している患者数が限られているため，VIEKIRA PAK と併用投与する場合は注意する必要がある。［副作用（*6.1*）を参照］

肝臓関連の臨床検査は，投与開始から最初の 4 週間実施し，その後は臨床的な必要な場合は実施する。ALT がベースライン値を超えた場合は，再検査を行い慎重にモニタリングを行うこと。

- 患者には，疲労，脱力，食欲不振，悪心及び嘔吐，黄疸又は変色便があらわれた場合は，直ちに医療従事者に相談するよう指示すること
- ULN の 10 倍を超える ALT 値が持続する場合は，VIEKIRA PAK の投与中止を考慮すること。
- ALT 増加に伴って肝臓炎症の徴候又は症状，若しくは抱合ビリルビン，アルカリホスファターゼ又は INR の増加が認められる場合は，VIEKIRA PAK の投与を中止する。

5.2 リバビリン併用療法に関連するリスク

VIEKIRA PAK とリバビリンを併用投与する場合には，リバビリンに対する警告及び使用上の注意，特に妊娠を避けることに対する警告がこの併用レジメンに適用される。リバビリンの警告及び使用上の注意の全一覧については，リバビリンの添付文書を参照のこと。

5.3 薬物相互作用による副作用又は治療効果減弱のリスク

VIEKIRA PAK と特定の他剤との併用により，既知又は潜在的に重大な薬物相互作用が生じる可能性があり，以下に至るおそれがある。

- VIEKIRA PAK の治療効果が減弱し，耐性が発現する可能性
- 併用薬又は VIEKIRA PAK の成分の曝露量が増加することによって，臨床的に重大な副作用が生じる可能性

この予想される，既知の重大な薬物相互作用を予防又は管理するための手段（推奨用量を含む）については，表 5 を参照のこと［薬物相互作用（7）を参照］。VIEKIRA PAK による治療前及び治療中は薬物相互作用が生じる可能性を考慮すること。VIEKIRA PAK 治療中は併用薬を確認し，併用薬と関連する副作用が発現していないかモニタリングを行うこと［併用薬（4）及び薬物相互作用（7）を参照］。

5.4 HCV/HIV-1 重複感染患者における HIV-1 プロテアーゼ阻害薬の薬剤耐性リスク

VIEKIRA PAK の成分であるリトナビルは HIV-1 プロテアーゼ阻害薬でもあることから，HIV-1 プロテアーゼ阻害薬耐性に関連する代替として選択される可能性がある。VIEKIRA PAK の投与を受ける HCV/HIV-1 重複感染患者は，HIV-1 プロテアーゼ阻害薬の耐性発現リスクを低減するため，抑制的な抗レトロウイルス薬レジメンも継続すべきである。

6 副作用

VIEKIRA PAK とリバビリン（RBV）を併用する場合，リバビリン関連の副作用一覧については，リバビリンの添付文書を参照のこと。

次の副作用については本添付文書の以下の項及びラベリングに記載している。

- ALT 増加のリスク増大［警告及び使用上の注意（5.1）を参照］。

6.1 臨床試験成績

広範な条件下で臨床試験が実施されたため，VIEKIRA PAK の臨床試験で認められた副作用の発生率は，他の薬剤の臨床試験における発生率と直接比較することはできず，診療で認められる発生率を反映しない可能性がある。

安全性評価は，リバビリンとの併用又は非併用により，12 又は 24 週間にわたって VIEKIRA PAK の投与を受けた 2,000 例を超える被験者を対象とした第 III 相試験 6 試験のデータに基づいている。

<u>プラセボ対照試験における VIEKIRA PAK とリバビリンの併用</u>

リバビリンと併用したときの VIEKIRA PAK の安全性は，プラセボ対照試験 2 試験（SAPPHIRE I 及び II 試験）において慢性 HCV 感染患者 770 例を対象として評価した［臨床試験（*14.1*，*14.2*）を参照］。プラセボ群と比較して VIEKIRA PAK＋リバビリン併用投与群で多く発生した副作用は，疲労，悪心，そう痒症，その他の皮膚反応，不眠及び無力症であった（表 3 参照）。副作用の大半は軽度であった。被験者の 2%に重篤な有害事象（SAE）が発現した。副作用により投与を永続的に中止した被験者の割合は 1%未満であった。

表 3　慢性 HCV GT1 感染患者を対象とした 12 週間の VIEKIRA PAK＋リバビリン併用群においてプラセボ群と比較した発現頻度が 5%以上高かった副作用

	SAPPHIRE I 及び II 試験	
	VIEKIRA PAK + RBV 12 週間 N = 770 %	プラセボ 12 週間 N = 255 %
疲労	34	26
悪心	22	15
そう痒症*	18	7
皮膚反応$	16	9
不眠	14	8
無力症	14	7
*グループ化した用語「そう痒症」には，基本語のそう痒症と全身性そう痒症が含まれる。 $グループ化した用語：発疹，紅斑，湿疹，斑状丘疹状皮疹，斑状皮疹，皮膚炎，丘疹性皮疹，皮膚剥脱，そう痒性皮疹，紅斑性皮疹，全身発疹，アレルギー性皮膚炎，接触性皮膚炎，剥脱性発疹，光線過敏性反応，乾癬，皮膚反応，潰瘍，蕁麻疹	

レジメンによる比較試験における VIEKIRA PAK とリバビリンの併用及び非併用

VIEKIRA PAK とリバビリンの併用及び非併用は，臨床試験 3 試験（PEARL-II，PEARL-III 及び PEARL-IV 試験）において，各試験で慢性 HCV 感染患者 401 例及び 509 例を対象として評価した［臨床試験（*14.1*，*14.2*）を参照］。VIEKIRA PAK＋リバビリン併用投与群で発生頻度が高かった有害事象として，そう痒症，悪心，不眠及び無力症が確認された（表 4 参照）。有害事象の大半は軽度から中等度であった。有害事象により永続的に投与を中止した被験者の割合は，VIEKIRA PAK＋リバビリン併用投与群と VIEKIRA PAK 単独投与群のいずれにおいても 1%未満であった。

表 4　慢性 HCV GT1 感染患者を対象とした 12 週間の VIEKIRA PAK＋リバビリン併用群において VIEKIRA PAK 群と比較した発現頻度が 5%以上高かった副作用

	PEARL-II，-III 及び-IV 試験	
	VIEKIRA PAK + RBV 12 週間 N = 401 %	VIEKIRA PAK 12 週間 N = 509 %
悪心	16	8
そう痒症*	13	7
不眠	12	5
無力症	9	4
*グループ化した用語「そう痒症」には，基本語のそう痒症と全身性そう痒症が含まれる。		

代償性肝硬変を有する患者を対象とした VIEKIRA PAK とリバビリンの併用

VIEKIRA PAK とリバビリンの併用は，代償性肝硬変を有する患者 380 例（12 週間投与群：n＝208，24 週間投与群：n＝172）を対象として評価した（TURQUOISE II 試験）［臨床試験（*14.1*，*14.3*）を参照］。代償性肝硬変を有する被験者にみられた有害事象の種類及び重症度は，他の第 III 相試験における肝硬変のない被験者と同程度であった。疲労及び呼吸困難の発生率は 24 週間投与群の方が 5%以上高かった。有害事象の大半は両群で投与開始から 12 週間以内に発現した。ほとんどの有害事象は軽度から中等度であった。12 週間投与群と 24 週間投与群で SAE が発現した被験者の割合は，それぞれ 6%及び 5%であり，各投与群において 2%の被験者が有害事象により永続的に投与を中止した。

皮膚反応

PEARL-II，-III 及び-IV 試験において，VIEKIRA PAK 単独投与群の 7%及び VIEKIRA PAK＋リバビリン併用投与群の 10%で発疹関連事象が報告された。SAPPHIRE-I 及び-II 試験では，VIEKIRA PAK＋リバビリン併用投与群の 16%及びプラセボ群の 9%で皮膚反応が報告された。

TURQUOISE-II 試験において，VIEKIRA PAK＋リバビリン併用 12 週間及び 24 週間投与群のそれぞれ 18%及び 24%で皮膚反応が報告された。これらの事象の大半は軽度と判定された。スティーブンス・ジョンソン症候群（SJS），中毒性表皮壊死融解症（TEN），多形紅斑（EM），好酸球増加と全身症状を伴う薬疹（DRESS）などの重篤な事象又は重度の皮膚反応は認められなかった。

臨床検査値異常

血清 *ALT* 増加

VIEKIRA PAK を投与された被験者の約 1%において，ベースライン後の血清 ALT 値が投与開始後に正常値上限（ULN）の 5 倍を超えた。エチニルエストラジオールを含有する薬剤を併用している女性ではその発現率が 25%(4/16)に上昇した［禁忌（*4*）並びに警告及び使用上の注意（*5.1*）を参照］。エチニルエストラジオール以外のエストロゲン（例えばホルモン補充療法において使われるエストラジオールと抱合型エストロゲン）を使用している女性被験者の臨床的に関連する ALT 増加発生率は，3%(2/59)であった。

通常，ALT 増加は無症候性で，概ね投与開始から 4 週間以内［平均：20 日間（範囲：8～57 日）］に発現し大半が治療継続中に回復した。ALT 増加の大半が薬物性肝障害と判定された。概して，ALT 増加は一般的にビリルビン値上昇を伴わなかった。肝硬変は ALT 増加の危険因子ではなかった［警告及び使用上の注意（*5.1*）を参照］。

血清ビリルビン増加

ベースライン後に ULN の 2 倍以上のビリルビン値の増加を認めたのは VIEKIRA PAK 単独投与群で 2%であったのに対し，VIEKIRA PAK＋リバビリン併用投与群では 15%であった。このビリルビン増加は間接型ビリルビン優位であり，パリタプレビルによるビリルビントランスポーターOATP1B1/1B3 阻害とリバビリンによる溶血に関連していた。ビリルビン値は初回投与後に増加し，Week 1 までに最高値に達するが，概ね治療継続中に回復した。ビリルビン増加と血清 ALT 増加に関連性は認められなかった。

貧血／ヘモグロビン減少

第 III 相試験全体で，VIEKIRA PAK＋リバビリン併用投与群におけるヘモグロビン値のベースラインからの平均変化量は-2.4 g/dL であり，VIEKIRA PAK 単独投与群の平均変化量は-0.5 g/dL であった。ヘモグロビン値の減少は投与早期（Week 1～2）に起こり，さらに Week 3 まで減少した。ヘモグロビン値は残りの投与期間中も低値で推移し，Week 4 までにベースライン値まで回復した。VIEKIRA PAK＋リバビリン併用投与群で，投与期間中にヘモグロビン値が 8.0 g/dL 未満まで減少した被験者は 1%未満であった。VIEKIRA PAK＋リバビリン併用投与群の 7%は，ヘモグロビン値減少によりリバビリンを減量した。3 例が輸血を受け，5 例がエリスロポエチンの投与を必要とした。1 例が貧血のため投与を中止した。VIEKIRA PAK 単独投与群でヘモグロビン値が 10 g/dL 未満となった被験者はいなかった。

HCV/HIV-1 重複感染患者における VIEKIRA PAK

VIEKIRA PAK とリバビリンの併用は，安定した抗レトロウイルス療法を受けている HCV/HIV-1 重複感染患者 63 例を対象として評価した。被験者の少なくとも 10%以上に発現した主な有害事象は，疲労（48%），不眠（19%），悪心（17%），頭痛（16%），そう痒症（13%），咳嗽（11%），易刺激性（10%）及び黄疸眼（10%）であった。

ULN の 2 倍を超える総ビリルビンの増加（大部分は間接型）は 34 例（54%）で認められた。そのうち 15 例はビリルビン増加の時点でアタザナビルの投与も受けており，9 例で黄疸眼，黄

疸又は高ビリルビン血症の有害事象も認められた。高ビリルビン血症を認めた被験者で同時にアミノトランスフェラーゼが増加した被験者はいなかった［警告及び使用上の注意（*5.4*）並びに副作用（*6.1*）及び臨床試験（*14.6*）を参照］。グレード 3 の ALT 増加を認めた被験者はいなかった。

ベースライン後のヘモグロビン値が 1 回でも 10 g/dL 未満となった被験者は 7 例（11%）で，そのうち 6 例がリバビリンの用量を変更した。この小規模コホートでは，輸血又はエリスロポエチンの投与を必要とした被験者はいなかった。

CD4 陽性 T 細胞数減少の中央値は，12 週間及び 24 週間の投与終了時にそれぞれ 47 cells/mm3，62 cells/mm3 であり，大半は投与後にベースライン値まで回復した。投与期間中に，2 例で CD4 陽性 T 細胞数が 200 cells/mm3 未満に減少したが，CD4 の割合（%）は低下しなかった。AIDS に関連する日和見感染を発現した被験者はいなかった。

選択された肝移植患者における VIEKIRA PAK

VIEKIRA PAK とリバビリンの併用は，HCV 感染の再燃を認めた肝移植後の患者 34 例を対象として評価した。20%を超える被験者に発現した有害事象は，疲労（50%），頭痛（44%），咳嗽（32%），下痢（26%），不眠（26%），無力症（24%），悪心（24%），筋痙縮（21%）及び発疹（21%）であった。ベースライン後のヘモグロビン値が 1 回でも 10 g/dL 未満となった被験者は 10 例（29%）であった。ヘモグロビン減少のため 10 例がリバビリンの用量を変更し，3%（34 例中 1 例）がリバビリンを休薬した。5 例がエリスロポエチンの投与を受け，その全例が開始用量 1000～1200 mg/日でリバビリンの投与を開始した。輸血を受けた被験者はいなかった。［臨床試験（*14.5*）を参照］

7 薬物相互作用

禁忌（4），警告及び使用上の注意（5.3）並びに臨床薬理（12.3）も参照のこと。

7.1 VIEKIRA PAK の他の医薬品に対する影響

オムビタスビル，パリタプレビル及びダサブビルは UGT1A1 の阻害薬であり，リトナビルは CYP3A4 の阻害薬である。パリタプレビルは OATP1B1 及び OATP1B3 の阻害薬であり，パリタプレビル，リトナビル及びダサブビルは BCRP の阻害薬である。VIEKIRA PAK と CYP3A，UGT1A1，BCRP，OATP1B1 又は OATP1B3 の基質である薬剤を併用投与した場合，それらの薬剤の血漿中濃度が増加する可能性がある。

7.2 他の薬剤の VIEKIRA PAK の 1 つ以上の成分に対する影響

パリタプレビル及びリトナビルは主に CYP3A 酵素により代謝される。VIEKIRA PAK と強力な CYP3A 阻害薬を併用した場合，パリタプレビル及びリトナビルの濃度が増加する可能性がある。ダサブビルは主に CYP2C8 酵素により代謝される。VIEKIRA PAK と CYP2C8 を阻害する薬剤を併用した場合，血漿中のダサブビル濃度が増加する可能性がある。オムビタスビルは主に

アミド加水分解によって代謝されるが，CYP 酵素も副次的に代謝に関与している。オムビタスビル，パリタプレビル，ダサブビル及びリトナビルは P-gp の基質である。オムビタスビル，パリタプレビル及びダサブビルは BCRP の基質である。パリタプレビルは OATP1B1 及び OATP1B3 の基質である。P-gp，BCRP，OATP1B1 又は OATP1B3 を阻害した場合，VIEKIRA PAK の各成分の血漿中濃度が増加する可能性がある。

7.3 確立された薬物相互作用及び他の潜在的な薬物相互作用

VIEKIRA PAK を投与する目的で，併用薬の用量を調節する場合は，VIEKIRA PAK の投与終了後に再度用量を調節すること。VIEKIRA PAK の用量調節の必要はない。

VIEKIRA PAK の併用投与が併用薬の濃度に及ぼす影響及び併用薬が VIEKIRA PAK の各成分に及ぼす影響を表 5 に示す。VIEKIRA PAK との併用が禁忌の薬剤については禁忌（4）を参照のこと。その他の潜在的に重要な薬物相互作用については，リトナビルの添付文書を参照のこと。

表 5　　薬物相互作用試験によって確立された薬物相互作用

併用薬のクラス： 薬剤名	濃度に対する影響	臨床的見解
抗不整脈薬		
アミオダロン ベプリジル ジソピラミド フレカイニド リドカイン（全身性） メキシレチン プロパフェノン キニジン	↑抗不整脈薬	VIEKIRA PAK と併用投与する際は，注意を払う必要があり，抗不整脈薬における治療濃度（可能な場合）をモニタリングすることが推奨される。
抗真菌薬		
ケトコナゾール	↑ケトコナゾール	VIEKIRA PAK とケトコナゾールを併用投与する際は，ケトコナゾールの 1 日用量の上限を 200 mg/日までとすること。
ボリコナゾール	↓ボリコナゾール	リスク - ベネフィット比の評価によってボリコナゾールを使用することの正当性が示されない限り，VIEKIRA PAK とボリコナゾールの併用投与は推奨されない。
カルシウムチャネル遮断薬		
アムロジピン	↑アムロジピン	アムロジピンの減量を検討する。臨床症状のモニタリングが推奨される。
コルチコステロイド（吸入／経鼻）		
フルチカゾン	↑フルチカゾン	VIEKIRA PAK と吸入又は経鼻フルチカゾンとの併用により血清コルチゾール濃度が減少する可能性がある。特に長期にわたって使用する場合は，別のコルチコステロイドを検討すること。
利尿薬		
フロセミド	↑フロセミド（C_{max}）	患者の臨床症状をモニタリングすることが推奨される。また，患者の反応に基づいて治療を個別化すること。
HIV 抗ウイルス薬		
アタザナビル／リトナビル 1 日 1 回	↑パリタプレビル	VIEKIRA PAK と併用投与する場合は，朝にアタザナビル 300 mg のみ（リトナビルなし）を服用すること。
ダルナビル／リトナビル	↓ダルナビル（C_{trough}）	VIEKIRA PAK とダルナビル／リトナビルの併用投与は推奨されない。
ロピナビル／リトナビル	↑パリタプレビル	VIEKIRA PAK とロピナビル／リトナビルの併用投与は推奨されない。

併用薬のクラス： 薬剤名	濃度に対する影響	臨床的見解
リルピビリン	↑リルピビリン	高濃度のリルピビリンに伴いQT間隔が延長する可能性があるため，VIEKIRA PAKとリルピビリン1日1回の併用投与は推奨されない。
HMG CoA還元酵素阻害薬		
ロスバスタチン	↑ロスバスタチン	VIEKIRA PAKとロスバスタチンを併用投与する場合に，ロスバスタチンの用量は10 mg/日を超えてはならない。
プラバスタチン	↑プラバスタチン	VIEKIRA PAKとプラバスタチンを併用投与する場合に，プラバスタチンの用量は40 mg/日を超えてはならない。
免疫抑制薬		
シクロスポリン	↑シクロスポリン	VIEKIRA PAKによる治療を開始する場合は，シクロスポリンの用量を当該患者に対する現在の用量の5分の1に減量する。血中シクロスポリン濃度を測定し，その後の用量変更を決定する。VIEKIRA PAK治療完了後に，VIEKIRA PAK投与前の用量でシクロスポリンの投与を再開する適切な時期は，血中シクロスポリン濃度の評価に従うこと。腎機能及びシクロスポリン関連副作用については頻回の評価が推奨される。
タクロリムス	↑タクロリムス	VIEKIRA PAKによる治療を開始する場合は，タクロリムスを減量する必要がある。VIEKIRA PAK投与開始日にタクロリムスを投与しないこと。VIEKIRA PAKの投与を開始した翌日から，血中濃度に基づいてタクロリムスを減量した上で投与を再開する。通常，タクロリムス0.5 mgを7日に1回投与する。 血中タクロリムス濃度を測定し，用量又は投与頻度を調節し，その後の用量変更を決定する。VIEKIRA PAK治療完了後に，VIEKIRA PAK投与前の用量でタクロリムスの投与を再開する適切な時期は，血中タクロリムス濃度の評価に従うこと。腎機能及びタクロリムス関連副作用については頻回の評価が推奨される。
長時間作用型βアドレナリン受容体作動薬		
サルメテロール	↑サルメテロール	VIEKIRA PAKとサルメテロールの併用投与は推奨されない。この組み合わせは，QT延長，動悸及び洞性頻脈などのサルメテロールに関連した心血管系有害事象のリスク増大に至る可能性がある。
麻薬性鎮痛薬		
ブプレノルフィン／ナロキソン	↑ブプレノルフィン ↑ノルブプレノルフィ	VIEKIRA PAKとの併用投与時にブプレノルフィン／ナロキソンの用量調節は不要である。鎮静及び認知作用につい

併用薬のクラス： 薬剤名	濃度に対する影響	臨床的見解
	ン	て，患者を注意深く観察すること。
プロトンポンプ阻害薬		
オメプラゾール	↓オメプラゾール	オメプラゾールの効果減少について患者を観察すること。症状が十分にコントロールできない患者にはオメプラゾールの増量を検討すること。ただし，1 日 40mg を超えないこと。
鎮静薬／睡眠薬		
アルプラゾラム	↑アルプラゾラム	患者の臨床症状をモニタリングすることが推奨される。臨床効果に応じて，アルプラゾラムの減量を考慮してもよい。
臨床薬理の表 6 及び 7 を参照のこと。 矢印の方向は曝露量（C_{max} 及び AUC）の変化の方向を示す（↑＝20%を超える増加，↓＝20%を超える減少，↔＝変化なし，又は 20%未満の変化）。		

7.4 VIEKIRA PAK と臨床的に重要な相互作用を起こさない薬剤

VIEKIRA PAK とジゴキシン，デュロキセチン，エムトリシタビン／テノホビルジソプロキシルフマル酸塩，エスシタロプラム，メサドン，プロゲスチンのみの避妊薬，ラルテグラビル，ワルファリン及びゾルピデムの併用投与を行う場合，用量調節は推奨されない。

8 特別な患者集団への投与

8.1 妊娠

妊娠カテゴリーB

妊娠中の曝露登録

HCV/HIV-1 重複感染で抗レトロウイルス薬を併用している女性患者における妊娠結果をモニターする Antiretroviral Pregnancy Registry（妊娠中の抗レトロウイルス薬の使用に関する症例登録研究）がある。主治医は 1-800-258-426 に連絡し患者の登録を推奨される。

リスクの概要

妊婦を対象とした VIEKIRA PAK の適切かつ十分な比較対照試験は実施されていない。動物を用いた生殖発生毒性試験では，推奨臨床用量よりも高い曝露量でのオムビタスビル（マウス及びウサギ），パリタプレビル，リトナビル（マウス及びラット）又はダサブビル（ラット及びウサギ）投与により，催奇形性を示す証拠は認められなかった［データを参照］。動物を用い

た生殖発生毒性試験は必ずしもヒトの反応を予測するものではないことから，妊娠中は明らかに必要とされる場合にのみ VIEKIRA PAK を投与すること。

VIEKIRA PAK とリバビリンを併用投与する場合，妊婦及び女性パートナーが妊娠中の男性患者ではこの併用レジメンは禁忌である。妊娠中の投与に関する詳細については，リバビリンの添付文書を参照のこと。

データ

動物のデータ

動物を用いた生殖発生毒性試験では，妊娠中を通じてオムビタスビル及びヒトにおける主要な不活性代謝物（M29，M36），パリタプレビル，リトナビル又はダサブビルを投与された動物の仔に催奇形性を示す証拠は認められなかった。オムビタスビルについて検討した最高用量では，ヒトにおける推奨臨床用量での曝露量の約 28 倍（マウス）又は約 4 倍（ウサギ）の曝露量が得られた。同様にヒトにおける主要な不活性代謝物を検討した最高用量では，ヒトにおける推奨臨床用量での曝露量の約 26 倍の曝露量が得られた。パリタプレビル及びリトナビルについて検討した最高用量では，ヒトにおける推奨臨床用量での曝露量の約 98 倍（マウス）又は約 8 倍（ラット）の曝露量が得られた。ダサブビルについて検討した最高用量では，ヒトにおける推奨臨床用量での曝露量の約 48 倍（ラット）又は 12 倍（ウサギ）の曝露量が得られた。

8.3 授乳婦

VIEKIRA PAK の各成分又は代謝物のいずれかがヒト母乳中に移行するかどうかは不明である。オムビタスビルの未変化体，パリタプレビルとその加水分解物である M13 及びダサブビルは授乳ラットの乳汁中に認められた主要成分であり，授乳中の仔への影響は認められなかった。

母親にとっての VIEKIRA PAK の臨床的必要性や，VIEKIRA PAK によって，又は母体の基礎疾患によって母乳を与えられた児に有害作用が生じる可能性に加えて，授乳の発育上及び健康上の利益も考慮すること。

VIEKIRA PAK とリバビリンを併用投与する場合には，リバビリンの授乳婦に関する情報もこの併用レジメンに適用される（リバビリンの添付文書を参照のこと）。

8.4 小児等への投与

18 歳未満の小児患者における VIEKIRA PAK の安全性及び有効性は確立されていない。

8.5 高齢者への投与

高齢患者では VIEKIRA PAK の用量調節は不要である。VIEKIRA PAK の臨床試験における総被験者数に対し，65 歳以上は 8.5%（2053 例中 174 例）であった。65 歳以上の被験者と若年被験者との間に安全性又は有効性の全体的な差は認められず，報告された他の臨床使用経験からも高齢被験者と若年被験者における反応の差異は確認されていないが，感受性が亢進している一部の高齢者を除外することはできない。

8.6 肝障害

軽度の肝障害（Child-Pugh A）を有する患者の場合，VIEKIRA PAK の用量調節は不要である。中等度の肝障害（Child-Pugh B）を有する HCV 感染患者には VIEKIRA PAK は推奨されない。重度の肝障害（Child-Pugh C）を有する患者には，VIEKIRA PAK は禁忌である［禁忌（*4*）及び臨床薬理（*12.3*）を参照］。

8.7 腎機能障害

軽度，中等度又は重度の腎機能障害を有する患者では VIEKIRA PAK の用量調節は不要である。透析患者を対象とした VIEKIRA PAK の試験は実施されていない。リバビリンの投与が必要な場合，腎機能障害を有する患者への投与に関する情報については，リバビリンの添付文書を参照のこと［臨床薬理（*12.3*）を参照］。

8.8 他の HCV ジェノタイプ

HCV ジェノタイプが 1 型以外の患者における VIEKIRA PAK の安全性及び有効性は確立されていない。

10 過量投与

過量投与が生じた場合には，副作用の徴候又は症状の有無をモニタリングし，直ちに適切な対症療法を開始することが推奨される。

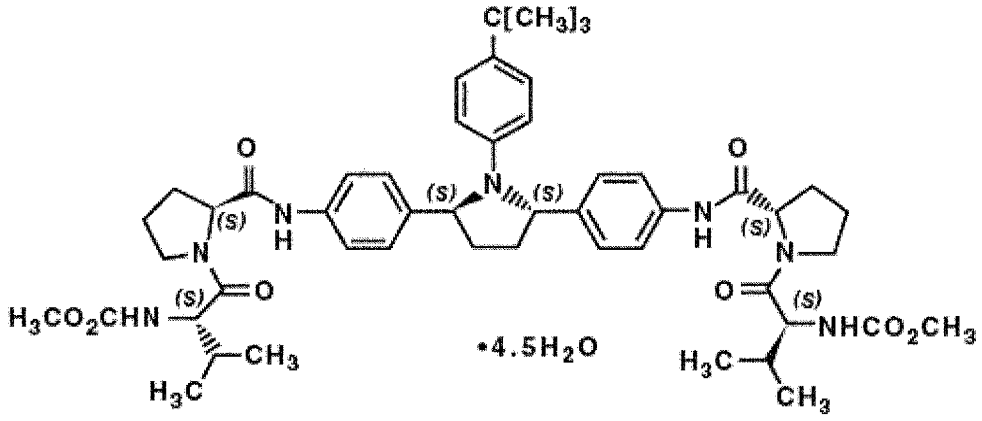
11 組成・性状

VIEKIRA PAK は，オムビタスビル，パリタプレビル，リトナビル配合錠とダサブビル錠の同梱製品である。

オムビタスビル，パリタプレビル，リトナビル配合錠には，C 型肝炎ウイルス NS5A 阻害薬（オムビタスビル），C 型肝炎ウイルス NS3/4A プロテアーゼ阻害薬（パリタプレビル）のほか，CYP3A によるパリタプレビルの代謝を阻害しパリタプレビルの血漿中濃度を増加させる CYP3A 阻害薬（リトナビル）が含まれる。ダサブビルは C 型肝炎ウイルス非ヌクレオシド NS5B palm 領域ポリメラーゼ阻害薬であり，同梱された別の錠剤として供給される。いずれの錠剤も経口投与である。

