Product Information as approved by the CHMP on 16 February 2012, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of boceprevir.

Excipient: each capsule contains 56 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Each capsule has a yellowish-brown, opaque cap with an "MSD" logo imprinted in red ink and off-white, opaque body with the code "314" imprinted in red ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Victrelis is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.
See sections 4.4 and 5.1.

4.2 Posology and method of administration

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

Posology
Victrelis must be administered in combination with peginterferon alfa and ribavirin. The Summary of Product Characteristics of peginterferon alfa and ribavirin (PR) must be consulted prior to initiation of therapy with Victrelis.

The recommended dose of Victrelis is 800 mg administered orally three times daily (TID) with food (a meal or light snack). Maximum daily dose of Victrelis is 2,400 mg. Administration without food could be associated with a net loss of efficacy due to sub-optimal exposure.

Patients without cirrhosis who are previously untreated or who have failed previous therapy
The following dosing recommendations differ for some subgroups from the dosing studied in the Phase 3 trials (see section 5.1).

Table 1

Duration of therapy using Response-Guided Therapy (RGT) guidelines in patients without cirrhosis who are previously untreated or who have failed previous therapy to interferon and ribavirin therapy

	ASSESSMENT* (HCV-RNA Results†)		**ACTION**
	At Treatment Week 8	**At Treatment Week 24**	
Previously Untreated Patients	Undetectable	Undetectable	*Treatment duration = 28 weeks* 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (peginterferon alfa and ribavirin [PR] + Victrelis) and finish through Treatment Week 28 (TW 28).
	Detectable	Undetectable	*Treatment duration = 48 weeks*‡ 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (PR + Victrelis) and finish through TW 36; and then 3. Administer peginterferon alfa and ribavirin and finish through TW 48.
Patients Who have Failed Previous Therapy	Undetectable	Undetectable	*Treatment duration = 48 weeks* 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (PR + Victrelis) and finish through TW 36, and then 3. Administer peginterferon alfa and ribavirin and finish through TW 48.
	Detectable	Undetectable	

***Stopping rule**

If the patient has hepatitis C virus ribonucleic acid (HCV-RNA) results greater than or equal to 100 IU/ml at TW 12; then discontinue three-medicine regimen.

If the patient has confirmed, detectable HCV-RNA at TW 24; then discontinue three-medicine regimen.

† In clinical trials, HCV-RNA in plasma was measured with the Roche COBAS Taqman 2.0 assay with a limit of detection of 9.3 IU/ml and a limit of quantification of 25 IU/ml.

‡This regimen has only been tested in subjects who have failed previous therapy who were late responders (see section 5.1).

All cirrhotic patients and null responders:

- Recommended treatment duration is 48 weeks: 4 weeks of bitherapy with peginterferon alfa+ ribavirin + 44 weeks of tritherapy with peginterferon alfa + ribavirin + Victrelis. (Refer to the stopping rule in Table 1 for all patients.)
    - The duration of the tritherapy after the first 4 weeks of bitherapy should not be less than 32 weeks. Given the incremental risk of adverse events with Victrelis (anaemia notably); in case the patient cannot tolerate the treatment, consideration could be given to pursue with 12 weeks of bitherapy for the final 12 weeks of treatment instead of tritherapy (see sections 4.8 and 5.1).

Missed doses
If a patient misses a dose and it is less than 2 hours before the next dose is due, the missed dose should be skipped.

If a patient misses a dose and it is 2 or more hours before the next dose is due, the patient should take the missed dose with food and resume the normal dosing schedule.

Dose reduction
Dose reduction of Victrelis is not recommended.

If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced. Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dose. Victrelis must not be administered in the absence of peginterferon alfa and ribavirin.

Special populations
Renal impairment
No dose adjustment of Victrelis is required in patients with any degree of renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment of Victrelis is required for patients with mild, moderate or severe hepatic impairment. Victrelis has not been studied in patients with decompensated cirrhosis (see section 5.2).

Paediatric population
The safety and efficacy of Victrelis in children aged below 18 years have not yet been established. No data are available.

Elderly
Clinical studies of Victrelis did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients (see section 5.2).

Method of administration
To obtain the hard capsules the foil of the blister should be peeled off. Victrelis is to be taken orally with food (a meal or light snack).

4.3 Contraindications

Victrelis, in combination with peginterferon alfa and ribavirin, is contraindicated in:

- Patients with hypersensitivity to the active substance or any of its excipients.
- Patients with autoimmune hepatitis.
- Co-administration with medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam and triazolam, bepridil, pimozide, lumefantrine,

halofantrine, tyrosine kinase inhibitors, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) (see section 4.5).
- Pregnancy (see section 4.6).

Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for additional information.

4.4 Special warnings and precautions for use

Anaemia
The onset of anaemia has been reported with peginterferon alfa and ribavirin therapy by Treatment Week 4. The addition of Victrelis to peginterferon alfa and ribavirin is associated with an additional decrease in haemoglobin concentrations of approximately 1 g/dl by Treatment Week 8 compared to standard of care (see section 4.8). Complete blood counts should be obtained pretreatment, Treatment Week 4, Treatment Week 8, and thereafter, as clinically appropriate. If haemoglobin is < 10 g/dl (or < 6.2 mmol/l) management of anaemia may be warranted (see section 4.8).

Please refer to the Summary of Product Characteristics for ribavirin for statements regarding dose reduction and/or interruption or discontinuation of ribavirin.

Neutropenia
The addition of Victrelis to peginterferon alfa–2b and ribavirin resulted in higher incidences of neutropenia and Grade 3-4 neutropenia compared with peginterferon alfa–2b and ribavirin alone (see section 4.8).

The frequency of severe or life threatening infections tends to be higher in Victrelis-containing arms than the control arm. Neutrophils counts should therefore be evaluated before treatment initiation and regularly thereafter. Prompt evaluation and treatment of infections is recommended.

Combined use with peginterferon alfa–2a as compared to alfa–2b:
As compared to the combination of Victrelis with peginterferon alfa–2b and ribavirin, the combination of Victrelis with peginterferon alfa–2a and ribavirin was associated with a higher rate of neutropenia (including grade 4 neutropenia) and a higher rate of infections.

Please refer to the Summary of Product Characteristics for peginterferon alfa.

Drospirenone-containing medicines
Caution should be exercised in patients taking drospirenone-containing medicines with conditions that predispose them to hyperkalaemia or patients taking potassium-sparing diuretics. Alternative contraceptives should be considered (see section 4.5).

Use in prior null responders
Based on a retrospective analysis performed with requalifying on the basis of their on treatment virologic response at treatment week 4 (using the peginterferon alfa/ribavirin lead in period) as compared to baseline, null responders might gain some benefit in adding Victrelis to the bitherapy. However, this cannot be reliably quantified from the retrospective analysis. Moreover, the optimal management of null responders remains to be established and might in the future require antiviral combination.

HCV protease monotherapy
Based on results of clinical studies, Victrelis must not be used alone due to the high probability of increased resistance without combination anti-HCV therapies (see section 5.1).

It is unknown what effect therapy with Victrelis will have on the activity of subsequently administered HCV protease inhibitors, including re-treatment with Victrelis.

Use in patients with HIV co-infection
The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection have not been established in patients co-infected with Human Immunodeficiency Virus (HIV) and HCV. Clinical studies are ongoing in patients under combination antiretroviral therapy (including boosted HIV protease inhibitors) that will provide efficacy and safety in these patients and also enable to determine the clinical relevance of the pharmacokinetic interactions between boceprevir and antiretroviral agents. For data regarding drug-drug interactions with antiretroviral agents in healthy subjects, see section 4.5.

Use in patients with HBV co-infection
The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in patients co-infected with hepatitis B Virus (HBV) and HCV have not been studied.

Use in patients with an organ transplant
The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied.

Use in patients having HCV genotypes other than genotype 1
The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotypes other than genotype 1 have not been established.

Use in patient who have previously failed treatment with an HCV protease inhibitor
The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection has not been studied in patients who have failed previous therapy with Victrelis or other HCV protease inhibitors.

Potent CYP3A4 inducers
The concomitant use of Victrelis with potent CYP3A4 inducers (rifampicin, carbamazepine, phenobarbital, phenytoin) is not recommended (see section 4.5).

Use in patients with rare hereditary disorders
Victrelis contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Proarrhythmic effects:
The data available (see section 5.3) warrant caution in patients at risk of QT prolongation (long congenital QT, hypokalaemia).

4.5 Interaction with other medicinal products and other forms of interaction

Victrelis is a strong inhibitor of CYP3A4/5. Medicines metabolized primarily by CYP3A4/5 may have increased exposure when administered with Victrelis, which could increase or prolong their therapeutic and adverse reactions (see Table 2). Victrelis does not inhibit or induce the other enzymes of the CYP450.

Boceprevir has been shown to be a P-gp and breast cancer resistant protein (BCRP) substrate *in vitro*. There is potential for inhibitors of these transporters to increase concentrations of boceprevir; the clinical implications of these interactions are not known.