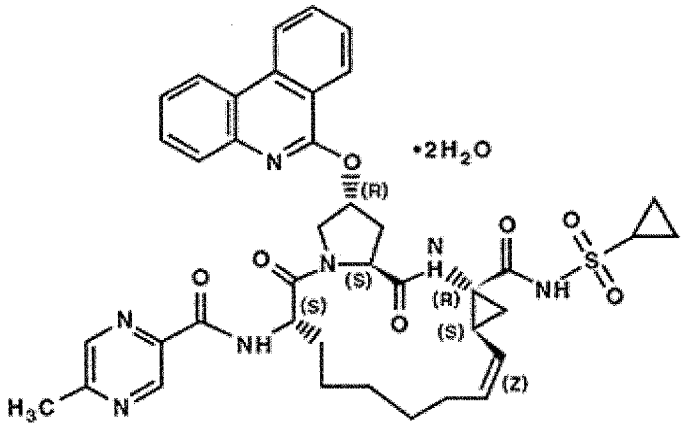
<u>オムビタスビル</u>

オムビタスビルの化学名は，Dimethyl ([(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate である。分子式は C50H67N7O8·4.5H2O（水和物）であり，原薬の分子量は 975.20（水和物）である。原薬は白色～淡黄色～淡紅色の粉末で，水性緩衝液にほとんど溶けず，エタノールに溶ける。オムビタスビルは以下の構造式である。



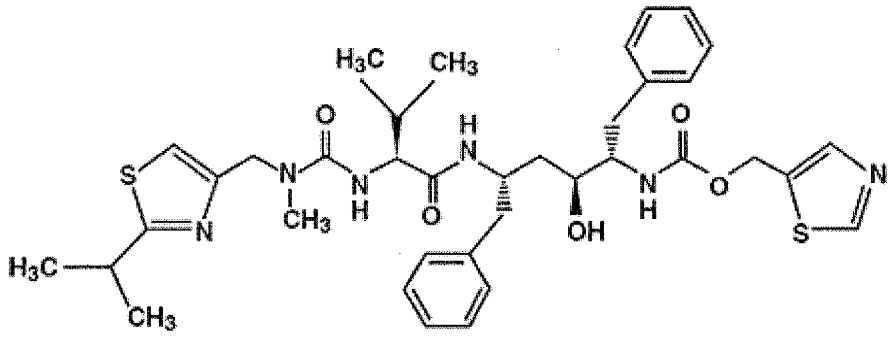
パリタプレビル

パリタプレビルの化学名は，(2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide dihydrate である。分子式は C40H43N7O7S·2H2O（二水和物）であり，原薬の分子量は 801.91（二水和物）である。原薬は白色～灰白色の粉末で，水に対する溶解性が極めて低い。パリタプレビルは以下の構造式である。



リトナビル

リトナビルの化学名は，[5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester である。分子式は C37H48N6O5S2 であり，原薬の分子量は 720.95 である。原薬は白色～灰白色～淡褐色の粉末で，水にほとんど溶けず，メタノール及びエタノールに溶けやすい。リトナビルは以下の構造式である。

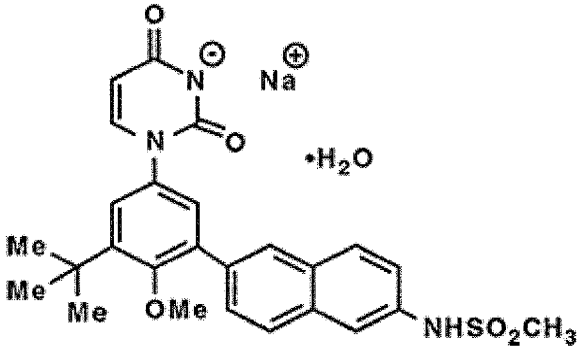


オムビタスビル，パリタプレビル，リトナビル配合錠

オムビタスビル，パリタプレビル，リトナビルフィルムコート錠は，即時放出型の配合錠である。錠剤には，K28 型コポビドン，コハク酸ビタミン E ポリエチレングリコール，モノラウリン酸プロピレングリコール I 型，モノラウリン酸ソルビタン，コロイド状二酸化ケイ素／コロイド状無水シリカ，フマル酸ステアリルナトリウム，ポリビニルアルコール，ポリエチレングリコール 3350／マクロゴール 3350，タルク，二酸化チタン，赤色酸化鉄を含む。錠剤の含量は，オムビタスビル 12.5 mg，パリタプレビル 75 mg，リトナビル 50 mg である。

ダサブビル

ダサブビルの化学名は，Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)である。分子式は C26H26N3O5S·Na·H2O（含水塩）であり，原薬の分子量は 533.57（含水塩）である。原薬は白色～淡黄色～淡紅色の粉末で，水に溶けにくく，メタノール及びイソプロピルアルコールに極めて溶けにくい。ダサブビルは以下の構造式である。



ダサブビルは即時放出型の 250 mg フィルムコート錠であり，微結晶性セルロース（D50-100 μm），微結晶性セルロース（D50-50 μm），乳糖一水和物，コポビドン，クロスカルメロースナトリウム，コロイド状二酸化ケイ素／コロイド状無水シリカ，ステアリン酸マグネシウム，ポリビニルアルコール，二酸化チタン，ポリエチレングリコール 3350／マクロゴール 3350，タルク，黄色酸化鉄，赤色酸化鉄及び黒色酸化鉄を含む。1 錠中にダサブビルナトリウム一水和物 270.3 mg（ダサブビルとして 250 mg）を含有する。

12 臨床薬理

12.1 作用機序

VIEKIRA PAK には，C 型肝炎ウイルスに対し異なる作用機序を示す直接作用型抗ウイルス薬 3 剤が配合されている［微生物学（*12.4*）を参照］。

リトナビルには HCV に対する作用はない。リトナビルは強力な CYP3A 阻害薬であり，パリタプレビルの血漿薬物濃度のピーク値及びトラフ値，並びに総薬物曝露量（曲線下面積）を増加させる。

12.2 薬力学

心臓電気生理学

健康被験者 60 例を対象とした無作為化，二重盲検，プラセボ実薬対照（モキシフロキサシン 400 mg）4 期クロスオーバーの綿密な QT 試験にて，オムビタスビル，パリタプレビル，リトナビル及びダサブビルの QTc 間隔への影響が評価された。パリタプレビル，オムビタスビル及びダサブビルの治療濃度の約 6 倍，1.8 倍及び 2 倍の濃度で配合した場合に，臨床的に意義のある QTc の延長は認められなかった。

12.3 薬物動態

吸収

オムビタスビル，パリタプレビル，リトナビル及びダサブビルは経口投与後に吸収され，Tmax の平均値は約 4～5 時間であった。オムビタスビル及びダサブビルの曝露量は用量比例的に増加したが，パリタプレビル及びリトナビルの曝露量は用量比を上回って増加した。オムビタスビル及びダサブビルの蓄積はごくわずかであり，リトナビル及びパリタプレビルの蓄積は約 1.5～2 倍であった。約 12 日間の投与後に定常状態の曝露量に達した。

ダサブビルの絶対的バイオアベイラビリティは約 70%と推定された。オムビタスビル，パリタプレビル及びリトナビルの絶対的バイオアベイラビリティは評価しなかった。

母集団薬物動態解析に基づき，HCV 感染患者に VIEKIRA PAK を投与したときのオムビタスビル，パリタプレビル及びリトナビルの定常状態での AUC0-24 の中央値はそれぞれ，1000，2220 及び 6180 ng·hr/mL であり，ダサブビルの定常状態での AUC0-12 の中央値は 3240 ng·hr/mL であった。HCV 感染患者に VIEKIRA PAK を投与したときのオムビタスビル，パリタプレビル，リトナビル及びダサブビルの定常状態での Cmax の中央値はそれぞれ，68，262，682 及び 667 ng/mL であった。

経口吸収への食物の影響

絶食条件と比較して，中程度の脂肪食（約 600 Kcal，カロリーの 20～30%が脂肪由来）とともにオムビタスビル，パリタプレビル，リトナビル及びダサブビルを投与した場合に，AUC の平均値はそれぞれ 82%，211%，49%及び 30%増加した。

絶食条件と比較して，高脂肪食（約 900 Kcal，カロリーの 60%が脂肪由来）とともにオムビタスビル，パリタプレビル，リトナビル及びダサブビルを投与した場合に，AUC の平均値はそれぞれ 76%，180%，44%及び 22%増加した。

オムビタスビル，パリタプレビル，リトナビル及びダサブビルは，常に食事と共に投与すべきである。

分布

オムビタスビル：オムビタスビルのヒト血漿蛋白結合率は 0.09～9 μg/mL の濃度範囲において約 99.9%であった。血液／血漿中濃度比の平均値は 0.49 であった。見かけの分布容積（V/F）は 50.1 L であった。

パリタプレビル：パリタプレビルのヒト血漿蛋白結合率は 0.08～8 μg/mL の濃度範囲において約 97～98.6%であった。血液／血漿中濃度比の平均値は 0.7 であった。見かけの分布容積（V/F）は 16.7 L であった。

リトナビル：リトナビルのヒト血漿蛋白結合率は 0.007～22 μg/mL の濃度範囲において 99%を上回った。血液／血漿中濃度比の平均値は 0.6 であった。見かけの分布容積（V/F）は 21.5 L であった。

ダサブビル：ダサブビルのヒト血漿蛋白結合率は 0.05～5 μg/mL の濃度範囲において 99.5%を上回った。血液／血漿中濃度比の平均値は 0.7 であった。見かけの分布容積（V/F）は 396 L であった。

代謝

オムビタスビル：オムビタスビルは主にアミド加水分解によって代謝され，その後，酸化による代謝が行われる。

パリタプレビル：パリタプレビルは主に CYP3A4 によって代謝され，その程度こそあまり大きくないものの CYP3A5 によっても代謝される。

リトナビル：リトナビルは主に CYP3A によって代謝され，その程度こそあまり大きくないものの CYP2D6 によっても代謝される。

ダサブビル：ダサブビルは主に CYP2C8 によって代謝され，その程度こそあまり大きくないものの CYP3A によっても代謝される。

排泄

オムビタスビル：14C-オムビタスビルを単回投与すると，放射能は，投与量の約 90.2%が糞中に排泄され，尿中への排泄（1.91%）は限定的であった。オムビタスビルの未変化体が糞中の放射能の 87.8%及び尿中の放射能の 0.03%を占めた。オムビタスビルの平均消失半減期は約 21～25 時間であった。

パリタプレビル：14C-パリタプレビルをリトナビル 100 mg と同時に単回投与すると，放射能は，投与量の約 88%が糞中に排泄され，尿中への排泄（8.8%）は限定的であった。パリタプレビルの未変化体が糞中の放射能の 1.1%及び尿中の放射能の 0.05%を占めた。パリタプレビルの平均血漿中半減期は約 5.5 時間であった。

リトナビル：リトナビルをオムビタスビル及びパリタプレビルと併用投与したときのリトナビルの平均血漿中半減期は約 4 時間であった。14C-リトナビル 600 mg を経口液剤で単回投与すると，放射能は，投与量の 86.4%が糞中に排泄され，11.3%が尿中に排泄された。]

ダサブビル：14C-ダサブビルを単回投与すると，放射能は，投与量の約 94.4%が糞中に排泄され，尿中への排泄（約 2%）は限定的であった。ダサブビルの未変化体が糞中の放射能の 26%及び尿中の放射能の 0.03%を占めた。ダサブビルの平均血漿中半減期は約 5.5～6 時間であった。

オムビタスビル，パリタプレビル，リトナビル及びダサブビルは，in vivo で有機アニオントランスポーター（OAT1）を阻害せず，in vitro データによると，臨床的に意義のある濃度で有機カチオントランスポーター（OCT2），有機アニオントランスポーター（OAT3）又は multidrug and toxin extrusion protein（MATE1 及び MATE2K）を阻害しないと予想される。

特別な患者集団

肝障害

軽度の肝障害（Child-Pugh A，スコア 5～6），中等度の肝障害（Child-Pugh B，スコア 7～9）及び重度の肝障害（Child-Pugh C，スコア 10～15）を有する非 HCV 感染患者を対象としてオムビタスビル，パリタプレビル，リトナビル及びダサブビルの単回投与時の薬物動態を評価した。

肝機能が正常の被験者と比べて，軽度の肝障害を有する被験者ではオムビタスビル，パリタプレビル及びリトナビルの AUC 値がそれぞれ 8%，29%及び 34%減少し，ダサブビルの AUC 値は 17%増加した。

肝機能が正常の被験者と比べて，中等度の肝障害を有する被験者ではオムビタスビル，リトナビル及びダサブビルの AUC 値がそれぞれ 30%，30%及び 16%減少し，パリタプレビルの AUC 値は 62%増加した。

肝機能が正常の被験者と比べて，重度の肝障害を有する被験者ではパリタプレビル，リトナビル及びダサブビルの AUC 値がそれぞれ 945%，13%及び 325%増加し，オムビタスビルの AUC 値は 54%減少した。

軽度の肝障害（Child-Pugh A）を有する患者の場合，VIEKIRA PAK の用量調節は不要である。中等度の肝障害（Child-Pugh B）を有する HCV 感染患者には，VIEKIRA PAK は推奨されない。重度の肝障害（Child-Pugh C）を有する患者には，VIEKIRA PAK は禁忌である［用法・用量（*3.4*），禁忌（*4*）及び特別な患者集団への投与（*8.6*）を参照］。

腎機能障害

軽度（CLcr：60～89 mL/min），中等度（CLcr：30～59 mL/min）及び重度（CLcr：15～29 mL/min）の腎機能障害を有する非 HCV 感染患者を対象としてオムビタスビル，パリタプレビル，リトナビル及びダサブビルの単回投与時の薬物動態を評価した。

概して，軽度，中等度及び重度の腎機能障害を有する非 HCV 感染患者におけるオムビタスビル，パリタプレビル，リトナビル及びダサブビルの曝露量の変化は，臨床的に重要でないと予想される。末期腎疾患（ESRD）を有する非 HCV 感染患者を対象とした VIEKIRA PAK の使用に関する薬物動態データは得られていない。

腎機能が正常の被験者と比べて，軽度の腎機能障害を有する被験者ではパリタプレビル，リトナビル及びダサブビルの AUC 値がそれぞれ 19%，42%及び 21%増加したが，オムビタスビルの AUC 値に変化は認められなかった。

腎機能が正常の被験者と比べて，中等度の腎機能障害を有する被験者ではパリタプレビル，リトナビル及びダサブビルの AUC 値がそれぞれ 33%，80%及び 37%増加したが，オムビタスビルの AUC 値に変化は認められなかった。

腎機能が正常の被験者と比べて，重度の腎機能障害を有する被験者ではパリタプレビル，リトナビル及びダサブビルの AUC 値がそれぞれ 45%，114%及び 50%増加したが，オムビタスビルの AUC 値に変化は認められなかった。［特別な患者集団への投与（*8.7*）を参照］

18 歳未満の小児患者における VIEKIRA PAK の薬物動態は確立されていない［特別な患者集団への投与（*8.4*）を参照］。

性別

性別又は体重に基づく用量調節は推奨されていない。

人種／民族

人種又は民族に基づく用量調節は推奨されていない。

年齢
高齢患者における用量調節は推奨されていない［特別な患者集団への投与（8.5）を参照］。

薬物相互作用試験
禁忌（4），警告及び使用上の注意（5.3）並びに薬物相互作用（7）も参照のこと。
表5で検討した薬剤が，VIEKIRA PAKの各成分の曝露量に及ぼす影響を表6に示す。臨床上の推奨事項に関する情報については，薬物相互作用（7）を参照のこと。

表6　薬物相互作用：併用薬の存在下におけるVIEKIRA PAKの各成分の薬物動態パラメータの変化

併用薬	併用薬の用量（mg）	n	直接作用型抗ウイルス薬（DAA）	DAAの薬物動態パラメータの比（併用薬あり／併用薬なし）（90%CI） 影響なし = 1.00		
				C_{max}	AUC	C_{min}
アルプラゾラム	0.5 mg単回投与	12	オムビタスビル	0.98 (0.93, 1.04)	1.00 (0.96, 1.04)	0.98 (0.93, 1.04)
			パリタプレビル	0.91 (0.64, 1.31)	0.96 (0.73, 1.27)	1.12 (1.02, 1.23)
			リトナビル	0.92 (0.84, 1.02)	0.96 (0.89, 1.03)	1.01 (0.94, 1.09)
			ダサブビル	0.93 (0.83, 1.04)	0.98 (0.87, 1.11)	1.00 (0.87, 1.15)
アムロジピン	5 mg単回投与	14	オムビタスビル	1.00 (0.95, 1.06)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
			パリタプレビル	0.77 (0.64, 0.94)	0.78 (0.68, 0.88)	0.88 (0.80, 0.95)
			リトナビル	0.96 (0.87, 1.06)	0.93 (0.89, 0.98)	0.95 (0.89, 1.01)
			ダサブビル	1.05 (0.97, 1.14)	1.01 (0.96, 1.06)	0.95 (0.89, 1.01)
アタザナビル／リトナビル[a]	アタザナビル300 mg及びリトナビル100 mg 1日1回（夕）	11	オムビタスビル	0.83 (0.72, 0.96)	0.90 (0.78, 1.02)	1.00 (0.89, 1.13)
			パリタプレビル	2.19 (1.61, 2.98)	3.16 (2.40, 4.17)	11.95 (8.94, 15.98)
			リトナビル	1.60 (1.38, 1.86)	3.18 (2.74, 3.69)	24.65 (18.64, 32.60)

			ダサブビル	0.81 (0.73, 0.91)	0.81 (0.71, 0.92)	0.80 (0.65, 0.98)
カルバマゼピン	200 mg 1日1回，その後200 mg 1日2回	12	オムビタスビル	0.69 (0.61, 0.78)	0.69 (0.64, 0.74)	NA
			パリタプレビル	0.34 (0.25, 0.48)	0.30 (0.23, 0.38)	NA
			リトナビル	0.17 (0.12, 0.24)	0.13 (0.09, 0.17)	NA
			ダサブビル	0.45 (0.41, 0.50)	0.30 (0.28, 0.33)	NA
シクロスポリン	30 mg 単回投与[b]	10	オムビタスビル	0.99 (0.92, 1.07)	1.08 (1.05, 1.11)	1.15 (1.08, 1.23)
			パリタプレビル	1.44 (1.16, 1.78)	1.72 (1.49, 1.99)	1.85 (1.58, 2.18)
			リトナビル	0.90 (0.78, 1.04)	1.11 (1.04, 1.19)	1.49 (1.28, 1.74)
			ダサブビル	0.66 (0.58, 0.75)	0.70 (0.65, 0.76)	0.76 (0.71, 0.82)
ダルナビル[c]	800 mg 1日1回	9	オムビタスビル	0.86 (0.77, 0.95)	0.86 (0.79, 0.94)	0.87 (0.82, 0.92)
			パリタプレビル	1.54 (1.14, 2.09)	1.29 (1.04, 1.61)	1.30 (1.09, 1.54)
			リトナビル	0.84 (0.72, 0.98)	0.85 (0.78, 0.93)	1.07 (0.93, 1.23)
			ダサブビル	1.10 (0.88, 1.37)	0.94 (0.78, 1.14)	0.90 (0.76, 1.06)
ダルナビル／リトナビル[d]	ダルナビル600 mg，1日2回及びリトナビル100 mg，1日1回（夕）	7	オムビタスビル	0.76 (0.65, 0.88)	0.73 (0.66, 0.80)	0.73 (0.64, 0.83)
			パリタプレビル	0.70 (0.43, 1.12)	0.59 (0.44, 0.79)	0.83 (0.69, 1.01)
			リトナビル	1.61 (1.30, 2.00)	1.28 (1.12, 1.45)	0.88 (0.79, 0.99)
			ダサブビル	0.84 (0.67, 1.05)	0.73 (0.62, 0.86)	0.54 (0.49, 0.61)
ダルナビル／リトナビル[e]	ダルナビル800 mg及びリトナビル100 mg 1日1回（夕）	12	オムビタスビル	0.87 (0.82, 0.93)	0.87 (0.81, 0.93)	0.87 (0.80, 0.95)
			パリタプレビル	0.70 (0.50, 0.99)	0.81 (0.60, 1.09)	1.59 (1.23, 2.05)
			リトナビル	1.19 (1.06, 1.33)	1.70 (1.54, 1.88)	14.15 (11.66, 17.18)

			ダサブビル	0.75 (0.64, 0.88)	0.72 (0.64, 0.82)	0.65 (0.58, 0.72)
エチニルエストラジオール／ノルゲスチメート	エチニルエストラジオール 0.035 mg 及びノルゲスチメート 0.25 mg 1 日 1 回	7[f]	オムビタスビル	1.05 (0.81, 1.35)	0.97 (0.81, 1.15)	1.00 (0.88, 1.12)
			パリタプレビル	0.70 (0.40, 1.21)	0.66 (0.42, 1.04)	0.87 (0.67, 1.14)
			リトナビル	0.80 (0.53, 1.21)	0.71 (0.54, 0.94)	0.79 (0.68, 0.93)
			ダサブビル	0.51 (0.22, 1.18)	0.48 (0.23, 1.02)	0.53 (0.30, 0.95)
フロセミド	20 mg 単回投与	12	オムビタスビル	1.14 (1.03, 1.26)	1.07 (1.01, 1.12)	1.12 (1.08, 1.16)
			パリタプレビル	0.93 (0.63, 1.36)	0.92 (0.70, 1.21)	1.26 (1.16, 1.38)
			リトナビル	1.10 (0.96, 1.27)	1.04 (0.92, 1.18)	1.07 (0.99, 1.17)
			ダサブビル	1.12 (0.96, 1.31)	1.09 (0.96, 1.23)	1.06 (0.98, 1.14)
ゲムフィブロジル[g]	600 mg 1 日 2 回	11	オムビタスビル	NA	NA	NA
			パリタプレビル	1.21 (0.94, 1.57)	1.38 (1.18, 1.61)	NA
			リトナビル	0.84 (0.69, 1.03)	0.90 (0.78, 1.04)	NA
			ダサブビル	2.01 (1.71, 2.38)	11.25 (9.05, 13.99)	NA
ケトコナゾール	400 mg 1 日 1 回	12	オムビタスビル	0.98 (0.90, 1.06)	1.17 (1.11, 1.24)	NA
			パリタプレビル	1.37 (1.11, 1.69)	1.98 (1.63, 2.42)	NA
			リトナビル	1.27 (1.04, 1.56)	1.57 (1.36, 1.81)	NA
			ダサブビル	1.16 (1.03, 1.32)	1.42 (1.26, 1.59)	NA
ロピナビル／リトナビル	400 mg/100 mg1 日 2 回	6	オムビタスビル	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
			パリタプレビル	2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
			リトナビル	1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)

			ダサブビル	0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
ロピナビル／リトナビル[h]	800 mg/200 mg 1 日 1 回	12	オムビタスビル	0.87 (0.83, 0.92)	0.97 (0.94, 1.02)	1.11 (1.06, 1.16)
			パリタプレビル	0.99 (0.79, 1.25)	1.87 (1.40, 2.52)	8.23 (5.18, 13.07)
			リトナビル	1.57 (1.34, 1.83)	2.62 (2.32, 2.97)	19.46 (15.93, 23.77)
			ダサブビル	0.56 (0.47, 0.66)	0.54 (0.46, 0.65)	0.47 (0.39, 0.58)
オメプラゾール	40 mg 1 日 1 回	11	オムビタスビル	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	1.04 (0.98, 1.11)
			パリタプレビル	1.19 (1.04, 1.36)	1.18 (1.03, 1.37)	0.92 (0.76, 1.12)
			リトナビル	1.04 (0.96, 1.12)	1.02 (0.97, 1.08)	0.97 (0.89, 1.05)
			ダサブビル	1.13 (1.03, 1.25)	1.08 (0.98, 1.20)	1.05 (0.93, 1.19)
プラバスタチン	10 mg 1 日 1 回	12	オムビタスビル	0.95 (0.89, 1.02)	0.94 (0.89, 0.99)	0.94 (0.89, 0.99)
			パリタプレビル	0.96 (0.69, 1.32)	1.13 (0.92, 1.38)	1.39 (1.21, 1.59)
			リトナビル	0.89 (0.73, 1.09)	0.95 (0.86, 1.05)	1.08 (0.98, 1.19)
			ダサブビル	1.00 (0.87, 1.14)	0.96 (0.85, 1.09)	1.03 (0.91, 1.15)
ロスバスタチン	5 mg 1 日 1 回	11	オムビタスビル	0.92 (0.82, 1.04)	0.89 (0.83, 0.95)	0.88 (0.83, 0.94)
			パリタプレビル	1.59 (1.13, 2.23)	1.52 (1.23, 1.90)	1.43 (1.22, 1.68)
			リトナビル	0.98 (0.84, 1.15)	1.02 (0.93, 1.12)	1.00 (0.90, 1.12)
			ダサブビル	1.07 (0.92, 1.24)	1.08 (0.92, 1.26)	1.15 (1.05, 1.25)
リルピビリン	25 mg 1 日 1 回（朝）[i]	10	オムビタスビル	1.11 (1.02, 1.20)	1.09 (1.04, 1.14)	1.05 (1.01, 1.08)
			パリタプレビル	1.30 (0.94, 1.81)	1.23 (0.93, 1.64)	0.95 (0.84, 1.07)
			リトナビル	1.10 (0.98, 1.24)	1.08 (0.93, 1.27)	0.97 (0.91, 1.04)

			ダサブビル	1.18 (1.02, 1.37)	1.17 (0.99, 1.38)	1.10 (0.89, 1.37)
タクロリムス	2 mg 単回投与	12	オムビタスビル	0.93 (0.88, 0.99)	0.94 (0.89, 0.98)	0.94 (0.91, 0.96)
			パリタプレビル	0.57 (0.42, 0.78)	0.66 (0.54, 0.81)	0.73 (0.66, 0.80)
			リトナビル	0.76 (0.63, 0.91)	0.87 (0.79, 0.97)	1.03 (0.89, 1.19)
			ダサブビル	0.85 (0.73, 0.98)	0.90 (0.80, 1.02)	1.01 (0.91, 1.11)

アタザナビル＋リトナビル 100 mg は夕（朝の VIEKIRA PAK 投与から 12 時間後）に投与した。
シクロスポリンは VIEKIRA PAK との併用で 30 mg を投与し，対照群（VIEKIRA PAK 非併用）では 100 mg を投与した。
ダルナビルと VIEKIRA PAK の併用投与（朝）とダルナビルとリトナビル 100 mg の併用投与（朝）を比較した。
ダルナビルと VIEKIRA PAK（朝）及びリトナビル 100 mg（夕）の併用投与とダルナビルとリトナビル 100 mg の併用投与（朝夕）を比較した。
ダルナビル＋リトナビル 100 mg は夕（朝の VIEKIRA PAK 投与から 12 時間後）に投与とリトナビル 100 mg とダルナビルの併用投与（夕）を比較した。

ダサブビル群は 3 例
パリタプレビル，リトナビル及びダサブビルを用いて試験を実施した。
ロピナビル／リトナビルは夕（朝の VIEKIRA PAK 投与から 12 時間後）に投与した。
リルピビンを食事とともに夕方に投与した場合，又は食事から 4 時間後に投与した場合にも同様の増加が観察された。