Victrelis is partly metabolized by CYP3A4/5. Co-administration of Victrelis with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure to Victrelis (see section 4.4). Victrelis, in combination with peginterferon alfa and ribavirin, is contraindicated when co-administered with medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam and triazolam, bepridil, pimozide, lumefantrine, halofantrine, and tyrosine

kinase inhibitors, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) (see section 4.3).

Boceprevir is primarily metabolized by aldoketo reductase (AKR). In medicine interaction trials conducted with AKR inhibitors diflunisal and ibuprofen, boceprevir exposure did not increase to a clinically significant extent. Victrelis may be co-administered with AKR inhibitors.

The concomitant use of Victrelis with rifampicin or anticonvulsants (such as phenytoin, phenobarbital or carbamazepine) may significantly reduce the plasma exposure of Victrelis. No data are available, therefore, the combination of boceprevir with these medicines is not-recommended (see section 4.4).

Caution should be exercised with medicines known to prolong QT interval such as amiodarone, quinidine, methadone, pentamidine and some neuroleptics.

Table 2
Pharmacokinetic interactions data

Medicinal products by therapeutic areas	**Interaction* (postulated mechanism of action, if known)**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole (ketoconazole 400 mg two times daily + Victrelis 400 mg single dose) Itraconazole, Posaconazole, Voriconazole	boceprevir AUC ↑ 131% boceprevir C_{max} ↑ 41% boceprevir C_{min} N/A Not studied	Caution should be exercised when boceprevir is combined with ketoconazole or azole antifungals (itraconazole, posaconazole, voriconazole).
Antiretroviral		
Nucleoside Reverse Transcriptase Inhibitor (NRTI)		
Tenofovir (tenofovir 300 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↔ 8%** boceprevir C_{max} ↔ 5% boceprevir C_{min} ↔ 8% tenofovir AUC ↔ 5% tenofovir C_{max} ↑ 32%	No dose adjustment required for Victrelis or tenofovir.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)		
Efavirenz (efavirenz 600 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↔ 19%** boceprevir C_{max} ↔ 8% boceprevir C_{min} ↓ 44% efavirenz AUC ↔ 20% efavirenz C_{max} ↔ 11%	Plasma trough concentrations of Victrelis were decreased when administered with efavirenz. The clinical outcome of this observed reduction of Victrelis trough concentrations has not been directly assessed.

Medicinal products by therapeutic areas	Interaction* (postulated mechanism of action, if known)	Recommendations concerning co-administration
HIV Protease Inhibitor (PI)		
Atazanavir/Ritonavir (atazanavir 300 mg / ritonavir 100 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↔ 5% boceprevir C_{max} ↔ 7% boceprevir C_{min} ↔ 18% atazanavir AUC ↓ 35% atazanavir C_{max} ↓ 25% atazanavir C_{min} ↓ 49% ritonavir AUC ↓ 36% ritonavir C_{max} ↓ 27% ritonavir C_{min} ↓ 45%	Co-administration of atazanavir/ritonavir with boceprevir resulted in lower exposure of atazanavir which may be associated with lower efficacy and loss of HIV control. This co-administration might be considered on a case by case basis if deemed necessary, in patients with suppressed HIV viral loads and with HIV viral strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring for HIV suppression is warranted.
Darunavir/Ritonavir (darunavir 600 mg / ritonavir 100 mg two times daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 32% boceprevir C_{max} ↓ 25% boceprevir C_{min} ↓ 35% darunavir AUC ↓ 44% darunavir C_{max} ↓ 36% darunavir C_{min} ↓ 59% ritonavir AUC ↓ 27% ritonavir C_{max} ↔ 13% ritonavir C_{min} ↓ 45%	It is not recommended to co-administer darunavir/ritonavir and Victrelis.
Lopinavir/Ritonavir (lopinavir 400 mg / ritonavir 100 mg two times daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 45% boceprevir C_{max} ↓ 50% boceprevir C_{min} ↓ 57% lopinavir AUC ↓ 34% lopinavir C_{max} ↓ 30% lopinavir C_{min} ↓ 43% ritonavir AUC ↓ 22% ritonavir C_{max} ↔ 12% ritonavir C_{min} ↓ 42%	It is not recommended to co-administer lopinavir/ritonavir and Victrelis.
Ritonavir (ritonavir 100 mg daily + Victrelis 400 mg three times daily)	boceprevir AUC ↔ 19% boceprevir C_{max} ↓ 27% boceprevir C_{min} ↔ 4%	When boceprevir is administered with ritonavir alone, boceprevir concentrations are decreased.

Medicinal products by therapeutic areas	Interaction* (postulated mechanism of action, if known)	Recommendations concerning co-administration
Integrase inhibitor		
Raltegravir	Not studied	Based on theoretical data, the combination of boceprevir and raltegravir is not expected to result in clinically significant interactions. However, while waiting for additional data, particular attention is warranted using the combination.
ORAL CONTRACEPTIVES		
Drospirenone/Ethinyl estradiol: (drospirenone 3 mg daily + ethinyl estradiol 0.02 mg daily + Victrelis 800 mg three times daily)	drospirenone AUC ↑ 99% drospirenone C_{max} ↑ 57% ethinyl estradiol AUC ↓ 24% ethinyl estradiol C_{max} ↔ (drospirenone - CYP3A4/5 inhibition)	Caution should be exercised in patients with conditions that predispose them to hyperkalaemia or patients taking potassium-sparing diuretics (see section 4.4). Alternative contraceptives should be considered for these patients.
SEDATIVES		
Midazolam (oral administration) (4 mg single oral dose + Victrelis 800 mg three times daily) **Triazolam** (oral administration)	midazolam AUC ↑ 430% midazolam C_{max} ↑ 177% (CYP3A4/5 inhibition) Interaction not studied (CYP3A4/5 inhibition)	Co-administration of oral midazolam and oral triazolam with Victrelis is contraindicated (see section 4.3).
Alprazolam, midazolam, triazolam (intravenous administration)	Interaction not studied (CYP3A4/5 inhibition)	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of Victrelis with intravenous benzodiazepines (alprazolam, midazolam, triazolam). Dose adjustment of the benzodiazepine should be considered.

Medicinal products by therapeutic areas	Interaction* (postulated mechanism of action, if known)	Recommendations concerning co-administration
Immunosuppressants	Not studied	Therapeutic medicine monitoring is recommended when administering Victrelis with CYP3A4/5 substrates that have a narrow therapeutic window (e.g., tacrolimus, cyclosporine). Individual patients may require additional titration of their immunosuppressant dosage when Victrelis is started or stopped to ensure clinically effective blood levels.
Statins (e.g., simvastatin and atorvastatin.)	Not studied	Therapeutic monitoring is recommended when administering Victrelis with simvastatin or atorvastatin, CYP3A4/5 substrates that have a narrow therapeutic window. Individual patients may require additional titration of their statin dosage when Victrelis is started or stopped to ensure clinically effective blood levels.
Methadone	Not studied	Therapeutic monitoring is recommended when administering Victrelis with CYP3A4/5 substrates that have a narrow therapeutic window. Individual patients may require additional titration of their methadone dosage when Victrelis is started or stopped to ensure clinically effective blood levels.

* Interaction of Victrelis with other medicinal products (change in mean ratio estimate of Victrelis in combination with co-administered medicine/Victrelis alone): ↓ equals a decrease in mean ratio estimate > 20%; ↑ equals an increase in mean ratio estimate > 25%; no effect (↔) equals a decrease in mean ratio estimate of ≤ 20% or increase in mean ratio estimate ≤ 25%.

** 0-8 hours

4.6 Fertility, pregnancy and lactation

Pregnancy
Victrelis in combination with ribavirin and peginterferon alfa is contraindicated in women who are pregnant (see section 4.3).

No effects on foetal development have been observed in rats and rabbits (see section 5.3). There are no data on the use of Victrelis in pregnant women.

Treated patients and their partners must use two effective forms of contraceptive methods when boceprevir is used in combination with peginterferon alfa and ribavirin. Refer to Summary of Product Characteristics for ribavirin and peginterferon alfa for additional information.

Breastfeeding
Boceprevir/metabolites are excreted in rat milk (see section 5.3). It is not known whether boceprevir is excreted in human breast milk.
A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy with Victrelis taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
No human data on the effect of Victrelis on fertility are available. Effects on fertility and Sertoli cells have been observed in rats but not in mice and monkeys. Clinical data (semen analyses and inhibin B levels – [a glycoprotein produced by Sertoli cells – used as a surrogate marker of testicular function]) showed no evidence of altered testicular function. Available pharmacodynamic/toxicological data in rats have shown effects of boceprevir/metabolites on fertility, which in females have been shown to be reversible (see section 5.3).

4.7 Effects on ability to drive and use machines

Combination therapy of Victrelis, peginterferon alfa and ribavirin may influence some patients' ability to drive and use machines. Patients should be informed that fatigue, dizziness, syncope, blood pressure fluctuations and blurred vision have been reported (see section 4.8).

4.8 Undesirable effects

The safety profile represented by approximately 1,500 patients for the combination of Victrelis with peginterferon alfa-2b and ribavirin was based on pooled safety data in two clinical trials in patients who were previously untreated and one clinical trial in patients who had failed prior therapy (see section 5.1).