NA：入手不可／該当なし；DAA：直接作用型抗ウイルス薬；CI:信頼区間
オムビタスビル，パリタプレビル及びリトナビルの用量はそれぞれ 25 mg，150 mg 及び 100 mg，ダサブビルの用量は 250 mg 又は 400 mg である。（両用量は同様の曝露量を示した。）
ゲムフィブロジル，ケトコナゾール及びカルバマゼピンを単回投与した試験を除き，上記のすべての試験においてオムビタスビル，パリタプレビル及びリトナビルを 1 日 1 回，ダサブビルを 1 日 2 回投与した。

VIEKIRA PAK の影響によって併用薬の薬物動態に認められた臨床的に意義のある変化を表 7 に要約する。臨床上の推奨事項に関する情報については，薬物相互作用（7）を参照のこと。

表 7　　薬物相互作用：VIEKIRA PAK の存在下における併用薬の薬物動態パラメータの変化

併用薬	併用薬の用量（mg）	n	併用薬の薬物動態パラメータの比（VIEKIRA PAK あり／VIEKIRA PAK なし）（90%CI），影響なし ＝1.00		
			C_{max}	AUC	C_{min}
アルプラゾラム	0.5 mg 単回投与	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
アムロジピン	5 mg 単回投与	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
アタザナビル／リトナビル [a]	アタザナビル 300 mg 及びリトナビル 100 mg 1 日 1 回（夕）	12	1.02 (0.92, 1.13) [b]	1.19 (1.11, 1.28) [b]	1.68 (1.44, 1.95) [b]
ブプレノルフィン	ブプレノルフィン 4～24 mg 1 日 1 回及びナロキソン 1～6 mg 1 日 1 回	10	2.18 (1.78, 2.68) [c]	2.07 (1.78, 2.40) [c]	3.12 (2.29, 4.27) [c]
ノルブプレノルフィン			2.07 (1.42, 3.01) [c]	1.84 (1.30, 2.60) [c]	2.10 (1.49, 2.97) [c]
ナロキソン			1.18 (0.81, 1.73)	1.28 (0.92, 1.79) [c]	NA
カルバマゼピン	200 mg 1 日 1 回，その後 200 mgl 日 2 回	12	1.10 (1.07, 1.14)	1.17 (1.13, 1.22)	1.35 (1.27, 1.45)
カルバマゼピンの代謝物であるカルバマゼピン-10,11-エポキシド（CBZE）			0.84 (0.82, 0.87)	0.75 (0.73, 0.77)	0.57 (0.54, 0.61)
シクロスポリン	30 mg 単回投与 [d]	10	1.01 (0.85, 1.20) [c]	5.82 (4.73, 7.14) [c]	15.80 (13.81, 18.09) [c]
ダルナビル [e]	800 mg 1 日 1 回	8	0.92 (0.87, 0.98) [b]	0.76 (0.71, 0.82) [b]	0.52 (0.47, 0.58) [b]
ダルナビル／リトナビル [f]	ダルナビル 600 mgl 日 2 回及びリトナビル 100 mg, 1 日 1 回（夕）	7	0.87 (0.79, 0.96) [b]	0.80 (0.74, 0.86) [b]	0.57 (0.48, 0.67) [b]
ダルナビル／リトナビル [g]	ダルナビル 800 mg 及びリトナビル 100 mg 1 日 1 回（夕）	10	0.79 (0.70, 0.90) [b]	1.34 (1.25, 1.43) [b]	0.54 (0.48, 0.62) [b]
エチニルエストラジオール	エチニルエストラジオール 0.035 mg 及びノルゲスチメ	8	1.16 (0.90, 1.50)	1.06 (0.96, 1.17)	1.12 (0.94, 1.33)
ノルゲストロミン		9	2.01	2.60	3.11

	ート 0.25 mg 1 日 1 回		(1.77, 2.29)	(2.30, 2.95)	(2.51, 3.85)
ノルゲステロル		9	2.26 (1.91, 2.67)	2.54 (2.09, 3.09)	2.93 (2.39, 3.57)
フロセミド	20 mg 単回投与	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
ケトコナゾール	400 mg 1 日 1 回	12	1.15 (1.09, 1.21)	2.17 (2.05, 2.29)	NA
ロピナビル／リトナビル	400 mg/100 mg 1 日 2 回	6	0.87 (0.76, 0.99) [b]	0.94 (0.81, 1.10) [b]	1.15 (0.93, 1.42) [b]
ロピナビル／リトナビル [h]	800 mg/200 mg 1 日 1 回	12	0.86 (0.80, 0.93) [b]	0.94 (0.87, 1.01) [b]	3.18 (2.49, 4.06) [b]
オメプラゾール	40 mg 1 日 1 回	11	0.62 (0.48, 0.80)	0.62 (0.51, 0.75)	NA
プラバスタチン	10 mg 1 日 1 回	12	1.37 (1.11, 1.69)	1.82 (1.60, 2.08)	NA
ロスバスタチン	5 mg 1 日 1 回	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)
リルピビリン	25 mg 1 日 1 回（朝）[i]	8	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
タクロリムス	2 mg 単回投与	12	3.99 (3.21, 4.97) [c]	57.13 (45.53, 71.69) [c]	16.56 (12.97, 21.16) [c]

アタザナビル＋リトナビル 100 mg は夕（朝の VIEKIRA PAK 投与から 12 時間後）に投与した。
アタザナビル，ダルナビル又はロピナピルのパラメータを報告した。
投与量補正したパラメータを報告した。
シクロスポリンは試験群では VIEKIRA PAK との併用で 30 mg を投与し，対照群では VIEKIRA PAK 非併用で 100 mg を投与した。
ダルナビルと VIEKIRA PAK の併用投与（朝）とダルナビルとリトナビル 100 mg の併用投与（朝）を比較した。
ダルナビルと VIEKIRA PAK（朝）及びリトナビル 100 mg（夕）の併用投与とダルナビルとリトナビル 100 mg の併用投与（朝夕）を比較した。
ダルナビル＋リトナビル 100 mg は夕（朝の VIEKIRA PAK 投与から 12 時間後）に投与とリトナビル 100 mg とダルナビルの併用投与（夕）を比較した。
ロピナビル／リトナビルは夕（朝の VIEKIRA PAK 投与から 12 時間後）に投与した。
リルピビンを食事とともに夕方に投与した場合，又は食事から 4 時間後に投与した場合にも同様の増加が観察された。
NA：入手不可／該当なし；CI:信頼区間
オムビタスビル，パリタプレビル及びリトナビルの用量はそれぞれ 25 mg，150 mg 及び 100 mg，ダサブビルの用量は 250 mg 又は 400 mg である。（両用量は同様の曝露量を示した。）
ケトコナゾール及びカルバマゼピンを単回投与した試験を除き，上記のすべての試験においてオムビタスビル，パリタプレビル及びリトナビルを 1 日 1 回，並びにダサブビルを 1 日 2 回投与した。

12.4 微生物学

作用機序

VIEKIRA PAK には，ウイルス生活環における複数の段階の C 型肝炎ウイルスに対し異なる作用機序を有し，耐性プロファイルが重複しない直接作用型抗ウイルス薬 3 剤が配合されている。

オムビタスビル

オムビタスビルは，ウイルス RNA の複製及びビリオンの集合に不可欠な HCV NS5A の阻害薬である。オムビタスビルの作用機序は，細胞培養での抗ウイルス活性及び薬剤耐性マッピング試験によって明らかにされている。

パリタプレビル

パリタプレビルは，HCV コード化ポリ蛋白の分解（NS3，NS4A，NS4B，NS5A 及び NS5B 蛋白の成熟型）に必要であり，かつウイルス複製に不可欠な HCV NS3/4A プロテアーゼの阻害薬である。生化学的アッセイにおいて，パリタプレビルは組換え HCV ジェノタイプ 1a 及び 1b NS3/4A プロテアーゼ酵素の蛋白分解活性を阻害し，IC50 値はそれぞれ 0.18 nM 及び 0.43 nM であった。パリタプレビルは，ジェノタイプ 2a，2b，3a 及び 4a の単一分離株から得られた NS3/4A 酵素の活性を阻害し，IC50 値はそれぞれ 2.4 nM，6.3 nM，14.5 nM 及び 0.16 nM であった。

ダサブビル

ダサブビルは，NS5B 遺伝子によってコードされる HCV RNA 依存性 RNA ポリメラーゼの非ヌクレオシド系阻害薬で，ウイルスゲノムの複製に不可欠である。生化学的アッセイにおいて，ダサブビルは数種類のジェノタイプ 1a 及び 1b NS5B ポリメラーゼを阻害し，IC50 値の中央値はそれぞれ 2.8 nM（範囲：2.4～4.2 nM，n＝3）及び 3.7 nM（範囲：2.2～10.7 nM，n＝4）であった。HCV ジェノタイプ 1a 及び 1b の薬剤耐性マッピング試験に基づき，ダサブビルは NS5B ポリメラーゼの palm 領域を標的としていることから，非ヌクレオシド系 NS5B palm ポリメラーゼ阻害薬と呼ばれる。ダサブビルは，HCV ジェノタイプ 2a，2b，3a 及び 4a 由来の NS5B ポリメラーゼに対する生化学的アッセイの活性を減弱させた（IC50 値は 900 nM～20 μM 以上）。

抗ウイルス活性

オムビタスビル

HCV レプリコン細胞培養アッセイにおいて，ジェノタイプ 1a-H77 及び 1b-Con1 株に対するオムビタスビルの EC50 値はそれぞれ 14.1 pM 及び 5 pM であった。未治療の被験者から得られた数種類のジェノタイプ 1a 及び 1b 分離株に由来する NS5B 遺伝子を含む HCV レプリコンに対するオムビタスビルの EC50 値の中央値は，それぞれ 0.68 pM（範囲：0.35～0.88 pM，n＝11）及び 0.94 pM（範囲：0.74～1.5 pM，n＝11）であった。ジェノタイプ 2a，2b，3a，4a，5a 及び 6a の単一分離株から得られた NS5A で構成されるキメラレプリコンに対するオムビタスビルの EC50 値はそれぞれ 12 pM，4.3 pM，19 pM，1.7 pM，3.2 pM 及び 366 pM であった。

パリタプレビル

HCV レプリコン細胞培養アッセイにおいて，ジェノタイプ 1a-H77 及び 1b-Con1 株に対するパリタプレビルの EC50 値はそれぞれ 1.0 nM 及び 0.21 nM であった。未治療の被験者から得られた数種類のジェノタイプ 1a 及び 1b 分離株に由来する NS3 遺伝子を含む HCV レプリコンに対するパリタプレビルの EC50 値の中央値は，それぞれ 0.68 nM（範囲：0.43～1.87 nM，n＝11）及び 0.06 nM（範囲：0.03～0.09 nM，n＝ 9）であった。HCV ジェノタイプ 2a-JFH-1 レプリコン細胞株に対するパリタプレビルの EC50 値は 5.3 nM，ジェノタイプ 3a，4a 及び 6a の単一分離株から得られた NS3 を含むレプリコン細胞株に対するパリタプレビルの EC50 値はそれぞれ 19 nM，0.09 nM 及び 0.68 nM であった。

HCV レプリコン細胞培養アッセイにおいて，リトナビルの直接的な抗ウイルス作用は示されず，リトナビルの存在によるパリタプレビルの抗ウイルス活性への影響は認められなかった。

ダサブビル

HCV レプリコン細胞培養アッセイにおいて，ジェノタイプ 1a-H77 及び 1b-Con1 株に対するダサブビルの EC50 値はそれぞれ 7.7 nM 及び 1.8 nM であった。未治療の被験者から得られた数種類のジェノタイプ 1a 及び 1b 分離株に由来する NS5B 遺伝子を含む HCV レプリコンに対するダサブビルの EC50 値の中央値は，それぞれ 0.6 nM（範囲：0.4～2.1 nM，n＝11）及び 0.3 nM（範囲：0.2～2 nM，n＝10）であった。

配合剤の抗ウイルス活性

HCV ジェノタイプ 1 レプリコン細胞培養アッセイにおいて，オムビタスビル，パリタプレビル，ダサブビル及びリバビリンを対で配合し評価した結果，抗ウイルス活性に対する拮抗作用を示す証拠は認められなかった。

耐性

細胞培養

HCV ジェノタイプ 1a 及び 1b レプリコンをオムビタスビル，パリタプレビル又はダサブビルに曝露した結果，薬剤耐性レプリコンが出現し，それぞれ NS5A，NS3 又は NS5B にアミノ酸置換が認められた。細胞培養で選択された，又は第 IIb 相及び第 III 相臨床試験で特定された NS5A，NS3 又は NS5B のアミノ酸置換は，ジェノタイプ 1a 又は 1b レプリコンにおいて表現型における特徴が明らかにされた。

オムビタスビルについては，HCV ジェノタイプ 1a レプリコンにおいて，単一の NS5A 置換が M28T/V，Q30E/R，L31V，H58D 及び Y93C/H/L/N に存在すると，オムビタスビルの抗ウイルス活性が 58～67,000 分の 1 に減弱した。ジェノタイプ 1b レプリコンでは，単一の NS5A 置換が L28T，L31F/V 及び Y93H に存在すると，オムビタスビルの抗ウイルス活性が 8～661 分の 1 に減弱した。概して，HCV ジェノタイプ 1a 又は 1b レプリコンにおいてオムビタスビル耐性に関連する置換を組み合わせると，オムビタスビルの抗ウイルス活性はさらに減弱した。

パリタプレビルについては，HCV ジェノタイプ 1a レプリコンにおいて，単一の NS3 置換が F43L，R155G/K/S，A156T 及び D168A/E/F/H/N/V/Y に存在すると，パリタプレビルの抗ウイルス活性が 7～219 分の 1 に減弱した。ジェノタイプ 1a レプリコンにおける NS3 Q80K 置換により，パリタプレビルの抗ウイルス活性は 3 分の 1 に減弱した。V36M，Y56H 又は E357K と R155K 又は D168 の置換を組み合わせると，ジェノタイプ 1a レプリコンにおける単一の R155K 又は D168 の置換と比べてパリタプレビルの活性がさらに 2～7 分の 1 に減弱した。ジェノタイプ 1b レプリコンでは，単一の NS3 置換が A156T 及び D168A/H/V に存在すると，パリタプレビルの抗ウイルス活性が 7～159 分の 1 に減弱した。Y56H と D168 の置換を組み合わせると，パリタプレビルの活性はジェノタイプ 1b レプリコンにおける単一の D168 置換と比べてさらに 16～26 分の 1 に減弱した。

ダサブビルについては，HCV ジェノタイプ 1a レプリコンにおいて，単一の NS5B 置換が C316Y，M414I/T，E446K/Q，Y448C/H，A553T，G554S，S556G/R 及び Y561H に存在すると，ダサブビルの抗ウイルス活性が 8～1,472 分の 1 に減弱した。ジェノタイプ 1b レプリコンでは，単一の NS5A 置換が C316H/N/Y，S368T，N411S，M414I/T，Y448C/H，A553V，S556G 及び D559G に存在すると，ダサブビルの抗ウイルス活性が 5～1,569 分の 1 に減弱した。

臨床試験

第 IIb 相及び第 III 相臨床試験において，リバビリンとの併用又は非併用でオムビタスビル，パリタプレビル及びダサブビルの投与を受けた被験者（12 週間又は 24 週間）の統合解析では，ウイルス学的失敗に至った被験者 64 例（治療中にウイルス学的失敗を認めた被験者 20 例，治療後に再燃した被験者 44 例）を対象として耐性の解析を実施した。これらの被験者のウイルス集団にみられた治療中に出現した置換を表 8 に示す。HCV ジェノタイプ 1a 感染 57 例中 30 例（53%）及び HCV ジェノタイプ 1b 感染 6 例中 1 例（17%）では，3 種類の HCV 薬剤標的すべてにおいて治療中に出現した置換が検出された。

表 8　　第 IIb 相及び第 III 相臨床試験における VIEKIRA PAK とリバビリン併用及び非併用レジメン（12 週間又は 24 週間）の統合解析において治療中に出現したアミノ酸置換

標的	出現したアミノ酸置換	ジェノタイプ 1a N = 58[a] % (n)	ジェノタイプ 1b N = 6 % (n)
NS3	次の NS3 置換のいずれか：V36A/M/T，F43L，V55I，Y56H，Q80L，I132V，R155K，A156G，D168（すべて），P334S，S342P，E357K，V406A/I，T449I，P470S，V23A（NS4A）	88 (51)	67 (4)
	V36A/M/T[b]	7 (4)	--
	V55I[b]	7 (4)	--

	Y56H[b]	10 (6)	50 (3)
	I132V[b]	7 (4)	--
	R155K	16 (9)	--
	D168（すべて）[d]	72 (42)	67 (4)
	D168V	59 (34)	50 (3)
	P334S[b,c]	7 (4)	--
	E357K[b,c]	5 (3)	17 (1)
	V406A/I[b,c]	5 (3)	--
	T449I[b,c]	5 (3)	--
	P470S[b,c]	5 (3)	--
	NS4A V23A[b]	--	17 (1)
	F43L[b], Q80L[b], A156G, S342P[b,c]	<5%	--
NS5A	次の NS5A 置換のいずれか：K24R, M28A/T/V, Q30E/K/R, H/Q54Y, H58D/P/R, Y93C/H/N	78 (45)	33 (2)
	K24R	5 (3)	--
	M28A/T/V	33 (19)	--
	Q30E/K/R	47 (27)	--
	H/Q54Y	--	17 (1)
	H58D/P/R	7 (4)	--
	Y93C/N	5 (3)	--
	Y93H	--	33 (2)
NS5B	次の NS5B 置換のいずれか：G307R, C316Y, M414I/T, E446K/Q, A450V, A553I/T/V, G554S, S556G/R, G558R, D559G/I/N/V, Y561H	67 (38)	33 (2)
	C316Y	4 (2)	17 (1)
	M414I	--	17 (1)
	M414T	5 (3)	17 (1)
	A553I/T/V	7 (4)	--
	S556G/R	39 (22)	17 (1)
	D559G/I/N/V	7 (4)	--
	Y561H	5 (3)	--
	G307R, E446K/Q, A450V, G554S, G558R	<5%	--

標的 NS5B については 57 例 NS3 の R155 又は D168 位で観察された置換は，他に出現した置換との組み合わせであった。 NS3 のヘリカーゼ領域に位置する。 D168A/F/H/I/L/N/T/V/Y

耐性に関連した置換の持続

第 II 相試験において，治療中にウイルスの薬剤標的における置換が 1 回以上出現し，投与後少なくとも 24 週間のデータが得られた HCV ジェノタイプ 1a 感染被験者を対象として，オムビタスビル，パリタプレビル及びダサブビルの投与中に出現した NS5A，NS3 及び NS5B におけるアミノ酸置換の持続を評価した。治療中に置換が出現したウイルス集団の持続を検出するため，集団及びクローンのヌクレオチド配列解析（測定感度は約 5～10%）を実施した。

オムビタスビルについては，治療中に耐性に関連する置換が 1 回以上 NS5A に出現したウイルス集団は，投与終了から少なくとも 24 週後までのデータが入手できた被験者 24 例全例（100%），投与終了から 48 週後までのデータが入手できた被験者 18 例全例（100%）において検出可能なレベルで持続した。

パリタプレビルについては，治療中に耐性に関連する置換が 1 回以上 NS3 に出現したウイルス集団は，投与終了から少なくとも 24 週後までのデータが入手できた被験者 29 例中 17 例（59%），投与終了から 48 週後までのデータが入手できた被験者 22 例中 5 例（23%）において検出可能なレベルで持続した。耐性に関連する変異株 R155K は，投与終了から 24 週後までのデータが入手できた被験者 5 例中 1 例（20%），投与終了から 48 週後までのデータが入手できた被験者 8 例中 5 例（63%）において検出可能であった。耐性に関連する D168 置換は，投与終了から 24 週後までのデータが入手できた被験者 22 例中 6 例（27%）において検出可能であったが，投与終了から 48 週後までには検出不能となった。

ダサブビルについては，治療中に耐性に関連する置換が 1 回以上 NS5B に出現したウイルス集団は，投与終了から少なくとも 24 週後までのデータが入手できた被験者 16 例中 11 例（69%），投与終了から 48 週後までのデータが入手できた被験者 15 例中 8 例（53%）において検出可能なレベルで持続した。治療中に出現した S556G は，投与終了から 48 週後までのデータが入手できた被験者 9 例中 6 例（67%）において持続した。

臨床試験における HCV ジェノタイプ 1b 感染例のウイルス学的不成功は 1%未満であったことから，このジェノタイプにおいて治療中に出現した置換については，その傾向を明らかにすることはできなかった。

耐性に関連する置換を含むウイルスが検出されないのは，耐性ウイルスが臨床的に重要なレベルで存在していないことを示すものではない。VIEKIRA PAK 耐性に関連する置換を含むウイルスの出現又は持続の長期にわたる臨床的影響は不明である。

ベースライン時の HCV 多型の治療反応に対する影響

ベースライン時の HCV NS5A，NS3 又は NS5B 耐性関連多型と治療成績との関連性を探索するため，リバビリンとの併用又は非併用でオムビタスビル，パリタプレビル及びダサブビルを検討した第 III 相臨床試験の被験者を対象として統合解析を実施した。ウイルス学的不成功を認めた HCV ジェノタイプ 1a 感染被験者（n＝47）と，人口統計学的に一致し SVR を達成した被験者（n＝94）のベースライン時の検体を解析し，この 2 集団における耐性関連多型の頻度を比較した。NS3 Q80K 多型は，この解析対象集団の約 38%で検出され，ウイルス学的不成功例では SVR 達成例の約 2 倍多かった。NS5A におけるオムビタスビル耐性関連多型（耐性関連の全アミノ酸位置のデータを統合）は，この解析対象集団の約 22%で検出され，同様にウイルス学的不成功例で約 2 倍多かった。NS5B におけるダサブビル耐性関連多型（耐性関連の全アミノ酸位置のデータを統合）は，この解析対象集団の約 5%で検出されたが，ウイルス学的不成功例で多くなかった。

第 III 相サブセット解析とは対照的に，第 IIb 相試験においてリバビリンとの併用又は非併用でオムビタスビル，パリタプレビル及びダサブビルの投与（12 週間又は 24 週間）を受けた非硬変性 HCV ジェノタイプ 1a 感染被験者（NS3：n＝174，NS5A：n＝183）を対象とした解析では，NS3 又は NS5A 多型と治療成績との関連性は認められなかった。

臨床試験においてウイルス学的不成功率が低いことを考慮すると，HCV のベースライン変異は HCV ジェノタイプ 1a 及び 1b 感染患者に対して VIEKIRA PAK が推奨されるレジメンで使用されるとき，SVR 達成率に実質的な影響を与えないと考えられる。

交叉耐性

NS5A 阻害薬，NS3/4A プロテアーゼ阻害薬及び非ヌクレオシド系 NS5B palm 阻害薬においては，薬剤クラスによる交叉耐性が予想される。単一 NS5B S282T 置換はヌクレオシド類似体である NS5B ポリメラーゼの阻害薬に対する耐性と関連するが，ダサブビルにはこの置換を含む HCV レプリコンに対する完全な活性がある。VIEKIRA PAK の臨床試験では，ウイルス学的に不成功の被験者において，ヌクレオシド類似体 NS5B ポリメラーゼの阻害薬に対する耐性と関連する可能性のある，治療中の置換の出現は認められなかった。

オムビタスビル，パリタプレビル又はダサブビルの治療歴が他の NS5A 阻害薬，NS3/4A プロテアーゼ阻害薬又は NS5B 阻害薬の有効性に及ぼす影響については検討していない。同様に，NS5A 阻害薬，NS3/4A プロテアーゼ阻害薬又は NS5B 阻害薬による前治療に無効であった被験者を対象として VIEKIRA PAK の有効性を検討する試験は実施していない。

13 非臨床毒性試験

13.1 がん原性，変異原性，受胎能障害

がん原性及び変異原性

オムビタスビル

トランスジェニックマウスを用いた 6 ヵ月間の試験では，検討した最高の投与量（150 mg/kg/日）においても，オムビタスビルにがん原性は認められなかった。
ラットを用いたオムビタスビルのがん原性試験を実施中である。
オムビタスビルと主要な不活性代謝物（M29，M36）は，バクテリア変異原性を含む一連の in vitro 又は in vivo 試験，ヒト末梢血リンパ球を用いた染色体異常試験，in vivo マウス小核試験において遺伝毒性を示さなかった。

パリタプレビル，リトナビル
トランスジェニックマウスを用いた 6 ヵ月間の試験では，検討した最高の投与量（300/30 mg/kg/日）においても，パリタプレビル及びリトナビルにがん原性は認められなかった。同様に，ラットを用いた 2 年間の試験においても，検討した最高の投与量（300/30 mg/kg/日）におけるパリタプレビルの曝露量は 150 mg でヒトに投与したときの曝露量の約 9 倍となるが，パリタプレビル及びリトナビルにがん原性は認められなかった。
パリタプレビルは，ヒトリンパ球を用いた in vitro 染色体異常試験で陽性であったが，バクテリア変異原性試験及び in vivo 遺伝毒性試験 2 試験（ラット骨髄小核試験及びラット肝コメット試験）では陰性であった。

ダサブビル
トランスジェニックマウスを用いた 6 ヵ月間の試験では，検討した最高の投与量（2000 mg/kg/日）においても，ダサブビルにがん原性は認められなかった。
ラットを用いたダサブビルのがん原性試験を実施中である。
ダサブビルは，バクテリア変異原性を含む一連の in vitro 又は in vivo 試験，ヒト末梢血リンパ球を用いた染色体異常試験，in vivo ラット小核試験において遺伝毒性を示さなかった。
VIEKIRA PAK とリバビリンを併用投与する場合，がん原性及び変異原性に関する情報については，リバビリンの添付文書を参照のこと。

<u>受胎能障害</u>
オムビタスビル
マウスを用いて最高 200 mg/kg/日までの投与量で評価した場合に，胚・胎児の生存性又は受胎能に対するオムビタスビルの影響は認められなかった。この投与量におけるオムビタスビルの曝露量は，推奨臨床用量でヒトに投与したときの曝露量の約 25 倍であった。

パリタプレビル，リトナビル
ラットを用いて最高 300/30 mg/kg/日までの投与量で評価した場合に，胚・胎児の生存性又は受胎能に対するパリタプレビル及びリトナビルの影響は認められなかった。この投与量におけるパリタプレビルの曝露量は，推奨臨床用量でヒトに投与したときの曝露量の約 2～5 倍であった。

ダサブビル

ラットを用いて最高 800 mg/kg/日までの投与量で評価した場合に，胚・胎児の生存性又は受胎能に対するダサブビルの影響は認められなかった。この投与量におけるダサブビルの曝露量は，推奨臨床用量でヒトに投与したときの曝露量の約 33 倍であった。

VIEKIRA PAK とリバビリンを併用投与する場合の，受胎能障害に関する情報については，リバビリンの添付文書を参照のこと。

14 臨床試験

14.1 臨床試験の概要

VIEKIRA PAK の有効性及び安全性は，ジェノタイプ 1（GT1）慢性 C 型肝炎（HCV）感染患者 2,308 例を対象とした，無作為化多施設共同臨床試験 6 試験で評価した。そのうち 1 試験は肝硬変と軽度の肝障害（Child-Pugh A）を有する患者を対象としている。表 9 にその概要を示す。

表 9　慢性 HCV GT1 感染患者を対象としてリバビリン（RBV）との併用又は非併用で VIEKIRA PAK を検討した無作為化多施設共同試験

試験	対象集団	試験群 （投与例数）
SAPPHIRE-I （二重盲検）	GT1（a 及び b） TN[a]，肝硬変なし	VIEKIRA PAK＋RBV（473） プラセボ（158）
SAPPHIRE-II （二重盲検）	GT1（a 及び b） TE[b]，肝硬変なし	VIEKIRA PAK＋RBV（297） プラセボ（97）
PEARL-II （非盲検）	GT1b TE，肝硬変なし	VIEKIRA PAK＋RBV（88） VIEKIRA PAK（91）
PEARL-III （二重盲検）	GT1b TN，肝硬変なし	VIEKIRA PAK＋RBV（210） VIEKIRA PAK（209）
PEARL-IV （二重盲検）	GT1a TN，肝硬変なし	VIEKIRA PAK＋RBV（100） VIEKIRA PAK（205）
TURQUOISE-II （非盲検）	GT1（a 及び b） TN 及び TE，肝硬変あり	VIEKIRA PAK＋RBV（12 週間）（208） VIEKIRA PAK＋RBV（24 週間）（172）
TN（未治療）は，HCV 感染に対する前治療を受けていないことと定義した。 TE（治療歴あり）は，pegIFN／RBV に対し，前治療再燃例，partial responder 又は null responder のいずれかと定義した。		