The most frequently reported adverse reactions were fatigue, anaemia (see section 4.4), nausea, headache, and dysgeusia.

The most common reason for dose reduction was anaemia, which occurred more frequently in subjects receiving the combination of Victrelis with peginterferon alfa-2b and ribavirin than in subjects receiving peginterferon alfa-2b and ribavirin alone.

Adverse reactions are listed by System Organ Class (see Table 3). Within each system organ class, adverse reactions are listed under headings of frequency using the categories: 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).

Table 3
Adverse reactions in combination with Victrelis with peginterferon alfa-2b and ribavirin reported during clinical trials[† and ‡]

System Organ Class	Adverse Reactions
Infections and infestations	
Common:	Bronchitis*, cellulitis*, herpes simplex, influenza, oral fungal infection, sinusitis
Uncommon:	Gastroenteritis*, pneumonia*, staphylococcal infection*, candidiasis, ear infection, fungal skin infection, nasopharyngitis, onychomycosis, pharyngitis, respiratory tract infection, rhinitis, skin infection, urinary tract infection
Rare:	Epiglottitis*, otitis media, sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Thyroid neoplasm (nodules)
Blood and lymphatic system disorders	
Very common:	Anaemia*, neutropenia*
Common:	Leukopenia*, thrombocytopenia*
Uncommon:	Haemorrhagic diathesis, lymphadenopathy, lymphopenia
Rare:	Haemolysis
Immune system disorders	
Rare:	Sarcoidosis*, porphyria non-acute
Endocrine disorders	
Common:	Goitre, hypothyroidism
Uncommon:	Hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Decreased appetite*
Common:	Dehydration*, hyperglycaemia*, hypertriglyceridaemia, hyperuricaemia
Uncommon:	Hypokalaemia*¸ appetite disorder, diabetes mellitus, gout, hypercalcaemia
Psychiatric disorders	
Very common:	Anxiety*, depression*, insomnia, irritability
Common:	Affect lability, agitation, libido disorder, mood altered, sleep disorder
Uncommon:	Aggression*, homicidal ideation*, panic attack*, paranoia*, substance abuse*, suicidal ideation*, abnormal behaviour, anger, apathy, confusional state, mental status changes, restlessness
Rare:	Bipolar disorder*, completed suicide*, suicide attempt*, hallucination auditory, hallucination visual, psychiatric decompensation
Nervous system disorders	
Very common:	Dizziness*, headache*
Common:	Hypoaesthesia*, paraesthesia*, syncope*, amnesia, disturbance in attention, memory impairment, migraine, parosmia, tremour, vertigo
Uncommon:	Neuropathy peripheral*, cognitive disorder, hyperaesthesia, lethargy, loss of consciousness, mental impairment, neuralgia, presyncope
Rare:	Cerebral ischaemia*, encephalopathy

System Organ Class	Adverse Reactions
Eye disorders	
Common:	Dry eye, retinal exudates, vision blurred, visual impairment
Uncommon:	Retinal ischaemia*, retinopathy*, abnormal sensation in eye, conjunctival haemorrhage, conjunctivitis, eye pain, eye pruritus, eye swelling, eyelid oedema, lacrimation increased, ocular hyperaemia, photophobia
Rare:	Papilloedema
Ear and labyrinth disorders	
Common:	Tinnitus
Uncommon:	Deafness*, ear discomfort, hearing impaired
Cardiac disorders	
Common:	Palpitations
Uncommon:	Tachycardia*, arrhythmia, cardiovascular disorder
Rare:	Acute myocardial infarction*, atrial fibrillation*, coronary artery disease*, pericarditis*, pericardial effusion
Vascular disorders	
Common:	Hypotension*, hypertension
Uncommon:	Deep vein thrombosis*, flushing, pallor, peripheral coldness
Rare:	Venous thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough*, dyspnoea*
Common:	Epistaxis, nasal congestion, oropharyngeal pain, respiratory tract congestion, sinus congestion, wheezing
Uncommon:	Pleuritic pain*, pulmonary embolism*, dry throat, dysphonia, increased upper airway secretion, oropharyngeal blistering
Rare:	Pleural fibrosis*, orthopnoea, respiratory failure
Gastrointestinal disorders	
Very common:	Diarrhoea*, nausea*, vomiting* dry mouth, dysgeusia
Common:	Abdominal pain*, abdominal pain upper*, constipation*, gastrooesophageal reflux disease*, haemorrhoids*, abdominal discomfort, abdominal distention, anorectal discomfort, aphthous stomatitis, cheilitis, dyspepsia, flatulence, glossodynia, mouth ulceration, oral pain, stomatitis, tooth disorder
Uncommon:	Abdominal pain lower*, gastritis*, pancreatitis*, anal pruritus, colitis, dysphagia, faeces discoloured, frequent bowl movements, gingival bleeding, gingival pain, gingivitis, glossitis, lip dry, odynophagia, proctalgia, rectal haemorrhage, salivary hypersecretion, sensitivity of teeth, tongue discolouration, tongue ulceration
Rare:	Pancreatic insufficiency
Hepatobiliary disorders	
Uncommon:	Hyperbilirubinaemia
Rare:	Cholecystitis*

System Organ Class	Adverse Reactions
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, dry skin, pruritus, rash
Common:	Dermatitis, eczema, erythema, hyperhidrosis, night sweats, oedema peripheral, psoriasis, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, skin lesion
Uncommon:	Photosensitivity reaction, skin ulcer, urticaria
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia
Common:	Back pain*, pain in extremity*, muscle spasms, muscular weakness, neck pain
Uncommon:	Musculoskeletal chest pain*, arthritis, bone pain, joint swelling, musculoskeletal pain
Renal and urinary disorders	
Common:	Pollakiuria
Uncommon:	Dysuria, nocturia
Reproductive system and breast disorders	
Common:	Erectile dysfunction
Uncommon:	Amenorrhoea, menorrhagia, metrorrhagia
Rare:	Aspermia
General disorders and administration site conditions	
Very common:	Asthenia*, chills, fatigue*, pyrexia*, influenza-like illness
Common:	Chest discomfort*, chest pain*, malaise*, feeling of body temperature change, mucosal dryness, pain
Uncommon:	Feeling abnormal, impaired healing, non-cardiac chest pain
Investigations	
Very common:	Weight decreased
Uncommon:	Cardiac murmur, heart rate increased

* Includes adverse reactions which may be serious as assessed by the investigator in clinical trial subjects.

† Since Victrelis is prescribed with peginterferon alfa and ribavirin, please also refer to the respective Summary of Product Characteristics of peginterferon alfa and ribavirin.

‡ Injection-site reactions have not been included since Victrelis is administered orally.

Description of selected adverse reactions

Anaemia (see section 4.4)

Anaemia was observed in 49% of subjects treated with the combination of Victrelis with peginterferon alfa-2b and ribavirin compared with 29% of subjects treated with peginterferon alfa-2b and ribavirin alone. Victrelis was associated with an additional decrease of approximately 1 g/dl in haemoglobin concentration (see section 4.4). The mean decreases in haemoglobin values from baseline were larger in previously treated patients compared to patients who had never received prior therapy. Dose modifications due to anaemia/hemolytic anaemia occurred twice as often in patients treated with the combination of Victrelis with peginterferon alfa-2b and ribavirin (26%) compared to peginterferon alfa-2b and ribavirin alone (13%). In clinical trials, the proportion of subjects who received erythropoietin for the management of anaemia was 43% (667/1,548) of subjects in the Victrelis-containing arms compared to 24% (131/547) of subjects receiving peginterferon alfa-2b and ribavirin alone. The majority of the anaemia subjects received erythropoietin when having haemoglobin levels were were ≤ 10 g/dl (or 6.2 mmol/l). The proportion of subjects who received a transfusion for the management of anaemia was 3% of subjects in the Victrelis-containing arms compared to < 1% of subjects receiving peginterferon alfa-2b and ribavirin alone.

Neutrophils (see section 4.4)
The proportion of subjects with decreased neutrophils was higher in the Victrelis-containing arms compared to subjects receiving only peginterferon alfa-2b and ribavirin. The percentage of patients with Grades 3-4 neutropenia (neutrophil counts < 0.75 x 10^9/l) was higher in boceprevir-treated patients (29%) than in placebo-treated patients (17%), in combination with peginterferon alfa-2b and ribavirin. Seven percent of subjects receiving the combination of Victrelis with peginterferon alfa-2b and ribavirin had neutrophil counts of < 0.5 x 10^9/l (Grade 4 neutropenia) compared to 4% of subjects receiving only peginterferon alfa-2b and ribavirin.

Combined use with peginterferon alfa–2a see specific section in section 4.4.

Platelets
Platelet counts were decreased for subjects in the Victrelis containing-arms (3%) compared to subjects receiving peginterferon alfa-2b and ribavirin alone (1%). In both treatment arms, patients with cirrhosis were at a higher risk to experience Grade 3-4 thrombocytopenia compared with non cirrhotic patients.

Other laboratory findings
The addition of Victrelis to peginterferon alfa–2b and ribavirin was associated to higher incidences of increase in uric acid, triglycerides and cholesterol total compared to peginterferon alfa–2b and ribavirin only.

4.9 Overdose

Daily doses of 3,600 mg have been taken by healthy volunteers for 5 days without untoward symptomatic effects. There is no specific antidote for overdose with Victrelis. Treatment of overdose with Victrelis should consist of general supportive measures, including monitoring of vital signs, and observation of the patient's clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE12

Mechanism of action
Boceprevir is an inhibitor of the HCV NS3 protease. Boceprevir covalently, yet reversibly, binds to the NS3 protease active site serine (Ser139) through a (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells.

Antiviral activity in cell culture
The antiviral activity of boceprevir was evaluated in a biochemical assay for slow binding inhibitors of NS3 protease and in the genotype 1a and 1b HCV replicon system. The IC_{50} and IC_{90} values for boceprevir against different genotype 1b replicons ranged from 200 to 600 nM and 400 to 900 nM, respectively, in a 72-hour cell culture assay. Loss of replicon RNA appears to be first-order with respect to time of treatment. Treatment at IC_{90} for 72 hours resulted in a 1-log drop in replicon RNA. Prolonged exposure resulted in a 2-log decrease in RNA levels by Day 15. In a genotype 1a replicon, the IC_{50} and IC_{90} values for boceprevir were 900 nM and 1,400 nM, respectively.

Evaluation of varying combinations of boceprevir and interferon alfa-2b that produced 90% suppression of replicon RNA showed additivity of effect; no evidence of synergy or antagonism was detected.

Resistance
Resistance to boceprevir was characterized in biochemical and replicon assays. In replicon assays, the potency of boceprevir was reduced (2 – 16 fold) by the following major resistance resistant-associated

amino acid variants (RAVs): V36M, T54A, R155K, A156S, and V170A. A loss of potency (> 50 fold) was observed with resistant-associated amino acid variant: A156T. Of note, replicons carrying the A156T variant are less fit than replicons carrying other RAVs. Similar results were obtained with boceprevir in *in vitro* NS3 enzymatic studies, where potency was reduced (2 to 17 fold) by RAVs V36M, T54A, T54S, V55A, R155K, A156S and V170A. The loss of potency associated with A156T was > 50 fold. The fold increase in resistance for double RAVs was approximately equal to the product of fold resistances for the individual RAVs.

In a pooled analysis of subjects who were previously untreated and subjects who have failed previous therapy who received four weeks of peginterferon alfa-2b and ribavirin followed by Victrelis 800 mg three times daily in combination with peginterferon alfa-2b and ribavirin in two Phase III studies, post-baseline RAVs were detected in 15% of all subjects. In Victrelis-treated subjects who did not attain sustained virologic response (SVR) for whom samples were analyzed, 53% had post-baseline RAVs detected.

The most frequently (> 25% of subjects) detected post-baseline RAVs in these subjects were amino acid substitutions V36M (61%) and R155K (68%) in subjects infected with genotype 1a viruses and T54A (42%), T54S (37%), A156S (26%) and V170A (32%) in subjects infected with genotype 1b viruses.

In subjects treated with Victrelis, interferon responsiveness (as defined by $\geq$ 1-$\log_{10}$ decline in viral load at Treatment Week 4) was associated with detection of fewer RAVs, with 6% of these subjects having RAVs compared to 41% of subjects with < 1-$\log_{10}$ decline in viral load at Treatment Week 4 (poorly interferon responsive).

In subjects treated with Victrelis who did not achieve SVR and with post-baseline samples analyzed for RAVs, interferon responsiveness was associated with detection of fewer RAVs, with 31% of these subjects having post-baseline RAVs compared to 68% of subjects with < 1-$\log_{10}$ decline in viral load at Treatment Week 4.

RAVs were detected in 7% of patients at baseline by population sequencing. Overall, the presence of baseline RAVs did not appear to have a notable association with treatment response in subjects receiving the combination of Victrelis with peginterferon alfa-2b and ribavirin.

However, among poorly interferon-responsive patients to peginterferon alfa–2b/ribavirin during the 4-week lead-in period, the efficacy of Victrelis appeared to be reduced for those who had variants V36M, T54A, T54S, V55A or R155K detected at baseline. Subjects with these baseline variants and reduced response to peginterferon alfa–2b/ribavirin represented approximately 1% of the total number of subjects treated with Victrelis. The presence of baseline RAVs did not appear to have a notable association with treatment response in subjects receiving the combination of Victrelis with peginterferon alfa-2b and ribavirin.

An analysis of data from an ongoing, long-term follow-up study in subjects from these Phase III studies who did not achieve SVR examined the persistence of RAVs. During the 6-14 month post-therapy period, the majority of subjects (68%–94%) had RAVs that became undetectable by population sequencing.

Efficacy

The efficacy of Victrelis as a treatment for chronic hepatitis C (genotype 1) infection was assessed in approximately 1,500 adult subjects who were previously untreated (SPRINT-2) or who had failed previous therapy (RESPOND-2) in Phase III clinical studies. In both studies, the addition of Victrelis to the current standard of care (peginterferon alfa and ribavirin) significantly increased sustained virologic response (SVR) rates compared to the current standard of care alone. It should be noted that retrospective analyses bridging the data between the two pivotal studies have led to a recommended posology that differs from the regimen studied in some patient subgroups.

Patients who are previously untreated

SPRINT-2 (P05216) was a randomized, double blinded, placebo-controlled study comparing two therapeutic regimens of Victrelis 800 mg orally three times daily in combination with PR [peginterferon alfa-2b 1.5 µg/kg/week subcutaneously and weight-based dosing with ribavirin (600-1,400 mg/day orally divided twice daily)] to PR alone in adult subjects who had chronic hepatitis C (HCV genotype 1) infection with detectable levels of HCV-RNA and were not previously treated with interferon alfa therapy. Subjects were randomized in a 1:1:1 ratio in two cohorts (Cohort 1 N= 938/non-Black and Cohort 2 /Black N=159) and stratified by HCV genotype (1a or 1b) and by HCV-RNA viral load (≤ 400,000 IU/ml vs. > 400,000 IU/ml) to one of the following three treatment arms:

- Peginterferon alfa-2b + ribavirin for 48 weeks (PR48).
- Peginterferon alfa-2b + ribavirin for 4 weeks followed by Victrelis 800 mg three times daily + peginterferon alfa-2b + ribavirin for 24 weeks. The subjects were then continued on different regimens based on Treatment Week (TW) 8 response-guided therapy (Victrelis-RGT). All patients in this treatment arm were limited to 24 weeks of therapy with Victrelis.
    - Subjects with undetectable HCV-RNA at TW 8 (early responders) and who also had undetectable HCV-RNA through TW 24 discontinued therapy and entered follow-up at the TW 28 visit.
    - Subjects with detectable HCV-RNA at TW 8 or any subsequent treatment week but subsequently undetectable at TW 24 (late responders) were changed in a blinded fashion to placebo at the TW 28 visit and continued therapy with peginterferon alfa-2b + ribavirin for an additional 20 weeks, for a total treatment duration of 48 weeks.
- Peginterferon alfa-2b + ribavirin for four weeks followed by Victrelis 800 mg three times daily + peginterferon alfa-2b + ribavirin for 44 weeks (Victrelis-PR48).

All subjects with detectable HCV-RNA in plasma at TW 24 were discontinued from treatment. Sustained Virologic Response (SVR) to treatment was defined as undetectable[1] plasma HCV-RNA at follow-up week 24.

The addition of Victrelis to peginterferon alfa-2b and ribavirin significantly increased the SVR rates compared to peginterferon alfa-2b and ribavirin alone in the combined cohort (63% to 66% Victrelis-containing arms vs. 38% PR48 control) for randomized subjects who received at least one dose of any study medicine (Full-Analysis-Set population) and decreased the length of therapy to 28 weeks for early responders (see Table 4). A secondary analysis of subjects who received at least one dose of Victrelis or placebo after the four-week lead-in with peginterferon alfa-2b and ribavirin (Modified-Intent-to-Treat population) demonstrated SVR rates in the combined cohort of 67% to 68% Victrelis-containing arms vs. 40% PR48 control.

Table 4
Sustained Virologic Response (SVR)*, End of Treatment (EOT) and Relapse† Rates for patients who are previously untreated

Study Cohorts	Victrelis-RGT	Victrelis-PR48	PR48
All subjects §	n=368	n=366	n=363
SVR‡ % (n/N) 95% CI	63 (233/368) (58.4, 68.2)	66 (242/366) (61.3, 71.0)	38 (137/363) (32.8, 42.7)
EOT(Undetectable HCV-RNA) % (n/N) 95% CI	71 (261/368) (66.3, 75.6)	76 (277/366) (71.3, 80.1)	53 (191/363) (47.5, 57.8)
Relapse† %(n/N) 95% CI	9 (24/257) (5.8, 12.9)	9 (24/265) (5.6, 12.5)	22 (39/176) (16.0, 28.3)

[1] In clinical trials, HCV-RNA in plasma was measured with a Roche COBAS Taqman assay with a limit of detection of 9.3 IU/ml and a limit of quantification of 25 IU/ml.