- SAPPHIR-I 及び II 試験では，肝硬変を認めない患者を 12 週間の VIEKIRA PAK＋リバビリン併用投与群又はプラセボ群に無作為に割り付けた。プラセボ群の被験者は 12 週間に

わたってプラセボの投与を受け，その後，非盲検にて 12 週間の VIEKIRA PAK＋RBV 併用投与を受けた［臨床試験（*14.2*）を参照］。

- PEARL-II，-III 及び IV 試験では，肝硬変を認めない患者を VIEKIRA PAK＋RBV 併用投与群又は VIEKIRA PAK 投与群に無作為に割り付け，12 週間投与した［臨床試験（*14.2*）を参照］。
- 非盲検 TURQUOISE-II 試験では，代償性肝硬変を有し，未治療又はペグインターフェロン／RBV（pegIFN/RBV）治療歴のある患者（Child-Pugh A）を VIEKIRA PAK＋RBV の 12 週間投与群又は 24 週間投与群に無作為に割り付けた。過去に VIEKIRA PAK 又は他の直接作用型抗ウイルス薬を含む治療レジメンで効果が得られなかった患者は除外した［臨床試験（*14.3*）を参照］。

この 6 試験では，オムビタスビル，パリタプレビル及びリトナビルの用量を 25/150/100 mg 1 日 1 回，ダサブビルの用量を 250 mg 1 日 2 回とした。VIEKIRA PAK の薬剤の用量は調節しなかった。RBV の投与を受ける被験者における RBV の用量は，体重 75 kg 未満の場合は 1000 mg/日，75 kg 以上の場合は 1200 mg/日とした。RBV の用量調節は RBV の添付文書に従って実施した。

VIEKIRA PAK と RBV の併用については，以下の 2 試験においても評価した。

- HCV GT1 感染肝移植患者（CORAL-I 試験）［臨床試験（*14.5*）を参照］
- CV GT1 と HIV-1 の重複感染患者（TURQUOISE-I 試験）［臨床試験（*14.6*）を参照］

臨床試験全 8 試験において，ウイルス持続陰性化の定義を投与終了後 12 週時の HCV RNA が定量限界未満（＜LLOQ）であること（SVR12）とした。血漿 HCV RNA レベルは，High Pure System（定量下限 25 IU/mL）とともに使用するため，COBAS TaqMan HCV 検査（バージョン 2.0）で測定した。SVR12 を達成しなかった被験者の結果は，治療中のウイルス学的失敗（VF），投与後から Week 12 までのウイルス学的再燃，又は他の非ウイルス学的な理由（早期中止，有害事象，追跡不能，同意撤回等）による失敗と記録した。

14.2 肝硬変を認めない成人の慢性 HCV ジェノタイプ 1a 及び 1b 感染患者を対象とした臨床試験の結果

肝硬変を認めない慢性 HCV GT1a 感染被験者

SAPPHIRE-I 及び-II 試験，並びに PEARL-IV 試験［臨床試験（*14.1*）を参照］において，12 週間の VIEKIRA PAK＋RBV 併用投与を受けた肝硬変を認めない HCV GT1a 感染被験者の年齢中央値は 53 歳（範囲：18～70 歳）であった。被験者の 63%が男性であり，90%が白人，7%が黒人／アフリカ系アメリカ人，8%がヒスパニック又はラテン系であった。また，19%は肥満度指数（BMI）が 30 kg/m2 以上であった。被験者の 55%は米国の実施医療機関で登録された。72%は IL28B 非 CC ジェノタイプであり，85%はベースライン時の HCV RNA レベルが 800,000 IU/mL 以上であった。

SAPPHIRE-I 試験，PEARL-IV 試験及び SAPPHIRE-II 試験において 12 週間の VIEKIRA PAK＋RBV 併用投与を受けた HCV GT1a 被験者（未治療及び治療歴あり）の治療成績を表 10 に示す。

PEARL-IV 試験で 12 週間の投与を受けた肝硬変を認めない未治療の HCV GT1a 感染被験者では，VIEKIRA PAK＋RBV 併用投与群の方が VIEKIRA PAK 単独投与群よりも SVR12 率が高かっ

た［それぞれ 97%及び 90%，差は+7%（95%信頼区間：+1～+12）］。治療歴のある GT1a 感染患者における VIEKIRA PAK 単独投与については検討していない。

SAPPHIRE-I 試験及び SAPPHIRE-II 試験のプラセボ群では，投与期間中に HCV RNA＜25 IU/mL を達成した被験者はいなかった。

表 10　肝硬変を認めない HCV ジェノタイプ 1a 感染被験者（未治療又は PegIFN/RBV 治療歴あり）の SVR12

	VIEKIRA PAK＋RBV 12 週間 % (n/N)
GT1a 未治療	
SAPPHIRE I 試験の SVR12	96% (308/322)
SVR12 を達成しなかった被験者の治療成績	
治療中の VF	<1% (1/322)
再燃	2% (6/314)
その他	2% (7/322)
PEARL IV 試験の SVR12	97% (97/100)
SVR12 を達成しなかった被験者の治療成績	
治療中の VF	1% (1/100)
再燃	1% (1/98)
その他	1% (1/100)
GT1a 治療歴あり	
SAPPHIRE II 試験の SVR12	96% (166/173)
SVR12 を達成しなかった被験者の治療成績	
治療中の VF	0% (0/173)
再燃	3% (5/172)
その他	1% (2/173)
pegIFN による前治療の成績別 SVR12	
null responder	95% (83/87)
partial responder	100% (36/36)
再燃	94% (47/50)

肝硬変を認めない慢性 HCV GT1b 感染被験者

肝硬変を認めない HCV GT1b 被験者は，PEARL-II 及び-III 試験において 12 週間にわたり RBV 併用又は非併用で VIEKIRA PAK の投与を受けた［臨床試験（*14.1*）を参照］。被験者の年齢中央値は 52 歳（範囲：22～70 歳）であった。被験者の 47%が男性であり，93%が白人，5%が黒人／アフリカ系アメリカ人，2%がヒスパニック又はラテン系であった。また，21%は BMI が 30 kg/m2 以上であった。被験者の 21%は米国の実施医療機関で登録された。83%は IL28B 非

CC ジェノタイプであり，77%はベースライン時の HCV RNA レベルが 800,000 IU/mL 以上であった。

PEARL-II（既治療例：null responder，n=32；partial responder，n=26；relapser，n=33）及び PEARL-III（未治療例：n=209）における肝硬変を認めない HCV GT1b 被験者の RBV 非併用の VIEKIRA PAK 12 週間治療後の SVR 率は，100%であった。

14.3 代償性肝硬変を有する成人の慢性 HCV ジェノタイプ 1a 及び 1b 感染患者を対象とした臨床試験の結果

TURQUOISE-II 試験は，肝硬変と軽度の肝障害（Child-Pugh A）を有し，未治療又は pegIFN/RBV による前治療で SVR を達成しなかった HCV GT1a 及び 1b 患者 380 例を対象とした非盲検試験である。被験者は VIEKIRA PAK＋RBV の 12 週間投与群又は 24 週間投与群に無作為に割り付けられた。

投与を受けた被験者の年齢中央値は 58 歳（範囲：21～71 歳）であった。被験者の 70%が男性であり，95%が白人，3%が黒人／アフリカ系アメリカ人，12%がヒスパニック又はラテン系であった。また，28%は BMI が 30 kg/m2 以上であった。被験者の 43%は米国の実施医療機関で登録された。82%は IL28B 非 CC ジェノタイプであり，86%はベースライン時の HCV RNA レベルが 800,000 IU/mL 以上であった。69%が HCV GT1a 感染，31%が HCV GT1b 感染であり，42％が未治療，36％が前治療の pegIFN/RBV に対する null responder，8％が前治療の pegIFN/RBV に対する partial responder，14%が pegIFN/RBV による前治療後の再燃であった。被験者の 15%で血小板数が 90×109/L 未満であり，50%でアルブミンが 4.0 mg/dL 未満であった。

TURQUOIS-II 試験において 12 週間又は 24 週間の VIEKIRA PAK＋RBV 併用投与を受けた肝硬変を有する GT1 の被験者（未治療及び治療歴あり）の治療成績を表 11 に示す。GT1a 感染被験者において VIEKIRA PAK＋RBV の 24 週間投与群と 12 週間投与群の全 SVR12 率の差は+6%（95%信頼区間：-0.1～+13）であり，その差は前治療歴の有無で異なっていた。

表 11　TURQUOISE II 試験：肝硬変を有する慢性 HCV ジェノタイプ 1 感染被験者（未治療又は PegIFN/RBV 治療歴あり）の SVR12

	GT1a		GT1b
	VIEKIRA PAK+RBV 24 週間 % （n/N）	VIEKIRA PAK+RBV 12 週間 % （n/N）	VIEKIRA PAK+RBV 12 週間 % （n/N）

SVR12	95%（115/121）	89%（124/140）	99%（67/68）
SVR12 を達成しなかった被験者の治療成績			
治療中の VF	2%（3/121）	<1%（1/140）	0%（0/68）
再燃	1%（1/116）	8%（11/135）	1%（1/68）
その他	2%（2/121）	3%（4/140）	0%（0/68）
未治療の SVR12	95%（53/56）	92%（59/64）	100%（22/22）
pegIFN による前治療の成績別 SVR12			
null responder	93%（39/42）	80%（40/50）	100%（25/25）
partial responder	100%（10/10）	100%（11/11）	86%（6/7）
再燃	100%（13/13）	93%（14/15）	100%（14/14）

14.4 リバビリン減量が SVR12 に及ぼす影響

VIEKIRA PAK＋RBV 併用投与群の 7%（1551 例中 101 例）は，ヘモグロビン値の減少により RBV の用量を調節した。そのうち 98%（100 例中 98 例）は SVR12 を達成した。

14.5 選択された肝移植患者を対象とした臨床試験（CORAL I 試験）待機的

登録時点で移植から 12 ヵ月以上経過し，肝機能が正常，かつ線維症が軽度（Metavir 線維症スコア F2 以下）の HCV GT1 感染肝移植患者 34 例に 24 週間にわたって VIEKIRA PAK＋RBV を投与した。RBV の初回投与は，VIEKIRA PAK の投与開始時及び投与終了時に最も多く選択された用量範囲（600～800 mg/日）で治験担当医師が判断することとした。

登録された 34 例（HCV GT1a 感染 29 例及び HCV GT1b 感染 5 例）のうち，97%が SVR12 を達成した（GT1a 感染被験者の 97%及び GT1b 感染被験者の 100%）。HCV GT1a 感染被験者 1 例が投与後に再燃した。

14.6 HCV/HIV-1 重複感染患者を対象とした臨床試験（TURQUOISE I）

非盲検臨床試験において，HCV GT1 と HIV-1 の重複感染被験者 63 例を対象に，12 週間又は 24 週間にわたって VIEKIRA PAK＋RBV を投与した。被験者は，テノホビルジソプロキシルフマル酸塩＋エムトリシタビン又はラミブジンとリトナビルをブースターとするアタザナビル又はラルテグラビルの併用投与などの安定した HIV-1 抗レトロウイルス療法（ART）を受けていた。アタザナビル投与中の被験者は，VIEKIRA PAK＋RBV の投与開始時に HIV-1 ART レジメンの成分であるリトナビルの投与を中止した。アタザナビルは朝の VIEKIRA PAK とともに服用した。HIV-1 ART レジメンの一部としてのリトナビルは VIEKIRA PAK＋RBV による治療終了後に再開した。

投与を受けた被験者の年齢中央値は 51 歳（範囲：31～69 歳）であった。被験者の 24%が黒人であった。81%は IL28B 非 CC ジェノタイプであり，19%に代償性肝硬変を認めた。67%は

HCV 未治療であり，33%は pegIFN/RBV による前治療で効果が得られなかった。被験者の 89%は HCV ジェノタイプ 1a 感染であった。

SVR12 率は，HCV GT1a 感染被験者で 91%（56 例中 51 例），HCV GT1b 感染被験者では 100%（7 例中 7 例）であった。non-responder 5 例の内訳は，ウイルス再燃 1 例，投与中止 1 例，再燃 1 例及び投与後の HCV 再感染 2 例であった。

1 例で投与期間終了後に HIV-1 RNA が 400 コピー/mL を超えたことが確認された。この被験者に ART レジメンに対する耐性の証拠は認められなかった。血漿中 HIV-1 RNA 抑制の消失により ART レジメンを切り替えた被験者はいなかった。

14.7 奏効期間

非盲検臨床試験において，VIEKIRA PAK に含まれる直接作用型抗ウイルス薬と RBV の併用又は非併用による様々な組み合わせを投与された被験者の 92%（571 例中 526 例）が SVR12 を達成し，そのうち 99%は投与後 48 週間にわたって効果を維持した（SVR48）。

16 包装／保存及び取り扱い

VIEKIRA PAK は計 28 日分のマンスリーカートンで調剤される。各マンスリーカートンには，ウィークリーカートンが 4 箱入っている。各ウィークリーカートンには 1 日分の投与パックが 7 包入っている。

小児用安全対策が施された 1 日分の投与パックには，錠剤が 4 錠（オムビタスビル，パリタプレビル及びリトナビル 12.5/75/50 mg 配合錠 2 錠，ダサブビル 250 mg 錠 2 錠）が入っており，朝又は夕に服用すべき錠剤が示されている。NDC 番号は NDC 0074-3093-28 である。

オムビタスビル，パリタプレビル及びリトナビル 12.5/75/50 mg 配合錠は，桃色の両凸長楕円形のフィルムコーティング錠であり，片面には「AV1」の刻印がある。ダサブビル 250 mg 錠は，淡黄赤色の楕円形のフィルムコーティング錠であり，片面には「AV2」の刻印がある。

30℃（86° F）以下で保存すること。

17 患者に伝えるべき情報

FDA 承認済みの患者向け添付文書（医薬品ガイド）を参照。

リバビリンの医薬品ガイドを確認するよう患者に伝えること［警告及び使用上の注意（*5.2*）を参照］。

ALT 増加のリスク

疲労，脱力，食欲不振，悪心及び嘔吐などの初期の肝臓炎症の徴候や，黄疸，変色便などの遅発性の徴候に注意し，そのような症状が認められた場合には，直ちに医療従事者に相談するよう患者に伝えること［警告及び使用上の注意（*5.1*）及び副作用（*6*）を参照］。

妊娠

VIEKIRA PAK とリバビリンを併用している間は妊娠を避けるように患者を指導すること。妊娠した場合には，直ちに医療従事者に知らせるよう患者に伝えること。HCV/HIV-1 重複感染で抗レトロウイルス薬を併用している患者については，妊娠結果をモニタリングする Antiretroviral Pregnancy Registry（妊娠中の抗レトロウイルス薬の使用に関する症例登録研究）があることを妊娠患者に伝えること［特別な患者集団への投与*(8.1)*を参照］。

薬物相互作用

VIEKIRA PAK は一部の薬剤と相互作用を起こす可能性があることを患者に伝えること。そのため，処方薬，一般用医薬品，又はハーブ製品を使用した場合は，医療従事者に報告するよう患者を指導すること［禁忌（*4*），警告及び使用上の注意（*5.3*），薬物相互作用（*7*）を参照］。

エストラジオールを含有する避妊薬は VIEKIRA PAK と禁忌であることを伝えること［禁忌*(4)*，警告及び使用上の注意*(5.1)*を参照］。

C 型肝炎ウイルス伝播

C 型肝炎ウイルスの治療が伝播に及ぼす影響は不明であること，また，投与中に C 型肝炎ウイルスが伝播しないよう適切な予防策を講じるよう患者に伝えること。

服用し忘れた場合

オムビタスビル，パリタプレビル及びリトナビルを服用し忘れた場合は，12 時間以内であれば所定の錠剤を服用してよい。

ダサブビルを服用し忘れた場合は，6 時間以内であれば所定の錠剤を服用してよい。

オムビタスビル，パリタプレビル及びリトナビルを通常服用する時間から 12 時間以上経過している場合，又はダサブビルを通常服用する時間から 6 時間以上経過している場合には，服用し忘れた錠剤を服用してはならない。患者は通常の投与スケジュールに従って次回の錠剤を服用すること。

飲み忘れを補うために処方量以上を服用しないよう患者に指導すること。

製造元： AbbVie Inc., North Chicago, IL 60064

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患者向け医薬品ガイド
VIEKIRA PAK®
（オムビタスビル，パリタプレビル及びリトナビル配合錠，ダサブビル錠），経口投与組合せ製品

VIEKIRA PAK を服用し始める前や，処方されたときにこの医薬品ガイドを読んでください。情報が更新されている可能性があります。この情報は，あなたの病状や治療について，医療従事者に相談することに代わるものではありません。VIEKIRA PAK を服用し始める前や，定期検査の際には VIEKIRA PAK の治療について医療従事者と話し合ってください。VIEKIRA PAK を服用している間は，医療従事者の診察を受けてください。

VIEKIRA PAK をリバビリンと併用する場合はリバビリンの医薬品ガイドをあわせて参照してください。

VIEKIRA PAK について知らなければならない最も重要な情報
VIKIRA PAK により，特にエストラジオールを含む薬剤（避妊薬の一種）を使用している場合は肝機能検査値の結果が上昇するかもしれません。

- VIEKIRA PAK の治療を始める前に，エチニルエストラジオールを含む薬剤の使用を中止しなければなりません（このような薬のリストは「VIEKIRA PAK を服用するべきではない人」の項目を参照してください）。
- 避妊のためにこれらの薬を使用している場合，VIEKIRA PAK の治療を行っている間及び VIEKIRA PAK の治療が終わって約 2 週間は別の避妊法を使用してください。医療従事者がエチニルエストラジオールを含む薬剤の服用を始める時期をお知らせします。
- 医療従事者は VIEKIRA PAK による治療開始から 4 週間，必要であれば治療期間の間，肝機能を確認するための血液検査を実施します。
- 医療従事者はあなたに肝臓の問題の徴候があらわれた場合，VIEKIRA PAK の服用を中止するよう伝える場合があります。
- VIEKIRA PAK 服用中に以下の徴候があらわれた場合，又は悪化した場合は，医療従事者に知らせてください。
  - 疲労
  - 脱力
  - 食欲不振
  - 悪心，嘔吐
  - 皮膚や白目が黄色くなった
  - 便の色が変化した

VIEKIRA PAK について
VIEKIRA PAK は，ある種の肝硬変（代償性肝硬変）を含む，成人の慢性（長期にわたって続く）C 型肝炎ウイルス（HCV）感染の治療にリバビリンと併用（又は非併用）する処方薬です。

VIEKIRA PAK は進行した肝硬変（非代償性肝硬変）には使用しません。あなたが肝硬変である場合には VIEKIRA PAK を服用し始める前に医療従事者に相談してください。

VIEKIRA PAK には，2 種類の錠剤が入っています。慢性 C 型肝炎を治療するにはこの 2 種類の錠剤を処方通りに必ず組み合わせて使用しなければなりません。

- ピンクの錠剤：オムビタスビル，パリタプレビル及びリトナビル
- ベージュの錠剤：ダサブビル

VIEKIRA PAK とリバビリンを服用する場合は，リバビリンの医薬品ガイドも読んでください。

18 歳未満の小児が VIEKIRA PAK を服用することについて，安全で有効かどうかはわかっていません。

VIEKIRA PAK を服用してはならない人

以下の場合は VIEKIRA PAK を服用しないでください：

- 重い肝臓の異常を持っている場合
- 次の薬のいずれかを使用している人
  - アルフゾシン塩酸塩（Uroxatral®）
  - カルバマゼピン（Carbatrol®，Epitol®，Equetro®，Tegretol®）
  - エファビレンツ（Atripla®，Sustiva®）
  - 次の麦角を含む製剤：
    - エルゴタミン酒石酸塩（Cafergot®，Ergomar®，Ergostat®，Medihaler®，Migergot®，Wigraine®，Wigrettes®）
    - ジヒドロエルゴタミンメシル酸塩（D.H.E. 45®，Migranal®）
    - メチルエルゴメトリン（Methergine®）
  - エチニルエストラジオールを含む製剤：
    - Lo Loestrin® FE，Norinyl®，Ortho Tri-Cyclen Lo® ，Ortho Evra®などの内服避妊薬や貼付剤
    - NuvaRing®などのホルモン剤を用いた膣リング
    - ホルモン補充療法薬の 1 つである Fem HRT®
  - ゲムフィブロジル（Lopid®）
  - ロバスタチン（Advicor®，Altoprev®，Mevacor®）
  - ミダゾラム（内服する場合）
  - フェニトイン（Dilantin®，Phenytek®）
  - フェノバルビタール（Luminal®）
  - ピモジド（Orap®）
  - リファンピシン（Rifadin®，Rifamate®，Rifater®，Rimactane® 肺動脈高血圧（PAH）治療薬であるシルデナフィルクエン酸塩（Revatio®）服用中
  - シンバスタチン（Simcor®，Vytorin®，Zocor®）

- セント・ジョーンズ・ワート（セイヨウオトギリソウ）又はセイヨウオトギリソウを含む製品
- トリアゾラム（Halcion®）

- ・リトナビル（Norvir®）を服用した後で重い皮疹を経験したことのある人

VIEKIRA PAK 服用前に医療従事者に伝えておくこと

次に該当する人は，あなたの病状について医療従事者に伝えてください。

- C 型肝炎以外の肝臓に関する異常がある人。VIEKIRA PAK を服用してはならない人を参照ください。
- HIV に感染している人
- 肝移植を受けたことがある人。タクロリムス（Prograf®）やシクロスポリン（Gengref®, Neoral®, Sandimmune®）をあなたの移植後肝臓の拒否反応を防ぐために使用している場合は，これらの薬剤の濃度が VIEKIRA PAK を服用している間，増えすぎてしまう可能性があります。
  - 医療従事者はタクロリムスやシクロスポリンの濃度をチェックし，必要であればあなたの服用する量や回数を変更する場合があります。
  - VIEKIRA PAK の治療が終わった場合や，何らかの理由で VIEKIRA PAK の服用を中止した場合は，医療従事者がタクロリムスやシクロスポリンの服用する量や回数をお知らせします。
- その他の病状がある人
- 妊娠又はその予定がある人。VIEKIRA PAK が胎児に与える影響についてはわかっていません。リバビリンと併用する場合はリバビリンの医薬品ガイドの重要な妊婦情報を読んでください。妊娠登録制度：抗レトロウイルス薬を妊娠中に服用している女性が登録する制度があります。この登録制度の目的は妊婦と赤ちゃんの健康についての情報の収集です。もしあなたが HCV と HIV の両方に感染している妊娠女性である場合は，この登録制度に参加することについて医療従事者に相談してください。
- 授乳中又はその予定がある人。VIEKIRA PAK があなたの乳汁に分泌されるかどうかはわかっていません。VIEKIRA PAK を服用する場合は授乳に関するベストな方法を医療従事者に相談してください。.

処方薬，市販薬，ビタミン剤，ハーブ系サプリメントを含め，あなたが使用しているすべての薬を医療従事者に伝えてください。医療従事者や薬剤師に見せられるよう，あなたが使用している薬のリストを持ちましょう。

- あなたの薬のリストの中に VIEKIRA PAK を相互作用を起こす薬がある場合は，医療従事者や薬剤師に尋ねることができます。
- 医療従事者に相談しないで，新しい薬を使い始めないでください。医療従事者は他の薬と VIEKIRA PAK の飲み合わせが安全かどうかを確認して，あなたに伝えることができます。
- VIEKIRA PAK の治療が終了した場合:

- 医師にこれまで服用していた薬の量を変更するように指示されていた場合：VIEKIRA PAK 治療終了後のいつから元の量に戻したら良いかを尋ねてください。
- 医師にこれまで服用していた薬を止めるように指示されていた場合：VIEKIRA PAK 治療終了後のいつからこれらの薬を飲み始めて良いかを尋ねてください。

VIEKIRA PAK の使い方

- 医療従事者が使い方を教えます。そのとおり正確に VIEKIRA PAK を服用してください。医療従事者がそのように指示した場合を除き，飲む量を変えてはいけません。
- 医療従事者に相談せずに VIEKIRA PAK の服用を止めないでください。
- VIEKIRA PAK が処方された場合，28 日分の服用量が入った 1 か月分のカートンが渡されます。
- 1 か月分のカートンの中には 4 つのさらに小さいカートンが入っています。
- それぞれの小さいカートンは子供が扱えないようにされた毎日の服用パックが 7 日分（1 週間分）入っています。
- それぞれの毎日の服用パックはあなたが服用する 1 日分（4 錠）の VIEKIRA PAK が入っています。毎日の服用パックからの錠剤の取り出し方は指示に従ってください。
- VIEKIRA PAK を食事とともに服用してください。：
  - 2 つのピンクの錠剤（オムビタスビル，ダサブビル，リトナビル）と 1 つのベージュの錠剤（ダサブビル）を毎朝同じ時間に服用してください。
  - 2 回目のベージュの錠剤（ダサブビル）を毎夕同じ時間に飲んでください。
- ピンクの錠剤を服用し忘れたときは，通常の服用時間から 12 時間たっていない場合は，できるだけ早く食事とともに服用してください。次回の服用からは通常どおりの時間で構いません。
- ピンクの錠剤を服用し忘れたときは，通常の服用時間から 12 時間以上過ぎている場合は，その錠剤を服用しないでください。次回の服用時間から通常どおり食事とともに服用してください。
- ベージュの錠剤を服用し忘れたときは，通常の服用時間から 6 時間たっていない場合は，できるだけ早く食事とともに服用してください。次回の服用からは通常どおりの時間で構いません。
- ベージュの錠剤を服用し忘れたときは，通常の服用時間から 6 時間以上過ぎている場合は，その錠剤を服用しないでください。次回の服用からは通常どおり食事とともに服用してください。
- 服用忘れを補うために一度に処方された量を超えて服用しないでください。
- VIEKIRA PAK を服用し過ぎた場合は，直ちに医療従事者に連絡するか，お近くの救急治療室を受診してください。

予想される VIEKIRA PAK の副作用

「VIEKIRA PAK について知らなければならない最も重要な情報」を参照してください。

VIEKIRA PAK とリバビリンを併用した場合の副作用には以下のものがあります：

- 疲労
- 吐き気
- かゆみ
- あかみ，発疹のような皮膚反応
- 睡眠障害
- 無力感

VIEKIRA PAK とリバビリンを併用しなかった場合の副作用には以下のものがあります：

- 吐き気
- かゆみ
- 睡眠障害

副作用でお悩みの場合や治らない副作用があれば，医療従事者に伝えてください。

上記以外にも，VIEKIRA PAK の副作用が考えられます。詳しい情報については，担当の医療従事者か薬剤師にお尋ねください。

副作用に関する医学的な助言は主治医にお尋ねください。FDA（1-800-FDA-1088）に副作用を報告することもできます。

VIEKIRA PAK の保存方法

86° F（30℃）以下で保存してください。

VIEKIRA PAK 及びすべての薬を子供の手の届かないところに保管してください。

VIEKIRA PAK の安全性と有効性に関する一般情報

VIEKIRA PAK で治療することで，治療中に C 型肝炎ウイルスの別の人への感染を予防するかどうかについてはわかっていません。C 型肝炎ウイルスが広がるのを防ぐ方法については，医療従事者に相談してください。

薬は，医薬品ガイドに記載された目的以外でも処方されることがあります。VIEKIRA PAK が処方されていない病状に対して，VIEKIRA PAK を使用しないでください。たとえ同じ病状であったとしても，他の人に VIEKIRA PAK を渡さないでください。その人に害を及ぼす可能性があります。

VIEKIRA PAK についてさらに詳しい情報を知りたい場合は，医療従事者に相談してください。医療従事者向けに書かれた VIEKIRA PAK に関する情報を確認するには，薬剤師又は医療従事者にご相談ください。

VIEKIRA PAK の詳しい情報については，www.viekira.com をご覧になるか，1-800-633-9110 にお電話ください。

VIEKIRA PAK の成分

オムビタスビル，パリタプレビル，リトナビル錠：

有効成分：オムビタスビル，パリタプレビル及びリトナビル

添加物：K28 型コポビドン，コハク酸ビタミン E ポリエチレングリコール，モノラウリン酸プロピレングリコール I 型，モノラウリン酸ソルビタン，コロイド状二酸化ケイ素／コロイド状無水シリカ，フマル酸ステアリルナトリウム。フィルムコーティング剤：ポリビニルアルコール，ポリエチレングリコール 3350／マクロゴール 3350，タルク，二酸化チタン，赤色酸化鉄。

ダサブビル錠：

有効成分：ダサブビル

添加物：微結晶性セルロース（D50～100μm），微結晶性セルロース（D50～50μm），乳糖一水和物，コポビドン，クロスカルメロースナトリウム，コロイド状二酸化ケイ素／コロイド状無水シリカ，ステアリン酸マグネシウム，ポリビニルアルコール，二酸化チタン，ポリエチレングリコール 3350／マクロゴール 3350，タルク，黄色酸化鉄，赤色酸化鉄及び黒色酸化鉄（E172）。

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Manufactured by: AbbVie Inc.