Study Cohorts	Victrelis-RGT	Victrelis-PR48	PR48
[*] The Full Analysis Set (FAS) consisted of all randomized subjects (N=1,097) who received at least one dose of any study medicine (peginterferon alfa-2b, ribavirin, or Victrelis). Mean age of subjects randomized was 49.1 years. The race distribution of subjects was as follows: 82% White, 14% Black, 2% Asian, 1% multiracial, 1% American Indian or Alaskan Native. The distribution of subjects by gender was 60% men and 40% women. [†] Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects who were undetectable at EOT and not missing End of Follow-up (EOF) data. [‡] SVR: The last available value in the period at or after Follow-up Week (FW) 24. If there is no such value, the FW 12 value is carried forward. SVR24 rates (SVR with "missing=failure" approach) were nearly identical. All subjects: 37% Control; 62% Victrelis-RGT, 65% Victrelis-PR48. [§] The number of subjects with cirrhosis is limited (n=40).			

Interferon-responsiveness (as defined by ≥ 1-$\log_{10}$ decline in viral load at TW 4) was predictive of SVR. In subjects who demonstrated interferon responsiveness by TW 4, treatment with the combination of Victrelis with peginterferon alfa-2b and ribavirin resulted in SVR rates of 79-81%, compared to 51% in subjects treated with standard of care. In subjects with < 1-$\log_{10}$ decline in viral load at TW 4 (poor interferon-responsiveness), treatment with the combination of Victrelis with peginterferon alfa-2b and ribavirin resulted in SVR rates of 28–38%, respectively, compared to 4% in subjects treated with standard of care.

Sustained Virologic Response (SVR) in patients receiving similar therapy up to treatment week 28
Table 5 presents sustained virologic response per treatment arm in previously untreated patients who were early responders late responders and that received similar therapy up to treatment week 28. Fifty-seven percent (208/368) of subjects in the Victrelis-RGT arm and 56% (204/366) of subjects in the Victrelis-PR48 arm had undetectable HCV-RNA at TW 8 compared with 17% (60/363) of subjects in the PR arm.

Table 5
Sustained Virologic Response (SVR), End of Treatment (EOT), and Relapse in previously untreated patients (early and late responders)

	Victrelis-RGT	Victrelis-PR48	Point estimate of the difference (Victrelis-RGT minus Victrelis-PR48) [95% CI]
Early Responders (N=323)			
SVR %, (n/N)	96.3 (156/162)	96.3 (155/161)	0.0 [-4.1, 4.1]
EOT %, (n/N)	100.0 (162/162)	98.8 (159/161)	-
Relapse %, (n/N)	3.1 (5/161)	1.3 (2/157)	-
Late responders (N=141)			
SVR %, (n/N)	66.2 (45/68)	75.3 (55/73)	-9.2 [-24.4, 6.3]
EOT %, (n/N)	76.5 (52/68)	90.4 (66/73)	-
Relapse %, (n/N)	13.5 (7/52)	14.1 (9/64)	-

As a conservative measure in view of the limitations of the data, in treatment naïve patients–late responders, the treatment duration of the tritherapy is recommended to be prolonged to 32 weeks as compared to the tested 28 weeks duration of the tritherapy, for a total treatment duration of 48 weeks.

Patients who have failed previous therapy
RESPOND-2 (P05101) was a randomized, parallel-group, double-blinded study comparing two therapeutic regimens of Victrelis 800 mg orally three times daily in combination with PR

[peginterferon alfa-2b 1.5 µg/kg/week subcutaneously and weight-based ribavirin (600 – 1,400 mg BID) orally divided twice daily] compared to PR alone in adult subjects with chronic hepatitis C (HCV) genotype 1 infection with demonstrated interferon responsiveness (as defined historically by a decrease in HCV-RNA viral load ≥ 2 $\log_{10}$ by Week 12 or undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma) and who failed prior treatment with peginterferon alfa and ribavirin. Null responders (as defined historically by a decrease in HCV-RNA viral load < 2 $\log_{10}$ by Week 12 to prior therapy) were excluded. Subjects were randomized in a 1:2:2 ratio and stratified based on response to their previous qualifying regimen (relapsers vs. non-responders) and by HCV subtype (1a vs. 1b) to one of the following treatment arms:

- Peginterferon alfa–2b + ribavirin for 48 weeks (PR48).
- Peginterferon alfa–2b + ribavirin for 4 weeks followed by Victrelis 800 mg three times daily + peginterferon alfa–2b + ribavirin for 32 weeks. The subjects were then continued on different treatment regimens based on TW 8 response-guide therapy (Victrelis-RGT). All patients in this treatment arm were limited to 32 weeks of Victrelis.
    - Subjects with undetectable HCV-RNA at TW 8 (early responders) and TW 12 completed therapy at TW 36 visit.
    - Subjects with a detectable HCV-RNA at TW 8 but subsequently undetectable at TW 12 (late responders) were changed in a blinded fashion to placebo at the TW 36 visit and continued treatment with peginterferon alfa–2b + ribavirin for an additional 12 weeks, for a total treatment duration of 48 weeks.
- Peginterferon alfa-2b + ribavirin for 4 weeks followed by Victrelis 800 mg three times daily + peginterferon alfa-2b + ribavirin for 44 weeks (Victrelis-PR48).

All subjects with detectable HCV-RNA in plasma at TW 12 were discontinued from treatment. Sustained Virologic Response (SVR) to treatment was defined as undetectable[1] plasma HCV-RNA at FW 24.

The addition of Victrelis to the peginterferon alfa-2b and ribavirin therapy significantly increased the SVR rates compared to peginterferon alfa-2b and ribavirin therapy alone (59% to 66% Victrelis-containing arms vs. 21% PR48 control) for randomized subjects who received at least one dose of any study medicine (Full-Analysis-Set population) and decreased the length of therapy to 36 weeks for many previous treatment failures (see Table 6). A secondary analysis of subjects who received at least one dose of Victrelis or placebo after the four week lead-in with peginterferon alfa–2b and ribavirin (Modified-Intent-to-Treat population) demonstrated SVR rates of 61% to 67% in the Victrelis-containing arms compared to 22% PR48 control.

Achievement of SVR was associated with the subject's response to peginterferon alfa-2b and ribavirin therapy, whether defined by classification of response to previous treatment, or by a decrease in HCV-RNA at TW 4 (see Table 6). The TW 4 response was a stronger predictor of SVR compared to response to previous treatment and allowed the determination of the subject's on-treatment interferon responsiveness.

Table 6
Sustained Virologic Response (SVR)[*], End of Treatment (EOT), and Relapse[**] Rates for patients who have failed previous therapy

[1] In clinical trials, HCV-RNA in plasma was measured with a Roche COBAS Taqman assay with a limit of detection of 9.3 IU/ml and a limit of quantification of 25 IU/ml.

			Victrelis-RGT (N=162)	Victrelis-PR48 (N=161)	PR48 (N=80)
All Subjects[§]		SVR[‡‡] % (n/N) 95% CI	59 (95/162) (51.5, 66.2)	66 (107/161) (59.2, 73.8)	21 (17/80) (12.3, 30.2)
		EOT %, (n/N) 95% CI	70 (114/162) (63.3, 77.4)	77 (124/161) (70.5, 83.5)	31 (25/80) (21.1, 41.4)
		Relapse[**] %, (n/N) 95% CI	15 (17/111) (8.6, 22.0)	12 (14/121) (5.9, 17.3)	32 (8/25) (17.3, 50.3)
Previous Treatment Response	**Previous Non-Responders**[***]	SVR[‡‡] %, (n/N)	40 (23/57)	52 (30/58)	7 (2/29)
		EOT %, (n/N)	54 (31/57)	60 (35/58)	10 (3/29)
		Relapse[**] %, (n/N)	18 (5/28)	14 (5/35)	33 (1/3)
	Previous Relapsers[†]	SVR[‡‡] %, (n/N)	69 (72/105)	75 (77/103)	29 (15/51)
		EOT % (n/N)	79 (83/105)	86 (89/103)	43 (22/51)
		Relapse[**] %, (n/N)	14 (12/83)	10 (9/86)	32 (7/22)
Lead-In Response[‡] **(Viral Load Reduction)**	**< 1-log$_{10}$ decline**	SVR[‡‡] %, (n/N)	33 (15/46)	34 (15/44)	0 (0/12)
		EOT %, (n/N)	41 (19/46)	48 (21/44)	0 (0/12)
		Relapse[**] %, (n/N)	12 (2/17)	25 (5/20)	0 (0/0)
	≥ 1-log$_{10}$ decline	SVR[‡‡] %, (n/N)	73 (80/110)	79 (90/114)	25 (17/67)
		EOT %, (n/N)	86 (95/110)	89 (101/114)	37 (25/67)
		Relapse[**] %, (n/N)	16 (15/94)	9 (9/99)	32 (8/25)

[*] The Full Analysis Set (FAS) consisted of all randomized subjects (N=403) who received at least one dose of any study medicine (peginterferon alfa–2b, ribavirin, or Victrelis). Mean age of subjects randomized was 52.7 years. The race distribution of subjects was as follows: 85% White, 12% Black, 1% Asian, < 1% multiracial, < 1% Native Hawaiian or Other Pacific Islander. The distribution of subjects by gender was 67% men and 33% women.

[**] Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects who were undetectable at EOT and not missing End of Follow-up (EOF) data.

[***] Previous Non-Responder = subject who failed to achieve SVR after at least 12 weeks of previous treatment with peginterferon alfa and ribavirin, but demonstrated a ≥ 2 $\log_{10}$ reduction in HCV-RNA by Week 12.

[†] Previous Relapser = subject who failed to achieve SVR after at least 12 weeks of previous treatment with peginterferon alfa and ribavirin, but had undetectable HCV-RNA at the end of treatment.

[‡] Eleven subjects were missing TW 4 assessment (HCV-RNA) and were not included in the Lead-In response results.

[‡‡] Sustained Virologic Response (SVR): The last available value in the period at and after Follow-up Week (FW) 24. If there is no such value, the FW 12 value was carried forward. SVR rates (SVR with "missing=failure" approach) 17/80 [21.3%] PR48, 94/162 [58.0] Victrelis-RGT, 106/161 [65.8%] Victrelis-PR48.

[§] The number of subjects with cirrhosis is limited (n=39).

Sustained Virologic Response (SVR) in patients receiving similar therapy up to treatment week 36

Table 7 presents sustained virologic response per treatment arm in patients who had failed previous therapy that were early responders and late responders and that received similar therapy up to treatment week 36.

Table 7

Sustained Virologic Response (SVR), End of Treatment (EOT) and Relapse in patients who had failed previous therapy (early and late responders)

	Victrelis-RGT	**Victrelis-PR48**	**Point estimate of the difference (Victrelis-RGT minus Victrelis-PR48) [95% CI]**
Early Responders (N=144)			
SVR %, (n/N)	88.7 (63/71)	97.3 (71/73)	-8.5 [-16.8, -0.3]
EOT %, (n/N)	98.6 (70/71)	98.6 (72/73)	-
Relapse %, (n/N)	10.1 (7/69)	0 (0/71)	-
Late responders (N=75)			
SVR %, (n/N)	80.0 (28/35)	72.5 (29/40)	7.5 [-11.7, 26.7]
EOT %, (n/N)	97.1 (34/35)	92.5 (37/40)	-
Relapse %, (n/N)	17.6 (6/34)	19.4 (7/36)	-

As a conservative measure in view of limitations of the data, in treatment experienced patients early responders, the total treatment duration is recommended to be prolonged to 48 weeks as compared to the tested 36 weeks total treatment duration (tested RGT), with a 12 weeks of peginterferon ribavirin consolidation phase after the end of the tritherapy at week 36.

A study with peginterferon alfa–2a in treatment experienced patients gave consistent results as compared to the study P05101 (see section 4.4).

Exploratory pharmacogenomic analysis of IL28B in phase 3 studies of Victrelis
A genetic variant near the gene encoding interferon-lambda-3 (*IL28B* rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa–2b/ribavirin. *IL28B* rs12979860 was genotyped in 653 of 1,048 (62%) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPOND-2 (previous treatment failure) [see section 5.1 for the clinical trial descriptions]. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences of the sub-study population relative to the overall trial population.

The degree of added value of Victrelis on top of the bitherapy in C/C patients will depend on the likelihood of achieving SVR with the bitherapy only. In C/C patients receiving tritherapy 89% in treatment naive were HCV-RNA undetectable by TW 8 and eligible for shorter duration of therapy as compared to 52% in treatment naïve non C/C.

Table 8
Sustained Virologic Response (SVR) rates by *IL28B* rs12979860 genotype

Clinical Study	***IL28B rs12979860* Genotype**	**PR48* SVR, % (n/N)**	**Victrelis-RGT* SVR, % (n/N)**	**Victrelis-PR48* SVR, % (n/N)**
SPRINT-2 (previously untreated subjects)	C/C	78 (50/64)	82 (63/77)	80 (44/55)
	C/T	28 (33/116)	65 (67/103)	71 (82/115)
	T/T	27 (10/37)	55 (23/42)	59 (26/44)
RESPOND-2 (subjects who have failed previous therapy)	C/C	46 (6/13)	79 (22/28)	77 (17/22)
	C/T	17 (5/29)	61 (38/62)	73 (48/66)
	T/T	50 (5/10)	55 (6/11)	72 (13/18)

*Please see section 5.1 clinical trial descriptions for each treatment arm.

Whether on treatment early viral response and/or IL28B genotype could reliably identify those patients who are unlikely to retrieve significant benefit of boceprevir (higher SVR rates or short course treatment duration) on top of the bitherapy is currently under investigation.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Victrelis in one or more subsets of the paediatric population in chronic viral hepatitis C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Boceprevir was absorbed following oral administration with a median T_{max} of 2 hours. Steady state AUC, C_{max} and C_{min} increased in a less-than dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. Accumulation is minimal and pharmacokinetic steady state is achieved after approximately 1 day of three times daily dosing.

In healthy subjects who received 800 mg three times daily alone, boceprevir medicine exposure was characterized by AUC(τ) of 6,147 ng.hr/ml, C_{max} of 1,913 ng/ml, and C_{min} of 90 ng/ml. Pharmacokinetic results were similar between healthy subjects and HCV-infected subjects.

The absolute bioavailability of Victrelis has not been studied.

Effects of food on oral absorption
Victrelis should be administered with food. Food enhanced the exposure of boceprevir by up to 60% at the 800 mg three times daily dose when administered with a meal relative to the fasting state. The bioavailability of boceprevir is regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal.

Distribution
Boceprevir has a mean apparent volume of distribution (Vd/F) of approximately 772 l at steady state. Human plasma protein binding is approximately 75% following a single dose of Victrelis 800 mg. Boceprevir is administered as an approximately equal mixture of two diastereomers which rapidly interconvert in plasma. At steady-state, the exposure ratio for the two diastereomers is approximately 2:1, with the predominant diastereomer being pharmacologically active.

Biotransformation
Studies *in vitro* indicate that boceprevir primarily undergoes metabolism through the aldo-ketoreductase (AKR)-mediated pathway to ketone-reduced metabolites that are inactive against HCV. After a single 800 mg oral dose of ^{14}C-boceprevir, the most abundant circulating metabolites were a diasteriomeric mixture of ketone-reduced metabolites with a mean exposure approximately 4–fold greater than that of boceprevir. Boceprevir also undergoes, to a lesser extent, oxidative metabolism mediated by CYP3A4/5.

Elimination
Boceprevir is eliminated with a mean plasma half-life (t½) of approximately 3.4 hours. Boceprevir has a mean total body clearance (CL/F) of approximately 161 l/hr. Following a single 800 mg oral dose of ^{14}C-boceprevir, approximately 79% and 9% of the dose was excreted in faeces and urine, respectively, with approximately 8% and 3% of the dosed radiocarbon eliminated as boceprevir in faeces and urine. The data indicate that boceprevir is eliminated primarily by the liver.

Special populations

Hepatic impairment
In a study of patients with varying degrees of stable chronic liver impairment (mild, moderate and severe), no clinically significant differences in pharmacokinetic parameters were found, and no dose adjustment is recommended. Victrelis, in combination with peginterferon alfa and ribavirin, is contraindicated in cirrhotic patients with a Child-Pugh score > 6 (class B and C) (see section 4.3).

Renal impairment
No clinically significant differences in pharmacokinetic parameters were observed between patients with end-stage renal disease (ESRD) and healthy subjects. Boceprevir is not eliminated by dialysis. No dose adjustment is required in these patients and in patients with any degree of renal impairment.

Gender
No gender-related pharmacokinetic differences in the phase III studies have been observed in adult patients.

Race
Population pharmacokinetic analysis of Victrelis indicated that race had no apparent effect on exposure.

Age
Population pharmacokinetic analysis of Victrelis indicated that age had no apparent effect on exposure.

5.3 Preclinical safety data

In an *in vitro* dog Purkinje fiber study, boceprevir prolonged the action potential duration with inverse frequency dependence; the clinical relevance remains uncertain.

In repeat-dose toxicity studies boceprevir showed testicular degeneration in rats at systemic exposures lower than those in humans at the recommended human therapeutic dose. This is not observed in mice or monkeys.

Boceprevir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, human peripheral blood lymphocyte and mouse micronucleus assays.

In 2-year carcinogenicity studies, no carcinogenicity was observed, but there was an increased incidence of hepatocellular adenomas in mice, which was not statistically significant, at systemic exposures 5.7-fold higher than those in humans at the recommended therapeutic dose. No carcinomas or adenomas were observed in rats. The hepatocellular tumours are considered due to enzyme induction and therefore not relevant for humans.

Boceprevir/medicine derived material was shown to be transferred into the milk of lactating rats. Exposure to boceprevir in nursing human infants is estimated to be less than 1% of the dose.

In rats, boceprevir induced reversible effects on fertility and early embryonic development in female rats at exposures 1.2-fold the human exposure at the recommended therapeutic dose. Decreased fertility was also observed in male rats, most likely as a consequence of testicular degeneration (no testicular degeneration has been observed in mice or monkeys). Boceprevir was shown to be devoid of embryonic or teratogenic potential in both rats and rabbits at maternotoxic dose levels.