North Chicago, IL 60064

Issued: 2015 年 3 月

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03-B151

1.6.2.2 欧州における添付文書

SUMMARYOFPRODUCT CHARACTERISTICS

Viekirax 12.5 mg/75 mg/50 mg film-coated tablets（原文）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Viekirax 12.5 mg/75 mg/50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, oblong, biconvex, film-coated tablets of dimensions 18.8 mm x 10.0 mm, debossed on one side with 'AV1'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Viekirax is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4, and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Treatment with Viekirax should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

Posology

The recommended oral dose of Viekirax is two 12.5 mg / 75 mg / 50 mg tablets once daily with food.

Viekirax should be used in combination with other medicinal products for the treatment of HCV (see Table 1).

Table 1. Recommended co-administered medicinal product(s) and treatment duration for Viekirax by patient population

Patient population	Treatment*	Duration
Genotype 1b, without cirrhosis	Viekirax + dasabuvir	12 weeks
Genotype 1b, with compensated cirrhosis	Viekirax + dasabuvir + ribavirin	12 weeks
Genotype 1a, without cirrhosis	Viekirax + dasabuvir + ribavirin*	12 weeks
Genotype 1a, with compensated cirrhosis	Viekirax + dasabuvir + ribavirin*	24 weeks (see section 5.1.)
Genotype 4, without cirrhosis	Viekirax + ribavirin	12 weeks
Genotype 4, with compensated cirrhosis	Viekirax + ribavirin	24 weeks
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.		

For specific dosage instructions for dasabuvir and ribavirin, including dose modification, refer to the respective Summaries of Product Characteristics.

Missed doses
In case a dose of Viekirax is missed, the prescribed dose can be taken within 12 hours. If more than 12 hours have passed since Viekirax is usually taken, the missed dose should NOT be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

Special populations

HIV-1 Co-infection

Follow the dosing recommendations in Table 1. For dosing recommendations with HIV antiviral agents, refer to section 4.4 (Treatment of patients with HIV co-infection) and section 4.5. See section 5.1 for additional information.

Liver transplant recipients

Viekirax and dasabuvir in combination with ribavirin is recommended for 24 weeks in liver transplant recipients with genotype 1 HCV infection. Viekirax in combination with ribavirin is recommended in genotype 4 infection. Lower ribavirin dose at initiation may be appropriate. In the post-liver transplant study, ribavirin dosing was individualized and most subjects received 600 to 800 mg per day (see section 5.1). For dosing recommendations with calcineurin inhibitors see section 4.5.

Elderly

No dose adjustment of Viekirax is warranted in elderly patients (see section 5.2).

Renal impairment

No dose adjustment of Viekirax is required for patients with mild, moderate, or severe renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment of Viekirax is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Viekirax have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies. Viekirax is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.3 and 5.2).

Paediatric population

The safety and efficacy of Viekirax in children less than 18 years of age have not been established. No data are available.

Method of administration

The film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole (i.e. patients should not chew, break or dissolve the tablet). To maximise absorption, Viekirax tablets should be taken with food, without regard to fat and calorie content (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with severe hepatic impairment (Child-Pugh C) (see section 5.2).

Use of ethinylestradiol-containing medicinal products such as those contained in most combined oral contraceptives or contraceptive vaginal rings (see section 4.4 and 4.5).

Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events must not be co-administered with Viekirax (see section 4.5). Examples are provided below.

CYP3A4 substrates:

- alfuzosin hydrochloride
- amiodarone
- astemizole, terfenadine
- cisapride
- colchicine in patients with renal or hepatic impairment
- ergotamine, dihydroergotamine, ergonovine, methylergometrine
- fusidic acid
- lovastatin, simvastatin, atorvastatin
- oral midazolam, triazolam
- pimozide
- quetiapine
- quinidine
- salmeterol
- sildenafil (when used for the treatment of pulmonary arterial hypertension)
- ticagrelor

Co-administration of Viekirax with or without dasabuvir with medicinal products that are strong or moderate enzyme inducers is expected to decrease ombitasvir, paritaprevir, and ritonavir plasma

concentrations and reduce their therapeutic effect and must not be co-administered (see section 4.5). Examples of contraindicated strong or moderate enzyme inducers are provided below.

Enzyme inducers:

- carbamazepine, phenytoin, phenobarbital
- efavirenz, nevirapine, etravirine
- enzalutamide
- mitotane
- rifampicin
- St. John's Wort (*Hypericum perforatum*)

Co-administration of Viekirax with or without dasabuvir with medicinal products that are strong inhibitors of CYP3A4 is expected to increase paritaprevir plasma concentrations and must not be co-administered with Viekirax (see section 4.5). Examples of contraindicated strong CYP3A4 inhibitors are provided below.

CYP3A4 inhibitors:

- cobicistat
- indinavir, lopinavir/ritonavir, saquinavir, tipranavir,
- itraconazole, ketoconazole, posaconazole, voriconazole
- clarithromycin, telithromycin
- conivaptan

4.4 Special warnings and precautions for use

General

Viekirax is not recommended for administration as monotherapy and must be used in combination with other medicinal products for the treatment of hepatitis C infection (see sections 4.2 and 5.1).

Genotype-specific activity

Concerning recommended regimens with different HCV genotypes, see section 4.2. Concerning genotype-specific virological and clinical activity, see section 5.1.

The efficacy of Viekirax has not been established in patients with HCV genotypes 2, 3, 5 and 6; therefore Viekirax should not be used to treat patients infected with these genotypes.

There are no data on the use of Viekirax and ribavirin in patients with HCV genotype 4 infection with compensated cirrhosis and therefore the optimal treatment duration has not been established. Based on *in vitro* antiviral activity and available clinical data in HCV genotype 1, a conservative treatment duration of 24 weeks is recommended for patients with HCV genotype 4 and compensated cirrhosis.

Co-administration with other direct-acting antivirals against HCV

Viekirax safety and efficacy have been established in combination with dasabuvir and/or ribavirin. Co-administration of Viekirax with other antivirals has not been studied and therefore cannot be recommended.

Retreatment

The efficacy of Viekirax in patients previously exposed to Viekirax, or to medicinal products of the same classes as those of Viekirax (NS3/4A- or NS5A inhibitors), has not been demonstrated. Concerning cross-resistance, see also section 5.1.

Pregnancy and concomitant use with ribavirin

When Viekirax is used in combination with ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for 6 months after the treatment as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

ALT elevations

During clinical trials with Viekirax and dasabuvir with or without ribavirin, transient elevations of ALT to greater than 5 times the upper limit of normal occurred in approximately 1% of subjects (35 of 3,039). ALT elevations were asymptomatic and generally occurred during the first 4 weeks of treatment, without concomitant elevations of bilirubin, and declined within approximately two weeks of onset with continued dosing of Viekirax and dasabuvir with or without ribavirin.

These ALT elevations were significantly more frequent in the subgroup of subjects who were using ethinylestradiol-containing medicinal products such as combined oral contraceptives or contraceptive vaginal rings (6 of 25 subjects); (see section 4.3). In contrast, the rate of ALT elevations in subjects using other types of estrogens as typically used in hormonal replacement therapy (i.e., oral and topical estradiol and conjugated estrogens) was similar to the rate observed in subjects who were not using estrogen-containing products (approximately 1% in each group).

Patients who are taking ethinylestradiol-containing medicinal products (i.e. most combined oral contraceptives or contraceptive vaginal rings) must switch to an alternative method of contraception (e.g., progestin only contraception or non-hormonal methods) prior to initiating Viekirax and dasabuvir therapy (see sections 4.3 and 4.5).

Although ALT elevations associated with Viekirax and dasabuvir have been asymptomatic, patients should be instructed 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 discoloured faeces, and to consult a doctor without delay if such symptoms occur. Routine monitoring of liver enzymes is not necessary. Early discontinuation may result in drug resistance, but implications for future therapy are not known.

Use with glucocorticoids metabolised by CYP3A (e.g. fluticasone)

Caution should be used when administering Viekirax with fluticasone or other glucocorticoids that are metabolised by CYP3A4. Concomitant use of inhaled glucocorticoids metabolised with CYP3A can increase systemic exposures of the glucocorticoids, and cases of Cushing's syndrome and subsequent adrenal suppression have been reported with ritonavir-containing regimens. Concomitant use of Viekirax and glucocorticoids, particularly long-term use, should only be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.5).

Use with colchicine

The interaction between Viekirax with or without dasabuvir and colchicine has not been evaluated. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with

normal renal or hepatic function if treatment with Viekirax with or without dasabuvir is required (see section 4.5). In patients with renal or hepatic impairment, use of colchicine with Viekirax with or without dasabuvir is contraindicated (see section 4.3 and 4.5).

Use with statins

Simvastatin, lovastatin and atorvastatin are contraindicated (see section 4.3 and 4.5).

Rosuvastatin
Viekirax with dasabuvir is expected to increase the exposure to rosuvastatin more than 3-fold. If rosuvastatin treatment is required during the treatment period, the maximum daily dose of rosuvastatin should be 5 mg (see section 4.5, Table 2).The increase in rosuvastatin when combined with Viekirax without dasabuvir is less pronounced. In this combination, the maximum daily dose of rosuvastatin should be 10 mg (see section 4.5, Table 2).

Pitavastatin and fluvastatin
The interactions between pitavastatin and fluvastatin and Viekirax have not been investigated. Theoretically, Viekirax with and without dasabuvir is expected to increase the exposure to pitavastatin and fluvastatin. A temporary suspension of pitavastatin/fluvastatin is recommended for the duration of treatment with Viekirax. If statin treatment is required during the treatment period, a switch to a reduced dose of pravastatin/rosuvastatin is possible (see section 4.5, Table 2).

Treatment of patients with HIV co-infection

Low dose ritonavir, which is part of the fixed dose combination Viekirax, may select for PI resistance in HIV co-infected patients without ongoing antiretroviral therapy. HIV co-infected patients without suppressive antiretroviral therapy should not be treated with Viekirax.

Drug interactions need to be carefully taken into account in the setting of HIV co-infection (for details see section 4.5, Table 2).

Atazanavir can be used in combination with Viekirax and dasabuvir, if administered at the same time. To be noted, atazanavir should be taken without ritonavir, since ritonavir 100 mg once daily is provided as part of Viekirax. The combination carries an increased risk for hyperbilirubinemia (including ocular icterus), in particular when ribavirin is part of the hepatitis C regimen.

Darunavir, dosed 800 mg once daily, if administered at the same time as Viekirax and dasabuvir, can be used in the absence of extensive PI resistance (darunavir exposure lowered). To be noted, darunavir should be taken without ritonavir, since ritonavir 100 mg once daily is provided as part of Viekirax.

HIV protease inhibitors other than atazanavir and darunavir (e.g., indinavir, saquinavir, tipranavir, lopinavir/ritonavir) are contraindicated (see section 4.3).

Raltegravir exposure is substantially increased (2-fold). The combination was not linked to any particular safety issues in a limited set of patients treated for 12-24 weeks.

Rilpivirine exposure is substantially increased (3-fold) when rilpivirine is given in combination with Viekirax and dasabuvir, with a consequent potential for QT-prolongation. If an HIV protease inhibitor is added (atazanavir, darunavir), rilpivirine exposure may increase even further and is therefore not recommended. Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

NNRTIs other than rilpivirine (efavirenz, etravirine and nevirapine) are contraindicated (see section 4.3).

Hepatic impairment

No dose adjustment for Viekirax is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Viekirax have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies.
Viekirax is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.3 and 5.2).

HCV/HBV (Hepatitis B Virus) co-infection

The safety and efficacy of Viekirax have not been established in patients with HCV/HBV co-infection.

Paediatric population

The safety and efficacy of Viekirax in children below 18 years have not been established. No data are available.

4.5 Interaction with other medicinal products and other forms of interaction

Viekirax may be administered with or without dasabuvir. When co-administered, they exert mutual effects on each other (see section 5.2). Therefore, the interaction profile of the compounds must be considered as a combination.

Pharmacodynamic interactions

Coadministration with enzyme inducers may increase the risk of adverse events and ALT elevations (see Table 2). Coadministration with ethinylestradiol may increase the risk of ALT elevations (see sections 4.3 and 4.4). Examples of contraindicated enzyme inducers are provided in section 4.3.

Pharmacokinetic interactions

Potential for Viekirax to affect the pharmacokinetics of other medicinal products
In vivo drug interaction studies evaluated the net effect of the combination treatment, including ritonavir.

The following section describes the specific transporters and metabolizing enzymes that are affected by Viekirax with or without dasabuvir. See Table 2 for guidance regarding potential interactions with other medicinal products and dosing recommendations.

Medicinal products metabolised by CYP3A4
Ritonavir is a strong inhibitor of CYP3A. Co-administration of Viekirax with or without dasabuvir with medicinal products primarily metabolized by CYP3A may result in increased plasma concentrations of these medicinal products. Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events are contraindicated (see section 4.3 and Table 2).

CYP3A substrates evaluated in drug interaction studies which may require dose adjustment and/or clinical monitoring include (see Table 2) cyclosporine, tacrolimus, amlodipine, rilpivirine and alprazolam. Examples of other CYP3A4 substrates which may require dose adjustment and/or clinical monitoring include calcium channel blockers (e.g. nifedipine), and trazodone. Although buprenorphine and zolpidem are also metabolized by CYP3A, drug interaction studies indicate that no dose adjustment is needed when co-administering these medicinal products with Viekirax with or without dasabuvir (see Table 2).

Medicinal products transported by the OATP family and OCT1
Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Ritonavir is an *in vitro* inhibitor of OCT1, but the clinical relevance is unknown. Co-administration of Viekirax with or without dasabuvir with medicinal products that are substrates of OATP1B1, OATP1B3, OATP2B1 or OCT1 may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring. Such medicinal products include some statins (see Table 2), fexofenadine, repaglinide and angiotensin II receptor antagonists (e.g., valsartan).

OATP1B1/3 substrates evaluated in drug interaction studies include pravastatin and rosuvastatin (see Table 2).

Medicinal products transported by BCRP
Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP *in vivo*. Co-administration of Viekirax with or without dasabuvir together with medicinal products that are substrates of BCRP may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring. Such medicinal products include sulfasalazine, imatinib and some of the statins (see Table 2).

BCRP substrates evaluated in drug interaction studies include rosuvastatin (see Table 2).

Medicinal products transported by P-gp in the intestine
While paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, no significant change was observed in the exposure of the P-gp substrate digoxin when administered with Viekirax and dasabuvir. However, co-administration of digoxin with Viekirax without dasabuvir may result in increased plasma concentrations (see Table 2). Viekirax may increase the plasma exposure to medicinal products that are sensitive for changed intestinal P-gp activity (such as dabigatran etexilate).

Medicinal products metabolised by glucuronidation (UGT1A1)
Paritaprevir, ombitasvir and dasabuvir are inhibitors of UGT1A1. Co-administration of Viekirax with or without dasabuvir with medicinal products that are primarily metabolized by UGT1A1 result in increased plasma concentrations of such medicinal products; routine clinical monitoring is recommended for narrow therapeutic index medicinal products (i.e. levothyroxine). See also Table 2 for specific advice on raltegravir and buprenorphine, which have been evaluated in drug interaction studies.

Medicinal products metabolised by CYP2C19
Co-administration of Viekirax with or without dasabuvir can decrease exposures of medicinal products that are metabolized by CYP2C19 (e.g. lansoprazole, esomeprazole, s-mephenytoin), which may require dose adjustment/clinical monitoring. CYP2C19 substrates evaluated in drug interaction studies include omeprazole and escitalopram (see Table 2).

Medicinal products metabolised by CYP2C9
Viekirax administered with or without dasabuvir did not affect the exposures of the CYP2C9 substrate, warfarin. Other CYP2C9 substrates (NSAIDs (e.g. ibuprofen), antidiabetics (e.g. glimepiride, glipizide) are not expected to require dose adjustments.

Medicinal products metabolised by CYP2D6 or CYP1A2
Viekirax administered with or without dasabuvir did not affect the exposures of the CYP2D6/CYP1A2 substrate, duloxetine. Other CYP1A2 substrates (e.g. ciprofloxacin, theophylline and caffeine) and CYP2D6 substrates (e.g. desipramine, metoprolol and dextromethorphan) are not expected to require dose adjustments.

Medicinal products renally excreted via transport proteins
Ombitasvir, paritaprevir, and ritonavir do not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that ombitasvir, paritaprevir, and ritonavir are not inhibitors of organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Therefore, Viekirax with or without dasabuvir is not expected to affect medicinal products which are primarily excreted by the renal route via these transporters (see section 5.2).

Potential for other medicinal products to affect the pharmacokinetics of ombitasvir, paritaprevir, and dasabuvir

Medicinal products that inhibit CYP3A4
Co-administration of Viekirax with or without dasabuvir with strong inhibitors of CYP3A may increase paritaprevir concentrations (see section 4.3 and Table 2).

Enzyme inducers
Co-administration of Viekirax and dasabuvir with medicinal products that are moderate or strong enzyme inducers is expected to decrease ombitasvir, paritaprevir, ritonavir and dasabuvir plasma concentrations and reduce their therapeutic effect. Contraindicated enzyme inducers are provided in section 4.3 and Table 2.

Medicinal products that inhibit CYP3A4 and transport proteins
Paritaprevir is eliminated via CYP3A4 mediated metabolism and biliary excretion (substrate of the hepatic transporters OATP1B1, P-gp and BCRP). Caution is advised if co-administering Viekirax with medicinal products that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters (P-gp, BCRP and/or OATP1B1/ OATP1B3). These medicinal products may show clinically relevant increases in exposures of paritaprevir (e.g., ritonavir with atazanavir, erythromycin, diltiazem or verapamil).

Medicinal products that inhibit transport proteins
Potent inhibitors of P-gp, BCRP, OATP1B1 and/or OATP1B3 have the potential to increase the exposure to paritaprevir. Inhibition of these transporters is not expected to show clinically relevant increases in exposures of ombitasvir and dasabuvir.

Drug interaction studies

Recommendations for co-administration of Viekirax with and without dasabuvir for a number of medicinal products are provided in Table 2.

If a patient is already taking medicinal product(s) or initiating a medicinal product while receiving Viekirax with or without dasabuvir for which potential for drug interaction is expected, dose adjustment of the concomitant medicinal product(s) or appropriate clinical monitoring should be considered (Table 2).

If dose adjustments of concomitant medicinal products are made due to treatment with Viekirax or Viekirax with dasabuvir, doses should be re-adjusted after administration of Viekirax or Viekirax with dasabuvir is completed.

Table 2 provides the Least Squares Means Ratio (90% Confidence Interval) effect on concentration of Viekirax with or without dasabuvir and concomitant medicinal products.

The magnitude of interaction when administered with medicinal products listed in Table 2 are similar (≤25% difference in the Least Square Means ratio) for Viekirax with or without dasabuvir, unless otherwise noted. Drug interactions were evaluated for the Viekirax and dasabuvir regimen, but not for the Viekirax without dasabuvir, with carbamazepine, furosemide, zolpidem, darunavir twice daily, darunavir (evening administration), atazanavir (evening administration) or rilpivirine. Thus, for these medicinal products, results and dosing recommendations of the Viekirax and dasabuvir regimen can be extrapolated to Viekirax without dasabuvir.

The direction of the arrow indicates the direction of the change in exposures (C_{max}, and AUC) in paritaprevir, ombitasvir, dasabuvir and the co-administered medicinal product (↑ = *increase (more than 20%)*, ↓ = *decrease (of more than 20%)*, ↔ = *no change* or change less than 20%). This is not an exclusive list.

Table 2. Interactions between Viekirax with or without dasabuvir and other medicinal products

Medicinal Product/Possible Mechanism of Interaction	**GIVEN WITH**	**EFFECT**	**C_{max}**	**AUC**	**C_{min}**	**Clinical Comments**
ALPHA 1-ADRENORECEPTOR ANTAGONIST						
Alfuzosin Mechanism: CYP3A inhibition by ritonavir	Viekirax with or without dasabuvir	Not studied. Expected ↑ alfuzosin				Concomitant use is contraindicated (see section 4.3).
AMINOSALICYLATE						
Sulfasalazine Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ sulfasalazine				Caution should be used when sulfasalazine is co-administered with Viekirax with or without dasabuvir. .
ANGIOTENSIN RECEPTOR BLOCKER						
Valsartan Mechanism: OATP1B inhibition by paritaprevir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ valsartan				Clinical monitoring and dose reduction is recommended when Viekirax with or without dasabuvir is coadministered with valsartan.
ANTIARRYTHMICS						
Digoxin 0.5 mg single dose Mechanism: P-gp	Viekirax + dasabuvir	↔ digoxin	1.15 (1.04-1.27)	1.16 (1.09-1.23)	1.01 (0.97-1.05)	While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.
		↔ ombitasvir	1.03 (0.97-1.10)	1.00 (0.98-1.03)	0.99 (0.96-1.02)	
		↔ paritaprevir	0.92 (0.80-1.06)	0.94 (0.81-1.08)	0.92 (0.82-1.02)	
		↔ dasabuvir	0.99 (0.92-1.07)	0.97 (0.91-1.02)	0.99 (0.92-1.07)	
	Viekirax	↑ digoxin	1.58	1.36	1.24	Decrease digoxin dose by

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
inhibition by paritaprevir, ritonavir and dasabuvir.	without dasabuvir		(1.43-1.73)	(1.21-1.54)	(1.07-1.43)	30-50%. Appropriate monitoring of serum digoxin levels is recommended.
		↔ ombitasvir r	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir				
Amiodarone Quinidine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ amiodarone ↑ quinidine				Concomitant use is contraindicated (see section 4.3).
ANTIBIOTICS (SYSTEMIC ADMINISTRATION)						
Clarithromycin Telithromycin Mechanism: CYP3A4/P-gp inhibition by clarithromycin and ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ clarithromycin ↑ telithromycin ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (see section 4.3)
Erythromycin Mechanism: CYP3A4/P-gp inhibition by erythromycin, paritaprevir, ritonavir and dasabuvir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ erythromycin ↑ paritaprevir ↑ dasabuvir				Administration of Viekirax with or without dasabuvir with erythromycin may result in increased concentrations of erythromycin and paritaprevir. Caution is advised.
Fusidic Acid Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ fusidic acid				Concomitant use is contraindicated (see section 4.3).
ANTICANCER AGENTS						
Enzalutamide Mitotane Mechanism: CYP3A4 induction enzalutamide or mitotane.	Viekirax with or without dasabuvir	Not studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
Imatinib	Viekirax	Not Studied. Expected:				Clinical monitoring and

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	with or without dasabuvir	↑ imatinib				lower doses of imatinib are recommended.
ANTICOAGULANTS						
Warfarin 5 mg single dose	Viekirax + dasabuvir	↔ R-warfarin	1.05 (0.95-1.17)	0.88 (0.81-0.95)	0.94 (0.84-1.05)	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalised ratio (INR) is recommended.
		↔ S-warfarin	0.96 (0.85-1.08)	0.88 (0.81-0.96)	0.95 (0.88-1.02)	
		↔ ombitasvir	0.94 (0.89-1.00)	0.96 (0.93-1.00)	0.98 (0.95-1.02)	
		↔ paritaprevir	0.98 (0.82-1.18)	1.07 (0.89-1.27)	0.96 (0.85-1.09)	
		↔ dasabuvir	0.97 (0.89-1.06)	0.98 (0.91-1.06)	1.03 (0.94-1.13)	
	Viekirax without dasabuvir	↔ R-warfarin	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ S-warfarin				
		↔ paritaprevir				
		↔ ombitasvir				
Dabigatran etexilate Mechanism: Intestinal P-gp inhibition by paritaprevir and ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ dabigatran etexilate				Viekirax without dasabuvir may increase the plasma concentrations of dabigatran etexilate. Use with caution.
ANTICONVULSANTS						
Carbamazepine 200 mg once daily followed by 200 mg twice daily Mechanism:	Viekirax + dasabuvir	↔ carbamazepine	1.10 (1.07-1.14)	1.17 (1.13-1.22)	1.35 (1.27-1.45)	Concomitant use is contraindicated (see section 4.3).
		↓ carbamazepine 10, 11-epoxide	0.84 (0.82-0.87)	0.75 (0.73-0.77)	0.57 (0.54-0.61)	
		↓ ombitasvir	0.69 (0.61-0.78)	0.69 (0.64-0.74)	NA	
		↓ paritaprevir	0.34 (0.25-0.48)	0.30 (0.23-0.38)	NA	
		↓ dasabuvir	0.45 (0.41-0.50)	0.30 (0.28-0.33)	NA	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
CYP3A4 induction by carbamazepine	Viekirax without dasabuvir	Not studied: similar effect expected as observed with Viekirax + dasabuvir.				
Phenobarbital Mechanism: CYP3A4 induction by phenobarbital.	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
Phenytoin Mechanism: CYP3A4 induction by phenytoin.	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
S-mephenytoin Mechanism: CYP2C19 induction by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↓ S-mephenytoin				Clinical monitoring and dose adjustment maybe needed for s-mephenytoin.
ANTIDEPRESSANTS						
Escitalopram 10 mg single dose	Viekirax + dasabuvir	↔ es-citalopram	1.00 (0.96-1.05)	0.87 (0.80-0.95)	NA	No dose adjustment is necessary for escitalopram.
		↑ S-Desmethyl citalopram	1.15 (1.10-1.21)	1.36 (1.03-1.80)	NA	
		↔ ombitasvir	1.09 (1.01-1.18)	1.02 (1.00-1.05)	0.97 (0.92-1.02)	
		↔ paritaprevir	1.12 (0.88-1.43)	0.98 (0.85-1.14)	0.71 (0.56-0.89)	
		↔ dasabuvir	1.10 (0.95-1.27)	1.01 (0.93-1.10)	0.89 (0.79-1.00)	
	Viekirax without dasabuvir	↓ es-citalopram	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ S-Desmethyl citalopram	1.17 (1.08-1.26)	1.07 (1.01-1.13)	NA	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔				

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
		paritaprevir				
Duloxetine 60 mg single dose	Viekirax + dasabuvir	↓ duloxetine	0.79 (0.67-0.94)	0.75 (0.67-0.83)	NA	No dose adjustment is necessary for duloxetine. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.98 (0.88-1.08)	1.00 (0.95-1.06)	1.01 (0.96-1.06)	
		↓ paritaprevir	0.79 (0.53-1.16)	0.83 (0.62-1.10)	0.77 (0.65-0.91)	
		↔ dasabuvir	0.94 (0.81-1.09)	0.92 (0.81-1.04)	0.88 (0.76-1.01)	
	Viekirax without dasabuvir	↔ duloxetine	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir	1.07 (0.63-1.81)	0.96 (0.70-1.32)	0.93 (0.76-1.14)	
Trazodone Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ trazodone				Trazodone should be used with caution and a lower dose of trazodone may be considered.
ANTI-DIURETIC HORMONE						
Conivaptan Mechanism: CYP3A4/P-gp inhibition by conivaptan and paritaprevir/ ritonavir/ombitasvir	Viekirax with or without dasabuvir	Not studied. Expected: ↑conivaptan ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (see section 4.3)
ANTIFUNGALS						
Ketoconazole 400 mg once daily Mechanism: CYP3A4/P-gp inhibition by ketoconazole and paritaprevir/ ritonavir/ ombitasvir	Viekirax with dasabuvir	↑ keto-conazole	1.15 (1.09-1.21)	2.17 (2.05-2.29)	NA	Concomitant use is contraindicated (see section 4.3)
		↔ ombitasvir	0.98 (0.90-1.06)	1.17 (1.11-1.24)	NA	
		↑ paritaprevir	1.37 (1.11-1.69)	1.98 (1.63-2.42)	NA	
		↑ dasabuvir	1.16 (1.03-1.32)	1.42 (1.26-1.59)	NA	
	Viekirax without dasabuvir	↑ keto-conazole	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.72 (1.32-2.26)	2.16 (1.76-2.66)	NA	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Itraconazole Posaconazole Mechanism: CYP3A4 and/or P-gp inhibition by itraconazole, posaconazole and paritaprevir/ ritonavir/ombitasvir	Viekirax + dasabuvir	Not Studied. Expected: ↑ itraconazole ↑ posaconazole ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (see section 4.3)
	Viekirax without dasabuvir					
Voriconazole Mechanism: CYP2C19 induction and CYP3A4 inhibition by ritonavir	Viekirax with or without dasabuvir	Not studied. Expected in CYP2C19 Extensive Metabolisers: ↓ voriconazole ↑ paritaprevir ↑ dasabuvir Not studied. Expected in CYP2C19 Poor Metabolisers: ↑ voriconazole ↑ dasabuvir ↑ paritaprevir				Concomitant use is contraindicated (see section 4.3).
ANTI-GOUT						
Colchicine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ colchicine				A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with Viekirax with or without dasabuvir is required. Use of colchicine is contraindicated with Viekirax with or without dasabuvir in patients with renal or hepatic impairment (see sections 4.3 and 4.4)
ANTIHISTAMINES						
Astemizole	Viekirax	Not Studied. Expected:				Concomitant use is

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Terfenadine Mechanism: CYP3A4 inhibition by ritonavir.	with or without dasabuvir	↑ astemizole/terfenadine				contraindicated (see section 4.3).
Fexofenadine Mechanism: OATP1B1 inhibition by paritaprevir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ fexofenadine				Caution should be used when Viekirax with or without dasabuvir is coadministered with fexofenadine.
ANTIHYPERLIPIDAEMICS						
Gemfibrozil 600 mg twice daily Mechanism: Increase in dasabuvir exposure is possibly due to CYP2C8 inhibition and increase in paritaprevir possibly due to OATP1B1 inhibition by gemfibrozil.	Paritaprevir/ritonavir + dasabuvir	↑ paritaprevir	1.21 (0.94-1.57)	1.38 (1.18-1.61)	NA	Concomitant use of Viekirax with dasabuvir is contraindicated (see section 4.3).
		↑ dasabuvir	2.01 (1.71-2.38)	11.25 (9.05-13.99)	NA	
	Viekirax without dasabuvir	Not studied; No interaction expected when gemfibrozil is used in combination with Viekirax without dasabuvir.				No dose adjustment of gemfibrozil is necessary. No dose adjustment needed for Viekirax.
ANTIMYCOBACTERIALS						
Rifampicin Mechanism: CYP3A4 induction by rifampicin.	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
ANTIPSYCHOTICS						
Pimozide Quetiapine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ pimozide,quetiapine				Concomitant use is contraindicated (see section 4.3).
ANTITPLATELET AGENTS						

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Ticagrelor Mechanism: CYP3A4 inhibition by ritonavir	Viekirax with or without dasabuvir	Not studied. Expected: ↑ ticagrelor				Concomitant use is contraindicated (see section 4.3).
CALCIUM CHANNEL BLOCKERS						
Amlodipine 5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax + dasabuvir	↑ amlodipine	1.26 (1.11-1.44)	2.57 (2.31-2.86)	NA	Decrease amlodipine dose by 50% and monitor patients for clinical effects.
		↔ ombitasvir	1.00 (0.95-1.06)	1.00 (0.97-1.04)	1.00 (0.97-1.04)	
		↓ paritaprevir	0.77 (0.64-0.94)	0.78 (0.68-0.88)	0.88 (0.80-0.95)	
		↔ dasabuvir	1.05 (0.97-1.14)	1.01 (0.96-1.06)	0.95 (0.89-1.01)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				
Diltiazem Verapamil Mechanism: CYP3A4/P-gp inhibition.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ diltiazem, verapamil ↑ paritaprevir ↑/↔ dasabuvir				Caution is advised due to the expected increase in paritaprevir exposures. Dose decrease and clinical monitoring of calcium channel blockers is recommended when co-administered with Viekirax with and without dasabuvir.
Nifedipine Mechanism: CYP3A4 inhibition	Viekirax with or without dasabuvir	Not studied. Expected: ↑ nifedipine				Dose decrease and clinical monitoring of calcium channel blockers is recommended when co-administered with Viekirax with and without dasabuvir.
CONTRACEPTIVES						
Ethinylestradiol/ norgestimate 0.035/0.25 mg once daily Mechanism: possibly due to UGT	Viekirax with or without dasabuvir	↔ ethinylestradiol	1.16 (0.90-1.50)	1.06 (0.96-1.17)	1.12 (0.94-1.33)	Ethinylestradiol-containing oral contraceptives are contraindicated (see section 4.3).
		Norgestimate metabolites:				
		↑ norgestrel	2.26 (1.91-2.67)	2.54 (2.09-3.09)	2.93 (2.39-3.57)	
		↑ nor-elgestromine	2.01 (1.77-2.29)	2.60 (2.30-2.95)	3.11 (2.51-3.85)	
		↔ ombitasvir	1.05 (0.81-1.35)	0.97 (0.81-1.15)	1.00 (0.88-1.12)	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
inhibition by paritaprevir, ombitasvir and dasabuvir.		↓ paritaprevir	0.70 (0.40-1.21)	0.66 (0.42-1.04)	0.87 (0.67-1.14)	
		↓ dasabuvir	0.51 (0.22-1.18)	0.48 (0.23-1.02)	0.53 (0.30-0.95)	
Nor-ethindrone (progestin only pill) 0.35 mg once daily	Viekirax + dasabuvir	↔ nor-ethindrone	0.83 (0.69-1.01)	0.91 (0.76-1.09)	0.85 (0.64-1.13)	No dose adjustment is necessary for norethindrone or Viekirax with or without dasabuvir.
		↔ ombitasvir	1.00 (0.93-1.08)	0.99 (0.94-1.04)	0.97 (0.90-1.03)	
		↑ paritaprevir	1.24 (0.95-1.62)	1.23 (0.96-1.57)	1.43 (1.13-1.80)	
		↔ dasabuvir	1.01 (0.90-1.14)	0.96 (0.85-1.09)	0.95 (0.80-1.13)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
DIURETICS						
Furosemide 20 mg single dose Mechanism: possibly due to UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	Viekirax + dasabuvir	↑ furosemide	1.42 (1.17-1.72)	1.08 (1.00-1.17)	NA	Patients should be monitored for clinical effects; a decrease in furosemide dose of up to 50% may be required. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	1.14 (1.03-1.26)	1.07 (1.01-1.12)	1.12 (1.08-1.16)	
		↔ paritaprevir	0.93 (0.63-1.36)	0.92 (0.70-1.21)	1.26 (1.16-1.38)	
		↔ dasabuvir	1.12 (0.96-1.31)	1.09 (0.96-1.23)	1.06 (0.98-1.14)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
ERGOT ALKALOIDS						
Ergotamine Dihydroergotamine Ergonovine Methylergometrine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ ergot derivatives				Concomitant use is contraindicated (see section 4.3).
GLUCOCORTICOIDS (INHALED)						
Fluticasone Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ fluticasone				Concomitant use of fluticasone can increase systemic exposures of fluticasone. Concomitant use of Viekirax and fluticasone particularly long-term use, should only

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
						be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4).
GASTROINTESTINAL PRODUCTS (PROPULSIVE)						
Cisapride Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ cisapride				Concomitant use is contraindicated (see section 4.3).
HERBAL PRODUCTS						
St. John's Wort (*hypericum perforatum*) Mechanism: CYP3A4 induction by St. John's Wort	Viekirax with or without dasabuvir	Not studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contraindicated (see section 4.3).
HIV ANTIVIRALS: PROTEASE INHIBITORS For a general comment on treatment of HIV co-infected patients, including a discussion on different antiretroviral regimens that may be used, please see section 4.4 (Treatment of HIV co-infected patients).						
Atazanavir 300 mg once daily (given at the same time) Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir.	Viekirax + dasabuvir	↔ atazanavir	0.91 (0.84-0.99)	1.01 (0.93-1.10)	0.90 (0.81-1.01)	The recommended dose of atazanavir is 300 mg, without ritonavir, in combination with Viekirax with dasabuvir. Atazanavir must be administered at the same time as Viekirax with dasabuvir. Ritonavir dose in Viekirax will provide atazanavir pharmacokinetic enhancement). No dose adjustment needed for Viekirax with dasabuvir. Treatment with atazanavir + Viekirax without dasabuvir is not recommended-(↑ paritaprevir).
		↓ ombitasvir	0.77 (0.70-0.85)	0.83 (0.74-0.94)	0.89 (0.78-1.02)	
		↑ paritaprevir	1.46 (1.06-1.99)	1.94 (1.34-2.81)	3.26 (2.06-5.16)	
		↔ dasabuvir	0.83 (0.71-0.96)	0.82 (0.71-0.94)	0.79 (0.66-0.94)	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
						The combination of atazanavir and Viekirax + dasabuvir increase bilirubin levels, in particular when ribavirin is part of the hepatitis C regimen (see sections 4.4 and 4.8).
	Viekirax without dasabuvir	↔ atazanavir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	2.74 (1.76-4.27)	2.87 (2.08-3.97)	3.71 (2.87-4.79)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
Atazanavir/ ritonavir 300/100 mg once daily (administered 12 hours apart) Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir and CYP3A by the additional dose of ritonavir.	Viekirax + dasabuvir	↔ atazanavir	1.02 (0.92-1.13)	1.19 (1.11-1.28)	1.68 (1.44-1.95)	
		↔ ombitasvir	0.83 (0.72-0.96)	0.90 (0.78-1.02)	1.00 (0.89-1.13)	
		↑ paritaprevir	2.19 (1.61-2.98)	3.16 (2.40-4.17)	11.95 (8.94-15.98)	
		↔ dasabuvir	0.81 (0.73-0.91)	0.81 (0.71-0.92)	0.80 (0.65-0.98)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				
Darunavir 800 mg once daily (given at the same time) Mechanism: Unknown	Viekirax + dasabuvir	↓ darunavir	0.92 (0.87-0.98)	0.76 (0.71-0.82)	0.52 (0.47-0.58)	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as Viekirax + dasabuvir (ritonavir dose in Viekirax will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of
		↔ ombitasvir	0.86 (0.77-0.95)	0.86 (0.79-0.94)	0.87 (0.82-0.92)	
		↑ paritaprevir	1.54 (1.14-2.09)	1.29 (1.04-1.61)	1.30 (1.09-1.54)	
		↔ dasabuvir	1.10 (0.88-1.37)	0.94 (0.78-1.14)	0.90 (0.76-1.06)	
	Viekirax without dasabuvir	↔ darunavir	0.99 (0.92-1.08)	0. 92 (0.84-1.00)	0.74 (0.63-0.88)	
		↔	The magnitude of interaction was similar			

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
		ombitasvir	to that observed with Viekirax + dasabuvir.			darunavir associated RAMs), see also section 4.4. No dose adjustment needed for Viekirax with dasabuvir. Darunavir combined with Viekirax + dasabuvir is not recommended in patients with extensive PI resistance. Treatment with darunavir + Viekirax without dasabuvir is not recommended-(↑ paritaprevir).
		↑ paritaprevir	2.09 (1.35-3.24)	1.94 (1.36-2.75)	1.85 (1.41-2.42)	
Darunavir/ ritonavir 600/100 mg twice daily Mechanism: Unknown	Viekirax + dasabuvir	↔ darunavir	0.87 (0.79-0.96)	0.80 (0.74-0.86)	0.57 (0.48-0.67)	
		↓ ombitasvir	0.76 (0.65-0.88)	0.73 (0.66-0.80)	0.73 (0.64-0.83)	
		↓ paritaprevir	0.70 (0.43-1.12)	0.59 (0.44-0.79)	0.83 (0.69-1.01)	
		↓ dasabuvir	0.84 (0.67-1.05)	0.73 (0.62-0.86)	0.54 (0.49-0.61)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
darunavir/ ritonavir 800/100 mg once daily (administered 12 hours apart) Mechanism: Unknown	Viekirax + dasabuvir	↑ darunavir	0.79 (0.70-0.90)	1.34 (1.25-1.43)	0.54 (0.48-0.62)	
		↔ ombitasvir	0.87 (0.82-0.93)	0.87 (0.81-0.93)	0.87 (0.80-0.95)	
		↓ paritaprevir	0.70 (0.50-0.99)	0.81 (0.60-1.09)	1.59 (1.23-2.05)	
		↓ dasabuvir	0.75 (0.64-0.88)	0.72 (0.64-0.82)	0.65 (0.58-0.72)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				
Lopinavir / ritonavir	Viekirax + dasabuvir	↔ lopinavir	0.87 (0.76-0.99)	0.94 (0.81-1.10)	1.15 (0.93-1.42)	Concomitant use is contraindicated (see

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
400/100 mg twice daily[1] Mechanism: Increase in paritaprevir exposures may be due to inhibition of CYP3A/efflux transporters by lopinavir and higher dose of ritonavir		↔ ombitasvir	1.14 (1.01-1.28)	1.17 (1.07-1.28)	1.24 (1.14-1.34)	section 4.3).
		↑ paritaprevir	2.04 (1.30-3.20)	2.17 (1.63-2.89)	2.36 (1.00-5.55)	
		↔ dasabuvir	0.99 (0.75-1.31)	0.93 (0.75-1.15)	0.68 (0.57-0.80)	
	Viekirax without dasabuvir	↔ lopinavir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	4.76 (3.54-6.39)	6.10 (4.30-8.67)	12.33 (7.30-20.84)	
Indinavir Saquinavir Tipranavir Mechanism: CYP3A4 inhibition by protease inhibitors.	Viekirax with or without dasabuvir	Not studied. Expected ↑ paritaprevir				Concomitant use is contraindicated (see section 4.3).
HIV ANTIVIRALS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS						
Rilpivirine[2] 25 mg once daily administered in the morning, with food Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax + dasabuvir	↑ rilpivirine	2.55 (2.08-3.12)	3.25 (2.80-3.77)	3.62 (3.12-4.21)	Co-administration of Viekirax with rilpivirine once daily should only be considered in patients without known QT-prolongation, and without other QT-prolongation co-medications. If the combination is used, repeated ECG-monitoring should be done, see section 4.4. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	1.11 (1.02-1.20)	1.09 (1.04-1.14)	1.05 (1.01-1.08)	
		↑ paritaprevir	1.30 (0.94-1.81)	1.23 (0.93-1.64)	0.95 (0.84-1.07)	
		↔ dasabuvir	1.18 (1.02-1.37)	1.17 (0.99-1.38)	1.10 (0.89-1.37)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/300/200 mg once daily Mechanism: possible CYP3A4 induction by efavirenz.	Viekirax with or without dasabuvir	Co-administration of efavirenz (enzyme inducer) based regimens with paritaprevir/ritonavir + dasabuvir resulted in ALT elevations and therefore, early discontinuation of the study.				Concomitant use with efavirenz is contraindicated (see section 4.3).
Nevirapine etravirine	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contra-indicated (see section 4.3)
HIV ANTIVIRALS: INTEGRASE STRAND TRANSFER INHIBITOR						
Raltegravir 400 mg twice daily Mechanism: Increase in raltegravir exposures may be due to UGT1A1 inhibition by paritaprevir, ombitasvir. and dasabuvir	Viekirax + dasabuvir	↑ raltegravir	2.33 (1.66-3.27)	2.34 (1.70-3.24)	2.00 (1.17-3.42)	No dose adjustment is necessary for raltegravir or Viekirax with or without dasabuvir.
		No clinically relevant changes in dasabuvir, paritaprevir and ombitasvir exposures (based on comparison with historical data) were observed during co-administration.				
	Viekirax without dasabuvir	↑ raltegravir	1.22 (0.78-1.89)	1.20 (0.74-1.95)	1.13 (0.51-2.51)	
		No clinically relevant changes in dasabuvir, paritaprevir and ombitasvir exposures (based on comparison with historical data) were observed during co-administration.				
HIV ANTIVIRALS: NUCLEOSIDE INHIBITORS						
Em-tricitabine/ tenofovir 200 mg once daily/300 mg once daily	Viekirax + dasabuvir	↔ em-tricitabine	1.05 (1.00-1.12)	1.07 (1.00-1.14)	1.09 (1.01-1.17)	No dose adjustment is necessary for emtricitabine/tenofovir and Viekirax with or without dasabuvir.
		↔ tenofovir	1.07 (0.93-1.24)	1.13 (1.07-1.20)	1.24 (1.13-1.36)	
		↔ ombitasvir	0.89 (0.81-0.97)	0.99 (0.93-1.05)	0.97 (0.90-1.04)	
		↓ paritaprevir	0.68 (0.42-1.11)	0.84 (0.59-1.17)	1.06 (0.83-1.35)	
		↔ dasabuvir	0.85 (0.74-0.98)	0.85 (0.75-0.96)	0.85 (0.73-0.98)	
	Viekirax without	↔ em-tricitabine	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
	dasabuvir	↔ tenofovir	0.80 (0.71-0.90)	1.01 (0.96-1.07)	1.13 (1.06-1.21)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir	1.02 (0.63-1.64)	1.04 (0.74-1.47)	1.09 (0.88-1.35)	
HIV ANTIVIRALS: PHARMACOKINETIC ENHANCER						
Cobicistat-containing regimens Mechanism: CYP3A4 inhibition by cobicistat	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ ombitasvir ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (See section 4.3)
HMG CoA REDUCTASE INHIBITOR						
Rosuvastatin 5 mg once daily Mechanism: OATP1B inhibition by paritaprevir and BCRP inhibition by paritaprevir, ritonavir or dasabuvir.	Viekirax + dasabuvir	↑ rosuvastatin	7.13 (5.11-9.96)	2.59 (2.09-3.21)	0.59 (0.51-0.69)	The maximum daily dose of rosuvastatin should be 5 mg (see section 4.4). No dose adjustment needed for Viekirax with dasabuvir
		↔ ombitasvir	0.92 (0.82-1.04)	0.89 (0.83-0.95)	0.88 (0.83-0.94)	
		↑ paritaprevir	1.59 (1.13-2.23)	1.52 (1.23-1.90)	1.43 (1.22-1.68)	
		↔ dasabuvir	1.07 (0.92-1.24)	1.08 (0.92-1.26)	1.15 (1.05-1.25)	
	Viekirax without dasabuvir	↑ rosuvastatin	2.61 (2.01-3.39)	1.33 (1.14-1.56)	0.65 (0.57-0.74)	The maximum daily dose of rosuvastatin should be 10 mg (see section 4.4). No dose adjustment needed for Viekirax.
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.40 (1.12-1.74)	1.22 (1.05-1.41)	1.06 (0.85-1.32)	
Pravastatin 10 mg once daily Mechanism: OATP1B1 inhibition by paritaprevir.	Viekirax+ dasabuvir	↑ pravastatin	1.37 (1.11-1.69)	1.82 (1.60-2.08)	NA	Reduce pravastatin dose by 50%. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.95 (0.89-1.02)	0.89 (0.83-0.95)	0.94 (0.89-0.99)	
		↔ dasabuvir	1.00 (0.87-1.14)	0.96 (0.85-1.09)	1.03 (0.91-1.15)	
		↔ paritaprevir	0.96 (0.69-1.32)	1.13 (0.92-1.38)	1.39 (1.21-1.59)	
	Viekirax without dasabuvir	↑ pravastatin	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.44 (1.15-1.81)	1.33 (1.09-1.62)	1.28 (0.83-1.96)	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Fluvastatin Mechanism: OATP1B/BCRP inhibition by paritaprevir Pitavastatin Mechanism: OATP1B inhibition by paritaprevir	Viekirax with or without dasabuvir	Not studied. Expected: ↑ fluvastatin ↑ pitavastatin				Concomitant use with fluvastatin and pitavastatin is not recommended (see section 4.4). A temporary suspension of fluvastatin and pitavastatin is recommended for the duration of treatment with Viekirax. If statin treatment is required during the treatment period, a switch to dose reduced pravastatin or rosuvastatin is possible.
Lovastatin Simvastatin atorvastatin Mechanism: CYP3A4/OATP1B inhibition	Viekirax with or without dasabuvir	Not studied. Expected: ↑ lovastatin, simvastatin, atorvastatin				Concomitant use is contraindicated (see section 4.3).
IMMUNOSUPPRESSANTS						
Ciclosporin 30 mg once daily single dose[3] Mechanism: Effect on ciclosporin is due to CYP3A4 inhibition by ritonavir and increase in paritaprevir exposures may be due to OATP/BCRP/P-gp inhibition by ciclosporin.	Viekirax + dasabuvir	↑ ciclosporin	1.01 (0.85-1.20)	5.82 (4.73-7.14)	15.8 (13.8-18.09)	When starting co-administration with Viekirax, give one fifth of the total daily dose of ciclosporin once daily with Viekirax. Monitor ciclosporin levels and adjust dose and/or dosing frequency as needed. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.99 (0.92-1.07)	1.08 (1.05-1.11)	1.15 (1.08-1.23)	
		↑ paritaprevir	1.44 (1.16-1.78)	1.72 (1.49-1.99)	1.85 (1.58-2.18)	
		↓ dasabuvir	0.66 (0.58-0.75)	0.70 (0.65-0.76)	0.76 (0.71-0.82)	
	Viekirax without dasabuvir	↑ ciclosporin	0.83 (0.72-0.94)	4.28 (3.66-5.01)	12.8 (10.6-15.6)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.39 (1.10-1.75)	1.46 (1.29-1.64)	1.18 (1.08-1.30)	
Tacrolimus	Viekirax +	↑ tacrolimus	3.99	57.1	16.6	When starting co-

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
2 mg single dose[4] Mechanism: Effect on tacrolimus is due to CYP3A4 inhibition by ritonavir.	dasabuvir		(3.21-4.97)	(45.5-71.7)	(13.0-21.2)	administration with Viekirax, administer 0.5 mg tacrolimus once every week. Monitor tacrolimus levels and adjust dose and/or dosing frequency as needed. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.93 (0.88-0.99)	0.94 (0.89-0.98)	0.94 (0.91-0.96)	
		↓ paritaprevir	0.57 (0.42-0.78)	0.66 (0.54-0.81)	0.73 (0.66-0.80)	
		↔ dasabuvir	0.85 (0.73-0.98)	0.90 (0.80-1.02)	1.01 (0.91-1.11)	
	Viekirax without dasabuvir	↑ tacrolimus	4.27 (3.49-5.22)	85.8 (67.9-108)	24.6 (19.7-30.8)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↓ paritaprevir				
INHALED BETA AGONISTS						
Salmeterol Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ salmeterol				Concomitant use is contraindicated (see section 4.3).
INSULIN SECRETAGOGUES						
Repaglinide Mechanism: OATP1B1 inhibition by paritaprevir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ repaglinide				Caution should be used and dose decrease may be needed for repaglinide when administered with Viekirax with or without dasabuvir.
OPIOIDS						
Methadone 20-120 mg once daily[5]	Viekirax + dasabuvir	↔ R-Methadone	1.04 (0.98-1.11)	1.05 (0.98-1.11)	0.94 (0.87-1.01)	No dose adjustment is necessary for methadone and Viekirax with or without dasabuvir.
		↔ S-Methadone	0.99 (0.91-1.08)	0.99 (0.89-1.09)	0.86 (0.76-0.96)	
		↔ paritaprevir/ombitasvir/dasabuvir (based on the cross-study comparison)				
	Viekirax without dasabuvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.				
Buprenorphine	Viekirax + dasabuvir	↑ buprenorphine	2.18 (1.78-2.68)	2.07 (1.78-2.40)	3.12 (2.29-4.27)	No dose adjustment is necessary for buprenorphine/naloxone
		↑ norbu-	2.07	1.84	2.10	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
/ naloxone 4-24 mg/1-6 mg once daily[5] Mechanism: CYP3A4 inhibition by ritonavir and UGT inhibition by paritaprevir, ombitasvir and dasabuvir.		prenorphine	(1.42-3.01)	(1.30-2.60)	(1.49-2.97)	and Viekirax with or without dasabuvir.
		↑ naloxone	1.18 (0.81-1.73)	1.28 (0.92-1.79)	NA	
		↔ ombitasvir/paritaprevir/dasabuvir (based on the cross-study comparison)				
	Viekirax without dasabuvir	↑ bu-prenorphine	1.19 (1.01-1.40)	1.51 (1.27-1.78)	1.65 (1.30-2.08)	
		↑ norbu-prenorphine	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ naloxone				
		↔ ombitasvir/paritaprevir (based on the cross-study comparison)				
PHOSPHODIESTERASE-(PDE-5) INHIBITORS						
Sildenafil (when used for treatment of pulmonary hypertension) Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with and without dasabuvir	Not studied. Expected: ↑ sildenafil				Concomitant use is contraindicated (see section 4.3).
PROTON PUMP INHIBITORS						
Omeprazole 40 mg once daily Mechanism: CYP2C19 induction by ritonavir.	Viekirax + dasabuvir	↓ omeprazole	0.62 (0.48-0.80)	0.62 (0.51-0.75)	NA	If clinically indicated higher doses of omeprazole should be used. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	1.02 (0.95-1.09)	1.05 (0.98-1.12)	1.04 (0.98-1.11)	
		↔ paritaprevir	1.19 (1.04-1.36)	1.18 (1.03-1.37)	0.92 (0.76-1.12)	
		↔ dasabuvir	1.13 (1.03-1.25)	1.08 (0.98-1.20)	1.05 (0.93-1.19)	
	Viekirax without dasabuvir	↓ omeprazole	0.48 (0.29-0.78)	0.46 (0.27-0.77)	NA	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir				
Esomeprazole Lansoprazole Mechanism:	Viekirax with and without dasabuvir	Not studied. Expected: ↓ esomeprazole, lansoprazole				If clinically indicated, higher doses of esomeprazole/lansoprazole may be needed.

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
CYP2C19 induction by ritonavir.						
SEDATIVES / HYPNOTICS						
Zolpidem 5 mg single dose	Viekirax + dasabuvir	↔ zolpidem	0.94 (0.76-1.16)	0.95 (0.74-1.23)	NA	No dose adjustment is necessary for zolpidem. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	1.07 (1.00-1.15)	1.03 (1.00-1.07)	1.04 (1.00-1.08)	
		↓ paritaprevir	0.63 (0.46-0.86)	0.68 (0.55-0.85)	1.23 (1.10-1.38)	
		↔ dasabuvir	0.93 (0.84-1.03)	0.95 (0.84-1.08)	0.92 (0.83-1.01)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
Alprazolam 0.5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir	Viekirax + dasabuvir	↑ alprazolam	1.09 (1.03-1.15)	1.34 (1.15-1.55)	NA	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.98 (0.93-1.04)	1.00 (0.96-1.04)	0.98 (0.93-1.04)	
		↔ paritaprevir	0.91 (0.64-1.31)	0.96 (0.73-1.27)	1.12 (1.02-1.23)	
		↔ dasabuvir	0.93 (0.83-1.04)	0.98 (0.87-1.11)	1.00 (0.87-1.15)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
Oral midazolam Triazolam Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ midazolam or triazolam				Concomitant use is contraindicated (see section 4.3). If parenteral midazolam is co-administered with Viekirax with or without dasabuvir, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
THYROID HORMONES						
Levothyroxine Mechanism: UGT1A1 inhibition by paritaprevir,	Viekirax with or without dasabuvir	Not studied. Expected: ↑ levothyroxine				Clinical monitoring and dose adjustment may be required for levothyroxine

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
ombitasvir and dasabuvir.						

1. Lopinavir/ritonavir 800/200 mg once daily (administered in the evening) was also administered with Viekirax with or without dasabuvir. The effect on C_{max} and AUC of DAAs and lopinavir was similar to that observed when lopinavir/ritonavir 400/100 mg twice daily was administered with Viekirax with or without dasabuvir.
2. Rilpivirine was also administered in the evening with food and at night 4 hours after dinner with Viekirax + dasabuvir in other two arms in the study. The effect on rilpivirine exposures was similar to that observed when rilpivirine was administered in the morning with food with Viekirax + dasabuvir (shown in the table above).
3. Ciclosporin 100 mg dosed alone, 10 mg administered with Viekirax and 30 mg administered with Viekirax + dasabuvir. Dose normalized cyclosporine ratios are shown for interaction with Viekirax with or without dasabuvir.
4. Tacrolimus 2 mg was dosed alone and Tacrolimus 0.5 mg was administered with Viekirax and 2 mg was administered with Viekirax + dasabuvir. Dose normalized tacrolimus ratios are shown for interaction with Viekirax with or without dasabuvir.
5. Dose normalised parameters reported for methadone, buprenorphine and naloxone.

Note: Doses used for Viekirax and dasabuvir were: ombitasvir 25 mg, paritaprevir 150 mg, ritonavir 100 mg, once daily and dasabuvir 400 mg twice daily or 250 mg twice daily. The dasabuvir exposures obtained with the 400 mg formulation and the 250 mg tablet are similar. Viekirax with or without dasabuvir was administered as multiple doses in all the drug interaction studies except the drug interaction studies with carbamazepine, gemfibrozil and ketoconazole.

Paediatric population

Drug interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when Viekirax is taken in combination with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Women of childbearing potential and their male partners should not receive ribavirin unless they are using an effective form of contraception during treatment with ribavirin and for 6 months after treatment. Ethinylestradiol is contraindicated in combination with Viekirax (see sections 4.3 and 4.4).

Pregnancy

There are very limited data from the use of Viekirax in pregnant women. Studies with ombitasvir and paritaprevir/ritonavir in animals have shown malformations (see section 5.3). The potential risk for

humans is unknown. Viekirax should not be used during pregnancy or in women of childbearing potential not using effective contraception.

If ribavirin is co-administered with Viekirax, the contraindications regarding use of ribavirin during pregnancy apply (see also the Summary of Product Characteristics of ribavirin).

Breast-feeding

It is not known whether paritaprevir /ritonavir or ombitasvir and their metabolites are excreted in human breast milk. Available pharmacokinetic data in animals have shown excretion of active substance and metabolite in milk (see section 5.3). Because of the potential for adverse reactions from the medicinal product in breastfed infants, a decision must be made whether to discontinue breast-feeding or discontinue treatment with Viekirax, taking into account the importance of the therapy to the mother. For patients co-administered ribavirin refer to the Summary of Product Characteristics of ribavirin.

Fertility

No human data on the effect of Viekirax on fertility are available. Animal studies do not indicate harmful effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue has been reported during treatment with Viekirax in combination with dasabuvir and ribavirin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety summary is based on pooled data from phase 2 and 3 clinical trials in more than 2,600 subjects who received Viekirax and dasabuvir with or without ribavirin.

Viekirax and dasabuvir with ribavirin in subjects with genotype 1 hepatitis C infection (including subjects with compensated cirrhosis)

In subjects receiving Viekirax and dasabuvir with ribavirin, the most commonly reported adverse reactions (greater than 20% of subjects) were fatigue and nausea. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.2% (5/2,044). 0.2% (5/2,044) of subjects interrupted treatment due to adverse reactions. 4.8% (99/2,044) of subjects had ribavirin dose reductions due to adverse reactions.

With the exception of increased rates of transient hyperbilirubinemia, the safety profile of Viekirax and dasabuvir with ribavirin in subjects with compensated cirrhosis was similar to that of subjects without cirrhosis.

Viekirax and dasabuvir without ribavirin in subjects with genotype 1 hepatitis C infection

No subjects permanently discontinued treatment or had treatment interruptions due to adverse reactions.

Tabulated list of adverse reactions

Table 3 lists adverse reactions for which a causal relationship between paritaprevir/ombitasvir/ritonavir, in combination with dasabuvir and/or ribavirin, and the adverse event is at least a reasonable possibility. The

majority of adverse reactions presented in Table 3 were of grade 1 severity in Viekirax and dasabuvir-containing regimens.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000).

Table 3. Adverse drug reactions identified with Viekirax in combination with dasabuvir with and without ribavirin

Frequency	**Viekirax + dasabuvir + ribavirin* N = 2,044**	**Viekirax + dasabuvir N = 588**
Blood and lymphatic system disorders		
Common	Anaemia	
Psychiatric disorders		
Very common	Insomnia	
Gastrointestinal disorders		
Very common	Nausea	
Skin and subcutaneous tissue disorders		
Very common	Pruritus	
Common		Pruritus
General disorders and administration and administration site conditions		
Very common	Asthenia Fatigue	

*Data set includes all genotype 1-infected subjects in Phase 2 and 3 trials including subjects with cirrhosis.
Note: For laboratory abnormalities, refer to Table 4

Description of selected adverse reactions

Laboratory abnormalities

Changes in selected laboratory parameters are described in Table 4. A side-by-side tabulation is shown to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

Table 4. Selected treatment emergent laboratory abnormalities

Laboratory Parameters	SAPPHIRE I and II Viekirax and dasabuvir + ribavirin 12 weeks N = 770 n (%)	PEARL II, III, and IV Viekirax and dasabuvir 12 weeks N = 509 n (%)	TURQUOISE II (subjects with cirrhosis) Viekirax and dasabuvir + ribavirin 12 or 24 weeks N = 380 n (%)
ALT			
>5-20 × ULN* (Grade 3)	6/765 (0.8%)	1/509 (0.2%)	4/380 (1.1%)
>20 × ULN (Grade 4)	3/765 (0.4%)	0	2/380 (0.5%)
Haemoglobin			
<100-80 g/L (grade 2)	41/765 (5.4%)	0	30/380 (7.9%)
<80-65 g/L (grade 3)	1/765 (0.1%)	0	3/380 (0.8%)
<65 g/L (Grade 4)	0	0	1/380 (0.3%)
Total bilirubin			
>3-10 × ULN (grade 3)	19/765 (2.5%)	2/509 (0.4%)	37/380 (9.7%)
>10 × ULN (grade 4)	1/765 (0.1%)	0	0
*ULN: Upper limit of normal according to testing laboratory.			

Serum ALT elevations

In a pooled analysis of clinical trials with Viekirax and dasabuvir with and without ribavirin, 1% of subjects experienced serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. As the incidence of such elevations was 26% among women taking a concomitant ethinylestradiol-containing medicinal product, such medicinal products are contraindicated with Viekirax with or without dasabuvir. No increase in incidence of ALT elevations was observed with other types of estrogens commonly used for hormone replacement therapy (e.g. estradiol and conjugated estrogens). 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. Two patients discontinued Viekirax and dasabuvir due to elevated ALT, including one on ethinylestradiol. Three interrupted Viekirax and dasabuvir for one to seven days, including one on ethinylestradiol. The majority of these ALT elevations were transient and assessed as drug-related. Elevations in ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT (see section 4.4).

Serum bilirubin elevations

Transient elevations in serum bilirubin (predominantly indirect) were observed in subjects receiving Viekirax and dasabuvir with ribavirin, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced haemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with aminotransferase elevations. The frequency of indirect bilirubin elevations was lower among subjects who did not receive ribavirin.

Liver transplant recipients

The overall safety profile in HCV-infected transplant recipients who were administered Viekirax and dasabuvir and ribavirin (in addition to their immunosuppressant medications) was similar to subjects treated with Viekirax and dasabuvir and ribavirin in phase 3 clinical trials, although some adverse

reactions were increased in frequency. 10 subjects (29.4%) had at least one post baseline haemoglobin value of less than 10 g/dL. 10 of 34 subjects (29.4%) dose modified ribavirin due to decrease in haemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates. 5 subjects required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion.

HIV/HCV co-infected patients

The overall safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. Transient elevations in total bilirubin >3 x ULN (mostly indirect) occurred in 17 (27.0%) subjects; 15 of these subjects were receiving atazanavir. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases.

Paediatric population

The safety of Viekirax in children and adolescents aged < 18 years has not yet been established. No data are available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest documented single dose administered to healthy volunteers was 400 mg for paritaprevir (with 100 mg ritonavir), 200 mg for ritonavir (with 100 mg paritaprevir) and 350 mg for ombitasvir. No study related adverse reactions with paritaprevir, ritonavir, or ombitasvir were observed. Transient increases in indirect bilirubin were observed at the highest doses of paritaprevir/ritonavir. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct-acting antivirals, ATC code: not yet assigned

Mechanism of action

Viekirax, when co-administered with dasabuvir, combines three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle. Refer to the Summary of Product Characteristics of dasabuvir for its pharmacological properties.

Ritonavir

Ritonavir is not active against HCV. Ritonavir is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir.

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication.

Paritaprevir

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

Activity in cell culture and/or biochemical studies

Ombitasvir

The EC_{50} of ombitasvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 14.1 and 5 pM, respectively. The activity of ombitasvir was attenuated 11- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of ombitasvir against replicons containing NS5A from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.66 pM (range 0.35 to 0.88 pM; n=11) and 1.0 pM (range 0.74 to 1.5 pM; n=11), respectively. Ombitasvir has EC_{50} values of 12, 4.3, 19, 1.7, 3.2, and 366 pM against replicon cell lines constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 5a, and 6a, respectively.

Paritaprevir

The EC_{50} of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay was 1.0 and 0.21 nM, respectively. The activity of paritaprevir was attenuated 24 to 27 -fold in the presence of 40% human plasma. The mean EC_{50} of paritaprevir against replicons containing NS3 from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.86 nM (range 0.43 to 1.87 nM; n=11) and 0.06 nM (range 0.03 to 0.09 nM; n=9), respectively. Paritaprevir had an EC_{50} value of 5.3 nM against the 2a-JFH-1 replicon cell line, and EC_{50} values of 19, 0.09, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, and 6a, respectively
Ritonavir did not exhibit a direct antiviral effect on the replication of HCV subgenomic replicons, and the presence of ritonavir did not affect the *in vitro* antiviral activity of paritaprevir.

Resistance

In cell culture

Genotype 1

Resistance to paritaprevir and ombitasvir conferred by variants in NS3 and NS5A respectively, selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterised in the appropriate genotype 1a or 1b replicons.

In genotype 1a, substitutions F43L, R155K, A156T, and D168A/F/H/V/Y in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1a replicon, the activity of paritaprevir was reduced 20-, 37-, and 17-fold by the F43L, R155K and A156T substitutions, respectively. The activity of paritaprevir was reduced 96-fold by D168V, and 50- to 219-fold by each of the other D168 substitutions. The activity of paritaprevir in genotype 1a was not significantly affected (less than or equal to 3-fold) by single substitutions V36A/M, V55I, Y56H, Q80K or E357K. Double variants including combinations of V36LM, F43L, Y56H, Q80K or E357K with R155K or with a D168 substitution reduced the activity of paritaprevir by an additional 2 to 3-fold relative to the single R155K or D168 substitution. In the genotype

1b replicon, the activity of paritaprevir was reduced 76- and 159-and 337- fold by D168A, D168H, D168V, and D168Y respectively. Y56H alone could not be evaluated due to poor replication capacity, however, the combination of Y56H and D168A/V/Y reduced the activity of paritaprevir by 700- to 4118-fold.

In genotype 1a, substitutions M28T/V, Q30E/R, L31V, H58D, Y93C/H/N, and M28V + Q30R in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1a replicon, the activity of ombitasvir was reduced by 896-, 58- and 243-fold against the M28T/V and H58D substitutions, respectively, and 1326-, 800-, 155-foldand 1675- to 66740- fold by the Q30E/R, L31V and Y93C/H/N substitutions, respectively. Y93H, Y93N or M28V in combination with Q30R reduced the activity of ombitasvir by more than 42,802-fold. In genotype 1b, substitutions L28T, L31F/V, as well as Y93H alone or in combination with L28M, R30Q, L31F/M/V or P58S in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1b replicon, the activity of ombitasvir was reduced by less than 10-fold by variants at amino acid positions 30 and 31. The activity of ombitasvir was reduced by 661-, 77-, 284- and 142-fold against the genotype 1b substitutions L28T, Y93H, R30Q in combination with Y93H, and L31M in combination with Y93H, respectively. All other double substitutions of Y93H in combination with substitutions at positions 28, 31, or 58 reduced the activity of ombitasvir by more than 400-fold.

Genotype 4

In genotype 4a, resistance to paritaprevir or ombitasvir by variants in NS3 or NS5A, respectively, selected in cell culture were phenotypically characterised. Substitutions R155C, A156T/V, and D168H/V in HCV NS3 reduced susceptibility to paritaprevir by 40- to 323-fold. Substitution L28V in HCV NS5A reduced the susceptibility to ombitasvir by 21-fold.

Effect of baseline HCV substitutions/polymorphisms on treatment outcome

A pooled analysis of subjects with genotype 1 HCV infection, who were treated with ombitasvir, paritaprevir, and dasabuvir (a non-nucleotide NS5B inhibitor) with or without ribavirin in the Phase 2b and 3 clinical trials was conducted to explore the association between baseline NS3/4A, NS5A or NS5B substitutions/polymorphisms and treatment outcome in recommended regimens.

In the greater than 500 genotype 1a baseline samples in this analysis, the most frequently observed resistance-associated variants were M28V (7.4%) in NS5A and S556G (2.9%) in NS5B. Q80K, although a highly prevalent polymorphism in NS3 (41.2% of samples), confers minimal resistance to paritaprevir. Resistance-associated variants at amino acid positions R155 and D168 in NS3 were rarely observed (less than 1%) at baseline. In the greater than 200 genotype 1b baseline samples in this analysis, the most frequently observed resistance-associated variants observed were Y93H (7.5%) in NS5A, and C316N (17.0%) and S556G (15%) in NS5B. Given the low virologic failure rates observed with recommended treatment regimens for HCV genotype 1a- and 1b-infected subjects, the presence of baseline variants appears to have little impact on the likelihood of achieving SVR.

In clinical studies

Of the 2,510 HCV genotype 1 infected subjects who were treated with regimens containing ombitasvir, paritaprevir, and dasabuvir with or without ribavirin (for 8, 12, or 24 weeks) in Phase 2b and 3 clinical trials, a total of 74 subjects (3%) experienced virologic failure (primarily post-treatment relapse). Treatment-emergent variants and their prevalence in these virologic failure populations are shown in Table 5. In the 67 genotype 1a infected subjects, NS3 variants were observed in 50 subjects, NS5A variants were observed in 46 subjects, NS5B variants were observed in 37 subjects, and treatment-emergent variants were seen in all 3 drug targets in 30 subjects. In the 7 genotype 1b infected subjects, treatment-emergent variants were observed in NS3 in 4 subjects, in NS5A in 2 subjects, and in both NS3

and NS5A in 1 subject. No genotype 1b infected subjects had treatment-emergent variants in all 3 drug targets.

Table 5. Treatment-emergent amino acid substitutions in the pooled analysis of Viekirax and dasabuvir with and without RBV regimens in Phase 2b and Phase 3 clinical trials (N=2510)

Target	Emergent amino acid substitutions[a]	Genotype 1a N=67[b] % (n)	Genotype 1b N=7 % (n)
NS3	V55I[c]	6 (4)	--
	Y56H[c]	9 (6)	42.9 (3)[d]
	I132V[c]	6 (4)	--
	R155K	13.4 (9)	--
	D168A	6 (4)	--
	D168V	50.7 (34)	42.9 (3)[d]
	D168Y	7.5 (5)	--
	V36A[c], V36M[c], F43L[c], D168H, E357K[c]	< 5%	--
NS5A	M28T	20.9 (14)	--
	M28V[e]	9 (6)	--
	Q30R[e]	40.3 (27)	--
	Y93H		28.6 (2)
	H58D, H58P, Y93N	< 5%	--
NS5B	A553T	6.1 (4)	--
	S556G	33.3 (22)	--
	C316Y, M414T, G554S, S556R, G558R, D559G, D559N, Y561H	< 5%	--

a. Observed in at least 2 subjects of the same subtype.
b. N=66 for the NS5B target.
c. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.
d. Observed in combination in genotype 1b-infected subjects.
e. Observed in combination in 6% (4/67) of the subjects.

Note: The following variants were selected in cell culture but were not treatment-emergent: NS3 variants A156T in genotype 1a, and R155Q and D168H in genotype 1b; NS5A variants Y93C/H in genotype 1a, and L31F/V or Y93H in combination with L28M, L31F/V or P58S in genotype 1b; and NS5B variants Y448H in genotype 1a, and M414T and Y448H in genotype 1b.

Persistence of resistance-associated substitutions

The persistence of paritaprevir, ombitasvir, and dasabuvir resistance-associated amino acid substitutions in NS3, NS5A, and NS5B, respectively, was assessed in genotype 1a-infected subjects in Phase 2b trials. Paritaprevir treatment-emergent variants V36A/M, R155K or D168V were observed in NS3 in 47 subjects. Ombitasvir treatment-emergent variants M28T, M28V or Q30R in NS5A were observed in 32 subjects. Dasabuvir treatment-emergent variants M414T, G554S, S556G, G558R or D559G/N in NS5B were observed in 34 subjects.

NS3 variants V36A/M and R155K and NS5B variants M414T and S556G remained detectable at post-treatment Week 48, whereas NS3 variant D168V and all other NS5B variants were not observed at post-treatment Week 48. All treatment-emergent variants in NS5A remained detectable at post-treatment Week 48. Due to high SVR rates in genotype 1b, trends in persistence of treatment-emergent variants in this genotype could not be established.

The lack of detection of virus containing a resistance-associated substitution does not indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the

emergence or persistence of virus containing Viekirax- and dasabuvir-resistance-associated substitutions on future treatment is unknown.

Cross-resistance

Cross-resistance is expected among NS5A inhibitors, NS3/4A protease inhibitors, and non-nucleoside NS5B inhibitors by class. The impact of prior ombitasvir, paritaprevir or dasabuvir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied.

Clinical efficacy and safety

Clinical studies in subjects with genotype 1 hepatitis C infection

The efficacy and safety of Viekirax in combination with dasabuvir with and without ribavirin was evaluated in six randomised Phase 3 clinical trials, including one trial exclusively in subjects with cirrhosis (Child-Pugh A), in over 2,300 subjects with genotype 1 chronic hepatitis C infection as summarised in Table 6.

Table 6. Phase 3 randomised, global multicentre studies conducted with Viekirax and dasabuvir with or without ribavirin (RBV).

Trial[1]	Number of subjects treated[2]	HCV genotype (GT)	Summary of study design[3]
Treatment-naïve[4], without cirrhosis			
SAPPHIRE I	631	GT1	Arm A: Viekirax and dasabuvir + RBV Arm B: Placebo
PEARL III	419	GT1b	Arm A: Viekirax and dasabuvir + RBV Arm B: Viekirax and dasabuvir
PEARL IV	305	GT1a	Arm A: Viekirax and dasabuvir + RBV Arm B: Viekirax and dasabuvir
Peginterferon+ribavirin experienced-[5], without cirrhosis			
SAPPHIRE II	394	GT1	Arm A: Viekirax and dasabuvir + RBV Arm B: Placebo
PEARL II (open-label)	179	GT1b	Arm A: Viekirax and dasabuvir + RBV Arm B: Viekirax and dasabuvir
Treatment-naïve and peginterferon+ribavirin-experienced, with compensated cirrhosis			
TURQUOISE II (open-label)	380	GT1	Arm A: Viekirax and dasabuvir + RBV (12 weeks) Arm B: Viekirax and dasabuvir + RBV (24 weeks)

1 Double-blind unless otherwise noted.
2 Treated is defined as subjects who were randomised and received at least one dose of Viekirax and dasabuvir.
3 Treatment duration was 12 weeks for all arms, except for TURQUOISE II which included a 24 week arm.
4 Treatment naïve was defined as not having received any prior therapy for HCV infection.
5 Peginterferon+ribavirin-experienced subjects were defined as either: prior relapsers (subjects with HCV RNA undetectable at or after the end of at least 36 weeks of pegIFN/RBV treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up) or prior partial responders (received at least 20 weeks of pegIFN/RBV and achieved a greater than or equal to 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment) or prior null-responders (received at least 12 weeks of pegIFN/RBV treatment and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 or received at least 4 weeks of pegIFN/RBV treatment and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4).

In all six trials, the Viekirax dose was 25 mg/150 mg/100 mg once daily and the dasabuvir dose was 250 mg twice daily. For subjects who received ribavirin, the ribavirin dose was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate in the Phase 3 studies and was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12). Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels (no response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL.

Clinical trials in treatment-naïve adults

SAPPHIRE-I – genotype 1, treatment-naïve

SAPPHIRE-I was a randomised, global multicentre, double-blind, placebo-controlled trial conducted in 631 treatment-naïve adults with genotype 1 chronic hepatitis C virus infection without cirrhosis. Viekirax and dasabuvir were given for 12 weeks of treatment in combination with ribavirin. Subjects randomised to the placebo arm received placebo for 12 weeks, after which they received open-label Viekirax and dasabuvir in combination with ribavirin for 12 weeks.

Treated subjects (N=631) had a median age of 52 years (range: 18 to 70); 54.5% were male; 5.4% were Black; 16.2% had a body mass index of at least 30 kg/m^2; 15.2% had a history of depression or bipolar disorder; 69.3% had IL28B non-CC genotype; 79.1% had baseline HCV RNA levels of at least 800,000 IU/mL; 15.4% had portal fibrosis (F2) and 8.7% had bridging fibrosis (F3); 67.7% had HCV genotype 1a infection; 32.3% had HCV genotype 1b infection.

Table 7 shows the SVR12 rates for genotype 1-infected treatment-naïve subjects receiving Viekirax and dasabuvir in combination with ribavirin for 12 weeks in SAPPHIRE-I.

Table 7. SVR12 for genotype 1-infected treatment-naïve subjects in SAPPHIRE-I

Treatment outcome	Viekirax and dasabuvir with RBV for 12 weeks		
	n/N	%	95% CI
Overall SVR12	456/473	96.4	94.7, 98.1
HCV genotype 1a	308/322	95.7	93.4, 97.9
HCV genotype 1b	148/151	98.0	95.8, 100.0
Outcome for subjects without SVR12			
On-treatment VF[a]	1/473	0.2	
Relapse[b]	7/463	1.5	
Other[c]	9/473	1.9	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

No subjects with HCV genotype 1b infection experienced on-treatment virologic failure and one subject with HCV genotype 1b infection experienced relapse.

PEARL-III – genotype 1b, treatment-naïve

PEARL-III was a randomised, global multicentre, double-blind, controlled trial conducted in 419 treatment-naïve adults with genotype 1b chronic hepatitis C virus infection without cirrhosis. Subjects were randomised in a 1:1 ratio to receive Viekirax and dasabuvir with or without ribavirin for 12 weeks of treatment.

Treated subjects (N=419) had a median age of 50 years (range: 19 to 70), 45.8% were male; 4.8% were Black; 16.5% had a body mass index of at least 30 kg/m^2; 9.3% had a history of depression or bipolar disorder; 79.0% had IL28B non-CC genotype; 73.3% had baseline HCV RNA of at least 800,000 IU/mL; 20.3% had portal fibrosis (F2) and 10.0% had bridging fibrosis (F3).

Table 8 shows the SVR12 rates for genotype 1b-infected treatment-naïve subjects who received either Viekirax and dasabuvir with ribavirin or Viekirax and dasabuvir without ribavirin for 12 weeks in PEARL III. In this study Viekirax and dasabuvir without ribavirin had similar SVR12 rates (100%) compared to Viekirax and dasabuvir with ribavirin (99.5%).

Table 8. SVR12 for genotype 1b-infected treatment-naïve subjects in PEARL III

Treatment outcome	Viekirax and dasabuvir for 12 weeks					
	With RBV			Without RBV		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	209/210	99.5	98.6, 100.0	20 9/209	100	98.2, 100.0
Outcome for subjects without SVR12						
On-treatment VF[a]	1/210	0.5		0/209	0	
Relapse[b]	0/210	0		0/209	0	
Other[c]	0/210	0		0/209	0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

PEARL-IV – genotype 1a, treatment-naïve

PEARL-IV was a randomised, global multicentre, double-blind, controlled trial conducted in 305 treatment-naïve adults with genotype 1a chronic hepatitis C virus infection without cirrhosis. Subjects were randomised in a 1:2 ratio to receive Viekirax and dasabuvir with or without ribavirin for 12 weeks of treatment.

Treated subjects (N=305) had a median age of 54 years (range: 19 to 70); 65.2% were male; 11.8% were Black; 19.7% had a body mass index of at least 30 kg/m^2; 20.7% had a history of depression or bipolar disorder; 69.2% had IL28B non-CC genotype; 86.6% had baseline HCV RNA levels of at least 800,000 IU/mL; 18.4% had portal fibrosis (F2) and 17.7% had bridging fibrosis (F3).

Table 9 shows the SVR12 rates for genotype 1a-infected, treatment-naïve subjects who received Viekirax and dasabuvir with or without ribavirin for 12 weeks in PEARL IV. Viekirax and dasabuvir without ribavirin was not non-inferior to Viekirax and dasabuvir with ribavirin.

Table 9. SVR12 for genotype 1a-infected treatment-naïve subjects in PEARL IV

Treatment outcome	Viekirax and dasabuvir for 12 weeks					
	With RBV			Without RBV		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	97/100	97.0	93.7, 100.0	185/205	90.2	86.2, 94.3
Outcome for subjects without SVR12						
On-treatment VF[a]	1/100	1.0		6/205	2.9	
Relapse[b]	1/98	1.0		10/194	5.2	
Other[c]	1/100	1.0		4/205	2.0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Clinical trials in peginterferon+ribavirin-experienced adults

SAPPHIRE-II – genotype 1, peginterferon+ribavirin-experienced

SAPPHIRE-II was a randomised, global multicentre, double-blind, placebo-controlled trial conducted in 394 subjects with genotype 1 chronic hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. Viekirax and dasabuvir in combination with ribavirin were given for 12 weeks of treatment. Subjects randomised to the placebo arm received placebo for 12 weeks, after which they received Viekirax and dasabuvir in combination with ribavirin for 12 weeks.

Treated subjects (N=394) had a median age of 54 years (range: 19 to 71); 49.0% were prior pegIFN/RBV null responders; 21.8/% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers; 57.6% were male; 8.1% were Black; 19.8% had a body mass index of at least 30 kg/m^2; 20.6% had a history of depression or bipolar disorder; 89.6% had IL28B non-CC genotype; 87.1% had baseline HCV RNA levels of at least 800,000 IU per mL; 17.8% had portal fibrosis (F2) and 14.5% had bridging fibrosis (F3); 58.4% had HCV genotype 1a infection; 41.4% had HCV genotype 1b infection.

Table 10 shows the SVR12 rates for treatment-experienced subjects with genotype 1-infection receiving Viekirax and dasabuvir in combination with ribavirin for 12 weeks in SAPPHIRE-II.

Table 10. SVR12 for genotype 1-infected peginterferon+ribavirin-experienced subjects in SAPPHIRE-II

	Viekirax and dasabuvir with RBV for 12 weeks		
Treatment outcome	**n/N**	**%**	**95% CI**
Overall SVR12	286/297	96.3	94.1, 98.4
HCV genotype 1a	166/173	96.0	93.0, 98.9
Prior pegIFN/RBV null responder	83/87	95.4	91.0, 99.8
Prior pegIFN/RBV partial responder	36/36	100	100.0, 100.0
Prior pegIFN/RBV relapser	47/50	94.0	87.4, 100.0
HCV genotype 1b	119/123	96.7	93.6, 99.9
Prior pegIFN/RBV null responder	56/59	94.9	89.3, 100.0
Prior pegIFN/RBV partial responder	28/28	100	100.0, 100.0
Prior pegIFN/RBV relapser	35/36	97.2	91.9, 100.0
Outcome for subjects without SVR12			
On-treatment VF[a]	0/297	0	
Relapse[b]	7/293	2.4	
Other[c]	4/297	1.3	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

No subjects with HCV genotype 1b infection experienced on-treatment virologic failure and 2 subjects with HCV genotype 1b infection experienced relapse.

PEARL-II – genotype 1b, peginterferon+ribavirin-experienced

PEARL-II was a randomised, global multicentre, open-label trial conducted in 179 adults with chronic genotype 1b hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment pegIFN/RBV. Subjects were randomised in a 1:1 ratio to receive Viekirax and dasabuvir with or without ribavirin for 12 weeks of treatment.

Treated subjects (N=179) had a median age of 57 years (range: 26 to 70); 35.2% were prior pegIFN/RBV null responders; 28.5% were prior pegIFN/RBV partial responders, and 36.3% were prior pegIFN/RBV relapsers; 54.2% were male; 3.9% were Black; 21.8% had a body mass index of at least 30 kg/m^2; 12.8% had a history of depression or bipolar disorder; 90.5% had IL28B non-CC genotype; 87.7% had baseline HCV RNA levels of at least 800,000 IU/mL; 17.9% had portal fibrosis (F2) and 14.0% had bridging fibrosis (F3).

Table 11 shows the SVR12 rates for genotype 1b-infected, peginterferon+ribavirin-experienced subjects who received Viekirax and dasabuvir with or without ribavirin for 12 weeks in PEARL II. In this study, Viekirax and dasabuvir without ribavirin had similar SVR12 rate (100%) compared to Viekirax and dasabuvir with ribavirin (97.7%).

Table 11. SVR12 for genotype 1b-infected peginterferon+ribavirin-experienced subjects in PEARL II

Treatment outcome	Viekirax and dasabuvir for 12 weeks					
	With RBV			Without RBV		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	86/88	97.7	94.6, 100.0	91/91	100	95.9, 100.0
Prior pegIFN/RBV null responder	30/31	96.8	90.6, 100.0	32/32	100	89.3, 100.0
Prior pegIFN/RBV partial responder	24/25	96.0	88.3, 100.0	26/26	100	87.1, 100.0
Prior pegIFN/RBV relapser	32/32	100	89.3, 100.0	33/33	100	89.6, 100.0
Outcome for subjects without SVR12						
On-treatment VF[a]	0/88	0		0/91	0	
Relapse[b]	0/88	0		0/91	0	
Other[c]	2/88	2.3		0/91	0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR4 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Clinical trial in subjects with compensated cirrhosis

TURQUOISE-II – genotype 1, treatment-naïve or peginterferon+ribavirin-experienced subjects with compensated cirrhosis

TURQUOISE-II was a randomised, global multicentre, open-label trial conducted exclusively in 380 genotype 1-infected subjects with compensated cirrhosis (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Viekirax and dasabuvir in combination with ribavirin were administered for either 12 or 24 weeks of treatment.

Treated subjects (N=380) had a median age of 58 years (range: 21 to 71); 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders; 8.2% were prior pegIFN/RBV partial responders, 13.7% were prior pegIFN/RBV relapsers; 70.3% were male; 3.2% were Black; 28.4% had a body mass index of at least 30 kg/m^2; 14.7% had platelet counts of less than 90 x 10^9/L; 49.7% had albumin less than 40 g/L; 86.1% had baseline HCV RNA levels of at least 800,000 IU/mL; 81.8% had IL28B non-CC genotype; 24.7% had a history of depression or bipolar disorder; 68.7% had HCV genotype 1a infection, 31.3% had HCV genotype 1b infection.

Table 12 shows the SVR12 rates for genotype 1-infected subjects with compensated cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 12. SVR12 for genotype 1-infected subjects with compensated cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV

Treatment outcome	Viekirax and dasabuvir with RBV					
	12 weeks			24 weeks		
	n/N	%	CI[a]	n/N	%	CI[a]
Overall SVR12	191/208	91.8	87.6, 96.1	166/172	96.5	93.4, 99.6
HCV genotype 1a	124/140	88.6	83.3, 93.8	115/121	95.0	91.2, 98.9
Treatment naïve	59/64	92.2		53/56	94.6	
Prior pegIFN/RBV null responders	40/50	80.0		39/42	92.9	
Prior pegIFN/RBV partial responders	11/11	100		10/10	100	
Prior pegIFN/RBV Prior relapsers	14/15	93.3		13/13	100	
HCV genotype 1b	67/68	98.5	95.7, 100	51/51	100	93.0, 100
Treatment naïve	22/22	100		18/18	100	
Prior pegIFN/RBV null responders	25/25	100		20/20	100	
Prior pegIFN/RBV partial responders	6/7	85.7		3/3	100	
Prior pegIFN/RBV Prior relapsers	14/14	100		10/10	100	
Outcome for subjects without SVR12						
On-treatment VF[b]	1/208	0.5		3/172	1.7	
Relapse[c]	12/203	5.9		1/164	0.6	
Other[d]	4/208	1.9		2/172	1.21	

CI = confidence interval, VF = virologic failure

a. 97.5% confidence intervals are used for the primary efficacy endpoints (overall SVR12 rate); 95% confidence intervals are used for additional efficacy endpoints (SVR12 rates in HCV genotype 1a and 1b-infected subjects).

b. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

c. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for subjects assigned to 12 or 24 weeks of treatment, respectively.

d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Relapse rates in GT1a cirrhotic subjects by baseline laboratory values are presented in Table 13.

Table 13. TURQUOISE-II: Relapse Rates by Baseline Laboratory Values after 12 and 24 Weeks of Treatment in Subjects with Genotype 1a Infection and Compensated Cirrhosis

	Viekirax and dasabuvir with RBV 12-week arm	Viekirax and dasabuvir with RBV 24-week arm
Number of Responders at the End of Treatment	135	113
AFP* < 20 ng/mL, platelets ≥ 90 x 10^9/L, AND albumin ≥ 35 g/L prior to treatment		
Yes (for all three parameters listed above)	1/87 (1%)	0/68 (0%)
No (for any parameter listed above)	10/48 (21%)	1/45 (2%)
*AFP= serum alpha fetoprotein		

In subjects with all three favourable baseline laboratory values (AFP < 20 ng/mL, platelets ≥ 90 x 10^9/L, and albumin ≥ 35 g/L), relapse rates were similar in subjects treated for 12 or 24 weeks.

Pooled analyses of clinical trials

Durability of response

Overall, 660 subjects in Phase 2 and 3 clinical trials had HCV RNA results for both the SVR12 and SVR24 time points. Among these subjects, the positive predictive value of SVR12 on SVR24 was 99.8%.

Pooled efficacy analysis

In Phase 3 clinical trials, 1083 subjects (including 189 with compensated cirrhosis) with genotype 1 HCV infection received the recommended regimen for their HCV genotype 1 subtype, cirrhosis status and relevant baseline characteristics. Table 14 shows SVR rates for these subjects.

In subjects who received the recommended regimen, 97% achieved SVR overall (among which 189 subjects with compensated cirrhosis achieved 96% SVR), while 0.5% experienced virologic breakthrough and 1.3% experienced post-treatment relapse.

Table 14. SVR12 rates for recommended treatment regimens by patient population

	HCV Genotype 1b		HCV Genotype 1a	
	Without cirrhosis **Viekirax and dasabuvir**	**With compensated cirrhosis** **Viekirax and dasabuvir with RBV**	**Without cirrhosis** **Viekirax and dasabuvir with RBV**	**With compensated cirrhosis** **Viekirax and dasabuvir with RBV**
	12 weeks	**12 weeks**	**12 weeks**	**24 weeks**
Treatment-naïve	100% (210/210)	100% (22/22)	96% (403/420)	95% (53/56)
pegIFN+RBV experienced	100% (91/91)	98% (45/46)	96% (166/173)	95% (62/65)
Prior relapse	100% (33/33)	100% (14/14)	94% (47/50)	100% (13/13)
Prior partial response	100% (26/26)	86% (6/7)	100% (36/36)	100% (10/10)
Prior null response	100% (32/32)	100% (25/25)	95% (83/87)	93% (39/42)
TOTAL	100% (301/301)	99% (67/68)	96% (569/593)	95% (115/121)

Viekirax without ribavirin and without dasabuvir was also evaluated in genotype 1b infected subjects in Phase 2 studies M13-393 (PEARL-I) and M12-536. PEARL I was conducted in the US and Europe, M12-536 in Japan. The treatment-experienced subjects studied were primarily pegIFN+RBV null-responders. The doses of ombitasvir, paritaprevir, ritonavir were 25 mg 150 mg, 100 mg once daily in PEARL-I, while the dose of paritaprevir was 100 mg or 150 mg in study M12-536. Treatment duration was 12 weeks for treatment naïve subjects, 12-24 weeks for treatment experienced subjects and 24 weeks for subjects with cirrhosis. Overall, 107 of 113 subjects without cirrhosis and 147 of 155 subjects with cirrhosis achieved SVR12 after 12-24 weeks of treatment.

Viekirax with ribavirin & without dasabuvir was evaluated for 12 weeks in genotype 1 treatment naive and treatment experienced non-cirrhotic subjects in a phase 2 study M11-652 (AVIATOR). The doses of paritaprevir were 100 mg and 200 mg and ombitasvir 25 mg. Ribavirin was dosed based on weight (1000 mg – 1200 mg per day). Overall, 72 of 79 treatment-naive subjects (45 of 52 GT1a and 27 of 27 GT1b)

and 40 of 45 treatment-experienced subjects (21 of 26 GT1a and 19 of 19 GT1b) achieved SVR12 after 12 weeks of treatment.

Impact of ribavirin dose adjustment on probability of SVR

In Phase 3 clinical trials, 91.5% of subjects did not require ribavirin dose adjustments during therapy. In the 8.5% of subjects who had ribavirin dose adjustments during therapy, the SVR rate (98.5%) was comparable to subjects who maintained their starting ribavirin dose throughout treatment.

Clinical Trial in subjects with HCV genotype 1 infection/HIV-1 co-infection

In an open-label clinical trial (TURQUOISE-I) the safety and efficacy of 12 or 24 weeks of treatment with Viekirax and dasabuvir and ribavirin was evaluated in 63 subjects with genotype 1 chronic hepatitis C co-infected with HIV-1. See section 4.2 for dosing recommendations in HCV/HIV-1 co-infected patients. Subjects were on a stable HIV-1 antiretroviral therapy (ART) regimen that included ritonavir-boosted atazanavir or raltegravir, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine.

Treated subjects (N = 63) had a median age of 51 years (range: 31 to 69); 24% of subjects were Black; 81% of subjects had IL28B non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection.

Table 15 shows the SVR12 rates for subjects with HCV genotype 1 infection and HIV-1 co-infection in TURQUOISE-I.

Table 15. SVR12 for HIV-1 co-infected Subjects in TURQUOISE-I

Endpoint	Arm A 12 Weeks N = 31	Arm B 24 Weeks N = 32
SVR12, n/N (%) [95% CI]	29/31 (93.5) [79.3, 98.2]	29/32 (90.6) [75.8, 96.8]
Outcome for subjects not achieving SVR12		
On-treatment virologic failure[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

c. These virologic failures appear to have resulted from reinfection based on analyses of baseline and virologic failure samples

d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected subjects were consistent with SVR12 rates in the phase 3 trials of HCV mono-infected subjects. 7 of 7 subjects with genotype 1b infection and 51 of 56 subjects with genotype 1a infection achieved SVR12. 5 of 6 subjects with compensated cirrhosis in each arm achieved SVR12.

Clinical Trial in liver transplant recipients with HCV genotype 1 infection

In the CORAL-I study, the safety and efficacy of Viekirax and dasabuvir with ribavirin for 24 weeks was studied in 34 HCV genotype 1-infected liver transplant recipients who were at least 12 months post transplantation at enrolment. The dose of ribavirin was left to the discretion of the investigator, with most patients receiving 600 to 800 mg per day as a starting dose, and most patients also receiving 600 to 800 mg per day at the end of treatment.

34 subjects (29 with HCV genotype 1a infection and 5 with HCV genotype 1b infection) were enrolled who had not received treatment for HCV infection after transplantation and had a METAVIR fibrosis score of F2 or less. 33 out of the 34 subjects (97.1%) achieved SVR12 (96.6% in subjects with genotype 1a infection and 100% in subjects with genotype 1b infection). One subject with HCV genotype 1a infection relapsed post-treatment.

Clinical trial in patients receiving opioid substitution therapy

In a phase 2, multicentre, open-label, single arm study, 38 treatment-naïve or pegIFN/RBV treatment experienced, non-cirrhotic subjects with genotype 1 infection who were on stable doses of methadone (N=19) or buprenorphine +/- naloxone (N=19) received 12 weeks of Viekirax and dasabuvir with ribavirin. Treated subjects had a median age of 51 years (range: 26 to 64); 65.8% were male and 5.3% were Black. A majority (86.8%) had baseline HCV RNA levels of at least 800,000 IU/mL and a majority (84.2%) had genotype 1a infection; 68.4% had IL28B non-CC genotype; 15.8% had portal fibrosis (F2) and 5.3% had bridging fibrosis (F3); and 94.7% were naïve to prior HCV treatment.

Overall, 37 (97.4%) of 38 subjects achieved SVR12. No subjects experienced on-treatment virologic failure or relapse.

Clinical trial in subjects with genotype 4 chronic hepatitis C

PEARL- I– genotype 4, treatment-naïve or peginterferon + ribavirin experienced

PEARL-I- was a randomised, global multicentre, open-label trial conducted in 135 adults with genotype 4 chronic hepatitis C virus infection without cirrhosis who were treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Treatment naive subjects were randomised in a 1:1 ratio to receive ombitasvir, paritaprevir and ritonavir with or without ribavirin for 12 weeks of treatment. PegIFN/RBV-experienced subjects received ombitasvir, paritaprevir, and ritonavir in combination with ribavirin for 12 weeks

Treated subjects (N=135) had a median age of 51 years (range: 19 to 70); 63,7% were treatment-naïve, 17.0% were prior pegIFN/RBV null responders, 6.7% were prior pegIFN/RBV partial responders, 12.6% were prior pegIFN/RBV relapsers; 65.2%were male; 8.9% were Black, 14.1% had a body mass index of at least 30 kg/m^2; 69.6% had baseline HCV RNA levels at least 800,000 IU/mL; 78.5% had IL28B non-CC genotype; 6.7% had bridging fibrosis (F3).

Table 16 shows the SVR12 rates for genotype 4 infected subjects, treatment-naïve or previously treated with pegIFN/RBV, who received ombitasvir, paritaprevir and ritonavir with or without ribavirin for 12 weeks in PEARL I.

Table 16. SVR12 for genotype 4-infected, subjects who were treatment-naïve or previously treated with pegIFN/RBV in PEARL I

Treatment outcome	Ombitasvir + paritaprevir + ritonavir* for 12 weeks					
	Treatment-naïve With RBV		Treatment-naïve Without RBV		pegIFN + RBV-experienced With RBV	
	n/N	%	n/N	%	n/N	%
Overall SVR12	42/42	100%	40/44	90.9 %	49/49	100%
Outcome for subjects without SVR12						
On-treatment VF[a]	0/42	0	1/44	2.3%	0/49	0
Relapse[b]	0/42	0	2/44	4.5%	0/49	0
Other[c]	0/42	0	1/44	2.3%	0/49	0

VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed increase from nadir in HCV RNA > 1 $\log_{10}$ IU/mL during treatment, or HCV RNA ≥ 25 IU/mL persistently during treatment with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

* Ombitasvir tablets, paritaprevir tablets and ritonavir capsules administered separately.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Viekirax in one or more subsets of the paediatric populations in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the combination of Viekirax with dasabuvir have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Table 17 shows mean C_{max} and AUC of Viekirax 25 mg/150 mg/100 mg once daily with dasabuvir 250 mg twice daily following multiple doses with food in healthy volunteers.

Table 17. Geometric mean C_{max}, AUC of multiple doses of Viekirax 150 mg/100 mg/25 mg once daily with dasabuvir 250 mg twice daily with food in healthy volunteers

	C_{max} (ng/ml) (% CV)	AUC (ng*hr/ml) (% CV)
Ombitasvir	127 (31)	1420 (36)
Paritaprevir	1470 (87)	6990 (96)
Ritonavir	1600 (40)	9470 (41)

Absorption

Ombitasvir, paritaprevir and ritonavir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. While ombitasvir exposures increased in a dose proportional manner,

paritaprevir and ritonavir exposures increased in a more than dose proportional manner. Accumulation is minimal for ombitasvir and approximately 1.5- to 2-fold for ritonavir and paritaprevir. Pharmacokinetic steady state for the combination is achieved after approximately 12 days of dosing.

The absolute bioavailability of ombitasvir and paritaprevir was approximately 50% when administered with food as Viekirax.

Effect of paritaprevir/ritonavir on ombitasvir and dasabuvir

In the presence of paritaprevir/ritonavir, dasabuvir exposures decreased by approximately 50% to 60% while ombitasvir exposures increased by 31-47%.

Effect of ombitasvir on paritaprevir/ritonavir and dasabuvir

In the presence of ombitasvir, paritaprevir exposures were minimally affected (5% to 27% change) while dasabuvir exposures increase by approximately 30%.

Effect of dasabuvir on paritaprevir/ritonavir and ombitasvir

In the presence of dasabuvir, paritaprevir exposures increased by 50% to 65% while there was no change in ombitasvir exposures.

Effects of food

Ombitasvir, paritaprevir and ritonavir should be administered with food. All clinical trials with ombitasvir, paritaprevir and ritonavir have been conducted following administration with food.

Food increased the exposure (AUC) of ombitasvir, paritaprevir and ritonavir by up to 82%, 211% and 49%, respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). To maximise absorption, Viekirax should be taken with food without regard to fat or calorie content.

Distribution

Ombitasvir, paritaprevir and ritonavir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in subjects with renal or hepatic impairment. The blood to plasma concentration ratios in humans ranged from 0.6 to 0.8 indicating that ombitasvir and paritaprevir were preferentially distributed in the plasma compartment of whole blood. Ombitasvir was approximately 99.9% bound to human plasma proteins. Paritaprevir was approximately 97-98.6% bound to human plasma proteins. Ritonavir was greater than 99% bound to human plasma proteins.

In vitro data indicate that paritaprevir is a substrate for the human hepatic uptake transporters, OATP1B1 and OATP1B3.

Biotransformation

Ombitasvir

Ombitasvir is metabolised via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ^{14}C-ombitasvir given alone, unchanged parent drug accounted for 8.9% of total radioactivity in human plasma; a total of 13 metabolites were identified in human plasma. These metabolites are not expected to have antiviral activity or off-target pharmacologic activity.

Paritaprevir

Paritaprevir is metabolised predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200 mg/100 mg oral dose of ^{14}C paritaprevir /ritonavir to humans, the parent drug was the major circulating component, accounting for approximately 90% of the plasma radioactivity. At least 5 minor metabolites of paritaprevir have been identified in circulation that accounted for approximately 10% of plasma radioactivity. These metabolites are not expected to have antiviral activity.

Ritonavir

Ritonavir is predominantly metabolised by CYP3A and to a lesser extent, by CYP2D6. Nearly the entire plasma radioactivity after a single 600 mg dose of ^{14}C-ritonavir oral solution in humans was attributed to unchanged ritonavir.

Elimination

Ombitasvir

Following dosing of ombitasvir/paritaprevir/ritonavir with or without dasabuvir, mean plasma half-life of ombitasvir was approximately 21 to 25 hours. Following a single 25 mg dose of ^{14}C- ombitasvir approximately 90% of the radioactivity was recovered in faeces and 2% in urine. Unchanged parent drug accounted for 88% of total radioactivity recovered in faeces, indicating that biliary excretion is a major elimination pathway for ombitasvir.

Paritaprevir

Following dosing of ombitasvir/paritaprevir /ritonavir with or without dasabuvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ^{14}C -paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in faeces with limited radioactivity (8.8%) in urine. Metabolism as well as biliary excretion of parent drug contribute to the elimination of paritaprevir.

Ritonavir

Following dosing of ombitasvir/paritaprevir /ritonavir, mean plasma half-life of ritonavir was approximately 4 hours. Following a 600 mg dose of ^{14}C -ritonavir oral solution, 86.4% of the radioactivity was recovered in the faeces and 11.3% of the dose was excreted in the urine.

In vitro interaction data

Ombitasvir and paritaprevir do not inhibit organic anion transporter (OAT1) *in vivo* and are not expected to inhibit organic cation transporters (OCT1 and OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations. Ritonavir does not inhibit OAT1 and is not expected to inhibit OCT2, OAT3, MATE1 and MATE2K at clinically relevant concentrations.

Special populations

Elderly

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would result in approximately 10%

change in ombitasvir exposures, and ≤20% change in paritaprevir exposures. There is no pharmacokinetic information in patients >75 years.

Sex or body weight

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, female subjects would have approximately 55% higher, 100% higher and 15% higher ombitasvir, paritaprevir and ritonavir exposures than male subjects. However, no dose-adjustment based on gender is warranted. A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would results in <10% change in ombitasvir exposures, and no change in paritaprevir exposures. Body weight is not a significant predictor of ritonavir exposures.

Race or ethnicity

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, Asian subjects had 18% to 21% higher ombitasvir exposures, and 37% to 39% higher paritaprevir exposures than non-Asian subjects. The ritonavir exposures were comparable between Asians and non-Asians.

Renal impairment

The changes in ombitasvir, paritaprevir, and ritonavir exposures in subjects with mild, moderate and severe renal impairment are not considered to be clinically significant. No dose adjustment for Viekirax with and without dasabuvir is recommended in HCV-infected patients with mild, moderate or severe renal impairment (see section 4.2). Viekirax has not been studied in HCV-infected patients on dialysis.

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg, with or without dasabuvir 400 mg were evaluated in subjects with mild (CrCl: 60 to 89 ml/min), moderate (CrCl: 30 to 59 ml/min) and severe (CrCl: 15 to 29 ml/min) renal impairment.

Following administration of Viekirax and dasabuvir

Compared to the subjects with normal renal function, ombitasvir exposures were comparable in subjects with mild, moderate and severe renal impairment. Compared to the subjects with normal renal function, paritaprevir C_{max} values were comparable, but AUC values were 19%, 33% and 45% higher in mild, moderate and severe renal impairment, respectively. Ritonavir plasma concentrations increased when renal function was reduced: C_{max} and AUC values were 26% to 42% higher, 48% to 80% higher and 66% to 114% higher in subjects with mild, moderate and severe renal impairment, respectively.

Following administration of Viekirax

Following administration of Viekirax, the changes in ombitasvir, paritaprevir, and ritonavir exposures in subjects with mild, moderate and severe renal impairment were similar to those observed when Viekirax was administered with dasabuvir, and are not considered to be clinically significant.

Hepatic impairment

The changes in ombitasvir, paritaprevir, and ritonavir exposures in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment are not considered clinically significant. No dose adjustment for Viekirax or dasabuvir is recommended in HCV-infected patients with mild and moderate hepatic impairment (see section 4.2).

Following administration of Viekirax and dasabuvir

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg, with dasabuvir 400 mg were evaluated in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

In subjects with mild hepatic impairment, paritaprevir, ritonavir and ombitasvir mean C_{max} and AUC values decreased by 29% to 48%, 34% to 38% and up to 8%, respectively, compared to subjects with normal hepatic function.

In subjects with moderate hepatic impairment, ombitasvir and ritonavir mean C_{max} and AUC values decreased by 29% to 30% and 30 to 33%, respectively, while paritaprevir mean C_{max} and AUC values increased by 26% to 62% compared to subjects with normal hepatic function. The safety and efficacy of Viekirax have not been established in HCV-infected patients with moderate (Child-Pugh B) hepatic impairment; however, no dose adjustment is expected to be required based on pharmacokinetic studies (see section 4.2).

In subjects with severe hepatic impairment, paritaprevir mean C_{max} and AUC values increased by 3.2-to 9.5-fold; ritonavir mean C_{max} values were 35% lower and AUC values were 13% higher and ombitasvir mean C_{max} and AUC values decreased by 68% and 54%, respectively, compared to subjects with normal hepatic function, therefore, Viekirax must not be used in patients with severe hepatic impairment (see sections 4.2 and 4.4).

Following administration of Viekirax

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg were not evaluated in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. Results from the pharmacokinetic evaluation of the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg, with dasabuvir 400 mg can be extrapolated to the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg.

Paediatric population

The pharmacokinetics of Viekirax in paediatric patients has not been established (see section 4.2).

5.3 Preclinical safety data

Ombitasvir

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (150 mg/kg/day), resulting in ombitasvir AUC exposures approximately 26-fold higher than those in humans at the recommended clinical dose of 25 mg.

The carcinogenicity study of ombitasvir in rats is ongoing.

Ombitasvir has shown malformations in rabbits at maximal feasible exposures 4-fold higher than the AUC exposure at recommended clinical dose. Malformations at low incidence were observed mainly in the eyes (microphthalmia) and teeth (absent incisors). In mice, an increased incidence of open eye lid was present in foetuses of dams administered ombitasvir; however, the relationship to treatment with ombitasvir is

uncertain. The major, inactive human metabolites of ombitasvir were not teratogenic in mice at exposures approximately 26 times higher than in humans at the recommended clinical dose. Ombitasvir had no effect on fertility when evaluated in mice.
Unchanged ombitasvir was the predominant component observed in the milk of lactating rats, without effect on nursing pups. Ombitasvir-derived material was minimally transferred through the placenta in pregnant rats.

Paritaprevir/ritonavir

Paritaprevir was positive in an *in vitro* human chromosome aberration test. Paritaprevir was negative in a bacterial mutation assay, and in two *in vivo* genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

Paritaprevir /ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (300 mg/30 mg/kg/day), resulting in paritaprevir AUC exposures approximately 38-fold higher than those in humans at the recommended dose of 150 mg. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to the highest dosage tested (300 mg/30 mg/kg/day), resulting in paritaprevir AUC exposures approximately 8-fold higher than those in humans at 150 mg.

Paritaprevir/ritonavir has shown malformations (open eye lids) at a low incidence in mice at exposures 32/8-fold higher than the exposure in humans at the recommended clinical dose. Paritaprevir/ritonavir had no effects on embryo-foetal viability or on fertility when evaluated in rats at exposures 2- to 8-fold higher than the exposure in humans at the recommended clinical dose.
Paritaprevir and its hydrolysis product M13 were the predominant components observed in the milk of lactating rats, without effect on nursing pups. Paritaprevir -derived material was minimally transferred through the placenta in pregnant rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone
Vitamin E polyethylene glycol succinate
Propylene glycol monolaurate
Sorbitan monolaurate
Colloidal anhydrous silica (E551)
Sodium stearyl fumarate

Film-coating
Polyvinyl alcohol (E1203)
Polyethylene glycol 3350
Talc (E553b)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PCTFE aluminium foil blister packs.
56 tablets (multipack carton containing 4 inner cartons of 14 tablets each).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4XE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/982/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Viekirax 12.5 mg/75 mg/50 mg film-coated tablets（和文）