Data obtained in juvenile rats suggest that the pharmacokinetic profile of boceprevir may be different than in adult rats, possibly due to immaturity of some metabolic pathways. No clinical paediatric exposure data is available (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
- Sodium lauryl sulfate
- Microcrystalline cellulose
- Lactose monohydrate
- Croscarmellose sodium
- Pre-gelatinized starch
- Magnesium stearate

Capsule shell
- Gelatin
- Titanium dioxide (E171)
- Yellow iron oxide (E172)
- Red iron oxide (E172)

Red printing ink containing:
- Shellac
- Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Storage by the pharmacist
Store in a refrigerator (2°C – 8°C).

Storage by the patient
- Store in a refrigerator (2°C – 8°C) until expiry.

OR
- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry. After this period, the medicinal product should be disposed.

Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Clear polychlorotrifluoroethylene /PVC/aluminium blisters containing 4 hard capsules per blister cavity. Each blister cavity is heat sealed closed with the peelable lidding in a configuration of 3 blister cavities per blister card and packaged.
Pack sizes: carton of 84 hard capsules and multipack containing 336 (4 packs of 84) hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/704/001
EU/1/11/704/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

S-P Labo NV
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Victrelis are provided with a healthcare professional educational pack containing the following at launch:

- The Physician Educational Materials (PEM)
- The Summary of Product Characteristics (in full)
- The Patient Information Leaflet

The PEM should contain the following key elements:

- Detailed information about the risk of haematological disorders (notably anaemia) associated with Victrelis, consisting of factual description of the haematological disorders in terms of frequency and time to onset and related clinical symptoms

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.2 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

Obligation to complete post-authorisation measures
The MAH shall complete, within the stated timeframe, the following measures:

The Marketing Authorisation Holder should provide results of study P06086 to further substantiate the impact of the management of anaemia on the efficacy and safety of therapy with Victrelis. The results of the Study P06086 will be submitted by April 2012.

The Marketing Authorisation Holder should further substantiate the degree of added value of Victrelis depending on the likelihood of achieving SVR with the bitherapy only, based on predictive factors to interferon responsiveness (Il28b). The MAH will provide the results of a study addressing this issue by May 2014 according to an agreed protocol.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton with Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules
boceprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg boceprevir.

3. LIST OF EXCIPIENTS

Also contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 336 (4 packs of 84) hard capsules
84 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not push through blister.
Take with food.
Take 3 times per day; morning, afternoon and evening.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Storage by the pharmacist
Store in a refrigerator.

Storage by the patient
- Store in a refrigerator until expiry.

OR
- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry.

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/704/001	336 hard capsules
EU/1/11/704/002	84 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Victrelis

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Inner carton without Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules
boceprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg boceprevir.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 hard capsules. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not push through blister.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

- Store in a refrigerator until expiry.

OR

- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry.

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/704/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Victrelis

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules
boceprevir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Open here

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Victrelis 200 mg hard capsules
boceprevir

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT VICTRELIS IS AND WHAT IT IS USED FOR

What Victrelis is
Victrelis contains the active ingredient boceprevir which helps to fight against hepatitis C infection by stopping the virus multiplying. Victrelis must always be used together with two other medicines. These are called peginterferon alfa and ribavirin. Victrelis must not be used by itself.

What Victrelis is used for
Victrelis, in combination with peginterferon alfa and ribavirin, is used for chronic hepatitis C virus infection in adults of 18 years and older (also called HCV infection).
Victrelis may be used in adults who are previously untreated for HCV infection or who have previously used medicines called ‘interferons’ and ‘pegylated interferons’.

How Victrelis works
Victrelis works by lowering the amount of HCV in your body.

2. BEFORE YOU TAKE VICTRELIS

Do not take Victrelis in combination with peginterferon alfa and ribavirin if you:
- are **allergic** (hypersensitive) to boceprevir or any of the other ingredients of Victrelis (listed in section 6)
- are **pregnant**
- have a serious **liver** problem (other than hepatitis C)
- have a condition called ‘autoimmune hepatitis’
- are taking bepridil, pimozide, oral midazolam, oral triazolam, 'ergot’ type medicines (such as dihydro-ergotamine, ergonovine, ergotamine or methylergonovine), lumefantrine, halofantrine, or tyrosine kinase inhibitors.

Do not take Victrelis if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Victrelis.
Reminder: Please also read the “Do not use” section of the Package Leaflets for peginterferon alfa and ribavirin before you start taking Victrelis.

Take special care with Victrelis
Check with your doctor or pharmacist before taking your medicine if you:
- have ever had a blood problem such as **anaemia** (when you lack enough healthy red blood cells, which transport oxygen around your body)
- have ever had a blood problem such as neutropenia (lack of a certain type of white blood cells). Neutropenia affects the body's ability to fight off infections.
- have another **liver** problem in addition to hepatitis C infection
- have failed prior therapy and you have been told that you are a null responder
- have **HIV** (human immunodeficiency virus) or have ever had any other problems with your immune system
- were an organ transplant recipient
- have hepatitis C other than genotype 1
- were a patient who has previously failed treatment with an HCV protease inhibitor
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation"
- have low blood potassium (hypokalaemia)

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Victrelis.

Tests
Your doctor will have your blood tested regularly. These blood tests are done for a number of reasons:
- so your doctor knows if the treatment is working for you
- to help your doctor decide how long you will be treated with Victrelis.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription and herbal medicines.

In particular, do not take Victrelis if you are taking any of the following medicines:
- bepridil – used for heart problems
- pimozide – used for mental health problems
- oral midazolam or oral triazolam – a sedative, given by mouth
- 'ergot' type medicines, such as dihydro-ergotamine, ergonovine, ergotamine or methylergonovine – used for migraine and cluster headaches
- lumefantrine and halofantrine – anti-malaria medicines
- tyrosine kinase inhibitors – used as anti-cancer medicines

Do not take Victrelis if you are taking any of the medicines above. If you are not sure, talk to your doctor or pharmacist before taking Victrelis.

Also, tell your doctor or pharmacist if you are taking any of the following:
- birth control medicines (containing drospirenone).
- CYP3A4 inducer medicines (such as rifampicin, carbamazepine, phenobarbital, phenytoin)
- antiarrhythmic medicines- amiodarone, quinidine
- antimicrobial medicine – pentamidine
- some neuroleptics
- antifungal medicines - ketaconazole, itraconazole, posaconazole, voriconazole
- non-nucleoside reverse transcriptase inhibitor – efavirenz
- HIV protease inhibitors – atazanavir, darunavir, lopinavir, ritonavir
- integrase inhibitor – raltegravir
- intravenous sedatives - benzodiazepines (e.g., alprazolam, midazolam, triazolam)
- immunosuppressants – tacrolimus, cyclosporine
- statins - simvastatin or atorvastatin
- methadone

Pregnancy and breast-feeding
Pregnancy must be avoided due to the use of Victrelis with ribavirin during treatment and for 6 months after treatment has been completed. Treated patients and their partners must use two effective forms of contraception when boceprevir is used in combination with peginterferon alfa and ribavirin.

It is possible that boceprevir is excreted in human milk. If you are breastfeeding, your doctor will advise you to discontinue breastfeeding or to discontinue Victrelis while breastfeeding.

Reminder: Please also read the "Pregnancy and breast-feeding" section of the Package Leaflets for peginterferon alfa and ribavirin before you start taking Victrelis.

Driving and using machines
Victrelis does not affect your ability to drive or use tools or machines. However, the combination therapy of Victrelis, peginterferon alfa and ribavirin may make you feel tired, faint, a sensation of your head spinning, changes in blood pressure, confused or difficulty seeing clearly. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Victrelis
Victrelis contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars (you have an intolerance to some sugars), such as Lapp lactase deficiency, or glucosegalactose malabsorption, talk to your doctor before taking this medicine.

3. HOW TO TAKE VICTRELIS

Always take Victrelis exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much to take
The usual dose of Victrelis is 4 capsules three times a day (a total of 12 capsules a day). Take the capsules in the morning, afternoon and evening with a meal or light snack. The use without food could seriously compromise your chance of success of treatment.

How to take this medicine
- Peel back the tab to get to the capsule - do not push the capsule through the blister since pushing the capsule through the package may break the capsule.
- Take this medicine by mouth.
- This medicine should be taken with a meal or light snack.

Reminder: Please also read the "POSSIBLE SIDE EFFECTS" in the Package Leaflets for peginterferon alfa and ribavirin before you start taking Victrelis.

If you take more Victrelis than you should
If you take more Victrelis than you should, talk to a doctor or go to the nearest hospital emergency room straight away.

If you forget to take Victrelis
- If you forget a dose and it is more than 2 hours before your next dose is due, take the missed dose with food. Then continue taking your capsules as normal.
- However, if it is less than 2 hours before your next dose is due, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

If you have any questions about what to do, talk to your doctor.

If you stop taking Victrelis
Do not stop taking Victrelis unless your doctor tells you to.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Victrelis can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:
Stop taking Victrelis and see a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- difficulty breathing, wheezing or hives – these are signs of an allergic reaction.

Other side effects include:
Very common (affects more than 1 in 10 people)

General: headache; chills, fever; feeling sick (nausea); flu-like symptoms; feeling dizzy; not being able to sleep; low appetite, weight loss; shortness of breath
Mouth, nose or throat: cough; dry mouth; funny taste
Skin and hair: dry skin, itching, rash; hair loss or thining of hair
Joints and muscles: unusual weakness; painful, swollen joints; muscle ache not caused by exercise
Stomach and gut: diarrhoea; being sick (vomiting)
Mental illness: feeling anxious; feeling of deep sadness or of being worthless (depression); feeling irritable, tense and restless
Blood: drop in the number of red blood cells – the signs may include feeling tired, headaches, being short of breath when exercising; low number of white blood cells – the signs may include getting more infections than usual - including fever, severe chills, a sore throat or mouth ulcers

Common (affects less than 1 in 10 people)

General: shaking; fainting; difficulty breathing, low energy; feeling thirsty; trouble sleeping; throbbing headache; generally feeling unwell; feeling like you are spinning
Eyes or ears: dry eyes; ringing in the ears; changes in your vision
Mouth, nose or throat: mouth pain, tooth ache; pain when swallowing; nose bleed, stuffy nose; a change in how things smell; sore and raised patches in the mouth; feeling very thirsty with a dry mouth or dry skin; swelling of the thyroid gland, neck or voicebox; sores or swelling in the mouth, burning feeling on the tongue; feeling of tension or fullness in the nose, cheeks and behind the eyes - sometimes with a throbbing ache, fever or stuffy nose (sinusitis)
Skin and hair: cold sores, tingling or numbness of the skin; reduced feeling or sense of touch; skin rash, patchy skin rash, red skin; red raised skin rash sometimes with pus-filled blisters; hot, tender and red skin, sometimes with fever and chills; skin disease with thick patches of red skin – often with silvery scales
Joints and muscles: muscle spasm; feeling tired, muscle weakness, feeling cold; back pain, neck pain, pain in the arms or legs
Stomach and gut: pain in stomach and in the upper right side of the stomach or back; a burning feeling in the stomach, upset stomach; feeling bloated, burping (belching)
Anus: wind (flatulence); piles (haemorrhoids); difficulty passing stools (constipation)
Urinary: going to the toilet to urinate more often than usual
Sexual: a decrease in sex drive; difficulty getting or keeping an erection
Mental illness: changes in mood, feeling agitated; memory loss, trouble concentrating
Chest: difficulty breathing; chest discomfort, chest pain; heavy feeling in the chest, with difficulty breathing or wheezing
Heart or circulation: fast or uneven heart-beat; high or low blood pressure
Blood: drop in the number of blood platelets – the signs may include bleeding or bruising more easily than usual

Uncommon (affects less than 1 in 100 people)

General: fainting; light-headedness, arthritis; increased tendency to bleed; swollen glands in neck or armpit or groin; intense burning or stabbing pain; increased sensitivity to light, sound, what is felt, or food one tastes

Eyes or ears: pink eye; eye pain; deafness; trouble hearing; swelling around the eyelid; increased tearing; fluid draining from the ear or eye; abnormal feeling around the eye, red patch on the white of the eye

Mouth, nose or throat: hoarseness, dry throat or lips; painful or bleeding gums; sensitive tooth or toothache; tongue swollen, discoloured, or has sores; blistering by the tongue; severe pain when swallowing; chest pain close to the lungs; chest pain worsens when taking a deep breath; uncontrolled salivating, yellowing of the white part of the eyes or of the skin

Skin and hair: hives; increased sweating; open sore; intolerance to heat; markedly red face; pale face; yellow skin; rash due to sunlight; wound not healing normally

Feet or hands or legs or arms: sensation of pain, numbness, tingling or prickling; blood clot in a vein; feeling cold in an arm or leg

Stomach and gut: lower stomach pain; pancreatitis

Urinary: painful when urinating; burning feeling or difficulty urinating; get up several times during the night to urinate

Rectum or anus: anal itching; inability to pass stools or discoloured stools; more frequent bowel movements; haemorrhoids or bleeding from anus

Sexual: missing menstrual period; heavy or prolonged menstrual period; uterine bleeding

Mental illness: anger; hostile attitude or behaviour; threatening behaviour; substance abuse problems, abnormal behaviour; feeling of confusion; thoughts of suicide; sudden intense fear or apprehension; feeling you are being persecuted; difficulty solving problems

Muscles: pain in your bones; local or widespread pain

Chest: pneumonia

Heart or circulation: abnormal or rapid heart rate; heart disease caused by poor blood flow in the heart

Blood: high potassium levels in your blood

Rare (affects less than 1 in 1,000 people)

General: difficult breathing and swallowing; tumour of the thyroid; infection of the blood; swelling or lumps in organs of the body; disease which leads to increasing muscle paralysis; disease of the brain – signs may include headache and fever, paralysis of a part of the body, a stiff neck or being sensitive to light

Eyes or ears: ear ache; poor vision or blurred vision

Skin and hair: reddening of the skin; bacterial skin infection

Stomach and gut: problems digesting food; vomiting blood; diarrhoea, cramps or severe stomach (abdominal) pain

Sexual: drop in levels of sperm

Mental illness: changes in mood; feeling like your life is falling apart; seeing, feeling or hearing things that are not real (hallucinations); thoughts of killing yourself (suicide), trying to kill yourself; feeling of great happiness (mania) and then a feeling of deep sadness or not being worthy

Chest: being short of breath when lying flat; serious lung infection like pneumonia; sharp chest pains which are worse when breathing; pain behind breast bone which can spread to neck and shoulders

Heart or circulation: heart attack; stopping breathing; blood clot in the leg or arm; decreased blood flow to parts of the brain

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE VICTRELIS

Keep out of the reach and sight of children.

Do not use Victrelis after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Storage by the pharmacist
Store in a refrigerator (2°C – 8°C).

Storage by the patient
- Store in a refrigerator (2°C – 8°C) until expiry.

OR
- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry. After this period, the medicinal product should be disposed.

Store in the original blister in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Victrelis contains
- The active substance is boceprevir. Each hard capsule contains 200 mg of boceprevir.
- The other ingredients are sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pre-gelatinized starch, magnesium stearate, yellow iron oxide (E172), red iron oxide (E172), titanium dioxide (E171), gelatin, and shellac.

What Victrelis looks like and contents of the pack
The hard capsules have a yellowish-brown cap with the "MSD" logo printed in red ink and an off-white body with "314" printed in red ink.
Peelable blisters containing 12 hard capsules (3x4 capsule blister strip).
Pack sizes: carton of 84 hard capsules and multipack containing 336 (4 packs of 84) hard capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire
EN11 9BU
United Kingdom

Manufacturer
S-P Labo NV
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien
MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38693 (+32 (0)2 7766211)
dpoc_belux@merck.com

Luxembourg/Luxemburg
MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38693 (+32 (0)2 7766211)
dpoc_belux@merck.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@merck.com

Magyarország
MSD Magyarország Kft.
Tel.: +361 888 53 00
hungary_msd@merck.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 233 010 111
msd_cr@merck.com

Danmark
MSD Danmark ApS
Tlf: +45 4482 4000
dkmail@merck.com

Deutschland
MSD SHARP & DOHME GMBH
Tel: 0800 673 673 673
(+49 (0) 89 4561 2612)
e-mail@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel.: +372 6144 200
msdeesti@merck.com

Ελλάδα
MSD Α.Φ.Β.Ε.Ε.
Τηλ: +30 210 98 97 300
cora.greece.gragcm@merck.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@merck.com

France
MSD France
Tél: + 33-(0)1 80 46 40 40

Ireland
Merck Sharp and Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@merck.com

Ísland
Vistor hf.
Sími: +354 535 7000
ISmail@merck.com

Italia
MSD Italia S.r.l.
Tel: +39 06 361911
doccen@merck.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: +357 22866700
malta_info@merck.com

Nederland
Merck Sharp & Dohme B.V.
Tel: +31 (0) 800 9999000
(+31 (0) 23 5153153)
medicalinfo.nl@merck.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
msd-medizin@merck.com

Polska
MSD Polska Sp.z o.o.
Tel.: +48 22 549 51 00
msdpolska@merck.com

Portugal
Merck Sharp & Dohme, Lda
Tel: +351 21 4465700
clic@merck.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel: + 4021 529 29 00
msdromania@merck.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: + 386 1 5204201
msd_slovenia@merck.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
msd_sk@merck.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0) 9 804650
info@msd.fi

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: +800 00 673
(+357 22866700)
cyprus_info@merck.com

Latvija
SIA "Merck Sharp & Dohme Latvija"
Tel: +371 67364 224
msd_lv@merck.com

Lietuva
UAB "Merck Sharp & Dohme"
Tel.: +370 5 278 02 47
msd_lietuva@merck.com

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: 46 77 5700488
medicinskinfo@merck.com

United Kingdom
Merck Sharp and Dohme Limited
Tel: +44 (0) 1992 467272
medicalinformationuk@merck.com

This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu