INCIVO® SAFETY OVERVIEW

INCIVO® telaprevir

Prescribing information can be found on the back page.

CONTENTS

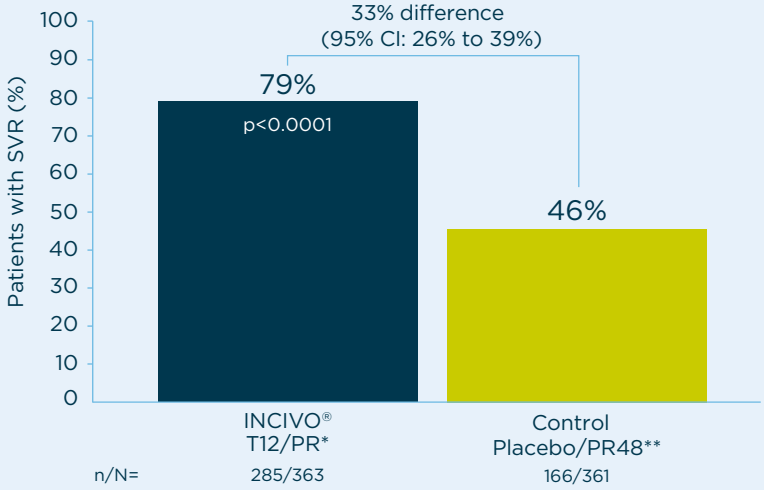
INTRODUCTION

INCIVO® (telaprevir) is approved for use in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders. INCIVO® is dosed at 750 mg every 8 hours with food, and is given in combination with peginterferon alfa and ribavirin for 12 weeks followed by peginterferon alfa and ribavirin alone for an additional 12 or 36 weeks.[1]

INCIVO® EFFICACY PROFILE

INCIVO®-based therapy significantly improves sustained virologic response (SVR) rates among HCV genotype 1-infected treatment-naïve and treatment-experienced patients compared with peginterferon alfa and ribavirin alone.[1]

ADVANCE: SVR rates in treatment-naïve patients treated with INCIVO®/PR compared with PR alone.[1]

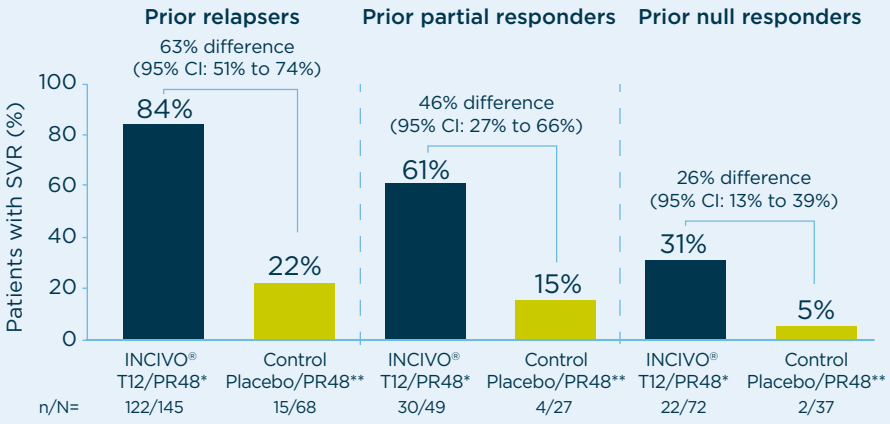


PR: peginterferon alfa-2a and ribavirin; SVR: sustained virologic response
*12 weeks of INCIVO® in combination with peginterferon alfa-2a and ribavirin (PR) given for 24 or 48 weeks depending on HCV-RNA status at weeks 4 and 12
**Placebo/PR48: Placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks
p<0.0001 for T12/PR versus Placebo/PR48

In the ADVANCE trial, INCIVO®-based treatment enabled 58% of treatment-naïve patients to qualify for a reduced treatment duration of 24 weeks.

The SVR rate in patients qualifying for this shorter treatment duration was 92%.[1]

REALIZE: SVR rates in treatment-experienced patients treated with INCIVO®/PR compared with PR alone.[1]



PR: peginterferon alfa-2a and ribavirin; SVR: sustained virologic response
*12 weeks of INCIVO® followed by placebo for 4 weeks in combination with 48 weeks of peginterferon alfa-2a and ribavirin
**Placebo/PR48: placebo for 16 weeks in combination with peginterferon alfa 2a and ribavirin for 48 weeks
p<0.001 forT12/PR48 versus placebo/PR48 for all comparisons

INCIVO® SAFETY PROFILE

Summary of adverse events in pooled placebo-controlled Phase II/III studies during the INCIVO®/placebo treatment phase.[2]

Adverse events (%)	INCIVO® T12/PR* n=1346	Control Placebo/PR48 n=764
Adverse events	98.3	96.9
Deaths, n (%)	0[a]	1 (0.13)[a,b]
Serious adverse events	6.9	2.9
Adverse events of at least Grade 3	23.8	12.3
Adverse events leading to permanent discontinuation of:		
INCIVO®/placebo All study drugs at one time	14.2 8.1	4.1 3.7
Adverse events at least possibly related to INCIVO®/placebo	94.7	92.5

PR: peginterferon alfa-2a and ribavirin

* 12 weeks of INCIVO® in combination with any duration of PR

a. Refers to the number (%) of patients who died as a result of an adverse event with onset during the INCIVO®/placebo treatment phase

b. One patient with a life-threatening adverse event that was not resolved at last study visit subsequently died due to this adverse event

Incidence of adverse events (all grades) reported in more than 20% of patients treated in pooled placebo-controlled Phase II/III studies (INCIVO®/placebo treatment phase).[2]

Patients (%)	INCIVO® T12/PR* n=1346	Control Placebo/PR48 n=764
Fatigue	52	51
Pruritus	47	25
Nausea	39	29
Headache	39	38
Influenza-like illness	33	31
Rash	33	17
Anemia	29	12
Insomnia	27	24
Diarrhea	26	19
Pyrexia	21	21

PR: peginterferon alfa-2a and ribavirin

* 12 weeks of INCIVO® in combination with any duration of PR

The incidence of adverse events highlighted in blue was ≥5% higher in the T12/PR group compared with the placebo/PR48 group

For adverse events that were reported in the 5–20% range, those observed more frequently (at least 5% higher in INCIVO®-treated patients than in patients treated with peginterferon alfa/ribavirin alone) were hemorrhoids, anorectal discomfort, anal pruritus and dysgeusia.[2]

Adverse drug reactions to INCIVO® in combination with peginterferon alfa and ribavirin in HCV-infected patients in the pooled placebo-controlled Phase II/III studies.[1]

System Organ Class (SOC)	Frequency category*	Adverse drug reactions INCIVO®, peginterferon alfa, and ribavirin combination therapy n=1346
Infections and infestations	common	oral candidiasis
Blood and lymphatic system disorders	very common	anemia
	common	thrombocytopenia[b], lymphopenia[b]
Endocrine disorders	common	hypothyroidism
Metabolism and nutrition disorders	common	hyperuricemia[b], hypokalemia[b]
	uncommon	gout
Nervous system disorders	common	dysgeusia, syncope
Eye disorders	uncommon	retinopathy
Gastrointestinal disorders	very common	nausea, diarrhea, vomiting, hemorrhoids, proctalgia
	common	anal pruritus, rectal hemorrhage, anal fissure
	uncommon	proctitis
Hepatobiliary disorders	common	hyperbilirubinemia[b]
Skin and subcutaneous tissue disorders	very common	pruritus, rash
	common	eczema, swelling face, exfoliative rash
	uncommon	drug rash with eosinophilia and systemic symptoms (DRESS), urticaria
	rare	Stevens-Johnson syndrome[a]
Renal and urinary disorders	uncommon	blood creatinine increased[b]
General disorders and administration site conditions	common	edema peripheral, product taste abnormal

* Very common: ≥1/10 patients; common: ≥1/100 to <1/10; uncommon: ≥1/1000 to <1/100; rare: ≥1/10,000 to <1/1000. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness

[a] Did not occur in placebo-controlled Phase II or Phase III studies

[b] Incidence rates are based on adverse event reporting rates

Selected laboratory abnormalities (DAIDS* Grade ≥2) that represent a worsening from baseline and are considered adverse drug reactions in HCV-infected patients treated with INCIVO® combination treatment from pooled placebo-controlled Phase II/III studies.[1]

Patients (%)	Grade 2	Grade 3	Grade 4
Increase**			
Uric acid	17.9% (10.1–12.0 mg/dl)	4.6% (12.1–15.0 mg/dl)	1.1% (>15.0 mg/dl)
Bilirubin	13.6% (1.6–2.5 x ULN)	3.6% (2.6–5.0 x ULN)	0.3% (>5.0 x ULN)
Total cholesterol	15.4% (6.20–7.77 mmol/l 240–300 mg/dl)	2.0% (>7.77 mmol/l >300 mg/dl)	NA
Low-density lipoprotein	6.9% (4.13–4.90 mmol/l 160–190 mg/dl)	2.5% (≥4.91 mmol/l ≥191 mg/dl)	NA
Creatinine	0.9% (1.4–1.8 x ULN)	0.2% (1.9–3.4 x ULN)	0% (>3.4 x ULN)
Decrease**			
Hemoglobin	27.0% (9.0–9.9 g/dl or any decrease 3.5–4.4 g/dl)	51.1% (7.0–8.9 g/dl or any decrease ≥4.5 g/dl)	1.1% (<7.0 g/dl)
Platelet count	24.4% (50,000–99,999/mm^3)	2.8% (25,000–49,999/mm^3)	0.2% (<25,000/mm^3)
Absolute lymphocyte count	13.1% (500–599/mm^3)	11.8% (350–499/mm^3)	4.8% (<350/mm^3)
Potassium	1.6% (2.5–2.9 mEq/l)	0% (2.0–2.4 mEq/l)	0% (<2.0 mEq/l)

NA: not applicable; PR: peginterferon alfa-2a and ribavirin; ULN: upper limit of normal

* The Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS, version 1.0, December 2004) was used in the pooled laboratory datasets

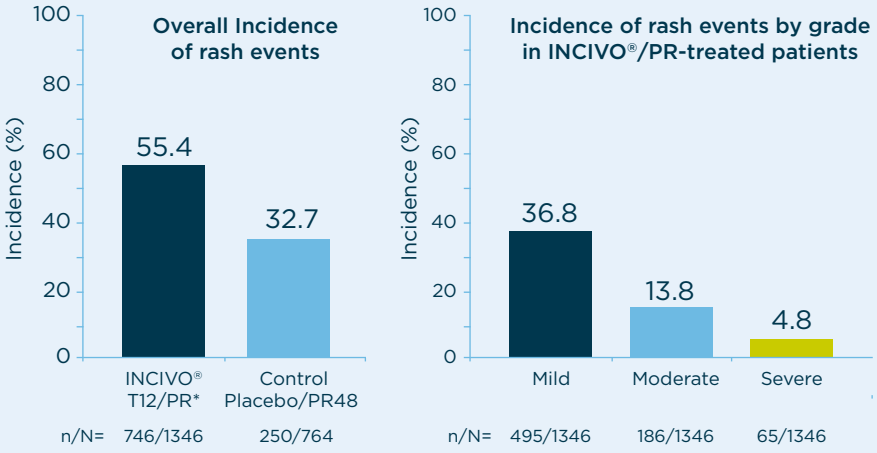
**The incidence was calculated by the number of patients for each parameter

Values between brackets correspond to the grade severity definition for each parameter

To comprehensively assess adverse events that occurred more frequently in the INCIVO® treatment arms that may be considered most relevant to individual patients, additional analyses were conducted on dermatological reactions, anemia, and anorectal signs and symptoms.

DERMATOLOGICAL REACTIONS

Incidence of rash adverse events (special search category) in INCIVO® Phase II/III placebo-controlled studies during the INCIVO®/placebo treatment phase.[2]



PR: peginterferon alfa-2a and ribavirin;
*12 weeks of INCIVO® in combination with any duration of PR

Additional information on rash adverse events (special search category) occurring during placebo-controlled Phase II/III clinical studies of INCIVO® (INCIVO®/placebo treatment phase).[2]

Patients (%)	INCIVO® T12/PR* n=1346	Control Placebo/PR48 n=764
Deaths	0	0
Serious adverse events	1.7	0
Discontinuation (INCIVO®/placebo treatment phase)		
INCIVO®/placebo alone All treatment at the same time	5.8 2.6	0.3 0

PR: peginterferon alfa-2a and ribavirin
* 12 weeks of INCIVO® in combination with any duration of PR

KEY POINTS ON INCIVO®-RELATED DERMATOLOGICAL REACTIONS:

- In placebo-controlled Phase II/III studies, rash was reported in 55% of INCIVO®-treated patients compared with 33% of patients treated with peginterferon alfa/ribavirin alone.[1]
- The typical form of the dermatological reaction observed with INCIVO®-based combination therapy is a pruritic, eczematous rash involving less than 30% of the body surface area.[1]
- The visual appearance and histopathology of rash associated with INCIVO®-based therapy is comparable with that associated with peginterferon alfa/ribavirin, though INCIVO®-associated rashes were of increased severity and extent.[2]
- Half of all rashes began during the first 4 weeks of treatment, but may occur at any time during INCIVO® combination treatment.[1]

- **More than 90% of rashes were of mild or moderate severity.[1]**
- **Discontinuation of INCIVO®-based combination treatment is not required for mild and moderate rashes, but patients should be monitored for progression.[1]**

- Progression to a more severe grade, however, was infrequent (less than 10% of cases).[1]
- Severe rash (primarily eczematous, pruritic and involving more than 50% of body surface area) was reported in 4.8% of all patients treated with INCIVO®-based therapy compared with 0.4% of patients treated with pegfinterferon alfa/ribavirin alone.[1]
- Overall, 5.8% of patients discontinued INCIVO® alone due to rash events and 2.6% of patients discontinued INCIVO®-based combination therapy for rash events, compared with no patients receiving peginterferon alfa/ribavirin alone.[1] Rash improves after INCIVO® dosing completion or discontinuation, but may take weeks to completely resolve.[1]
- In placebo-controlled Phase II/III trials, 0.4% of patients had suspected DRESS. In INCIVO® clinical experience, less than 0.1% of patients had Stevens-Johnson Syndrome (SJS). All of these reactions resolved with treatment discontinuation.[1]

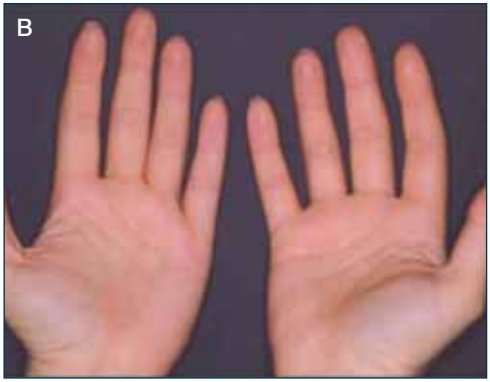
GENERAL GUIDANCE FOR MANAGING RASH

Patients should be fully informed about the risk of severe rashes, and advised to consult with their treating physician immediately if they develop a new rash or worsening of an existing rash. All rashes should be monitored for progression and until the rash is resolved. The rash may take several weeks to resolve. Other drugs associated with severe cutaneous reactions should be used with caution during administration of INCIVO® combination treatment, to avoid potential confusion as to which medicinal product could be contributing to a severe cutaneous reaction.[1]

- Consider emollient cream or lipid-rich lotion (not aqueous lotion or ointment), and ensure the correct dose and amount of emollient is used.
- Consider topical corticosteroids, preferably cream or lotion: one fingertip of corticosteroid cream equates to a 0.5g dose, sufficient to treat an area equivalent to two hands.

(A) One fingertip of corticosteroid cream equates to 0.5g of cream

(B) Sufficient to treat an area equivalent to two hands

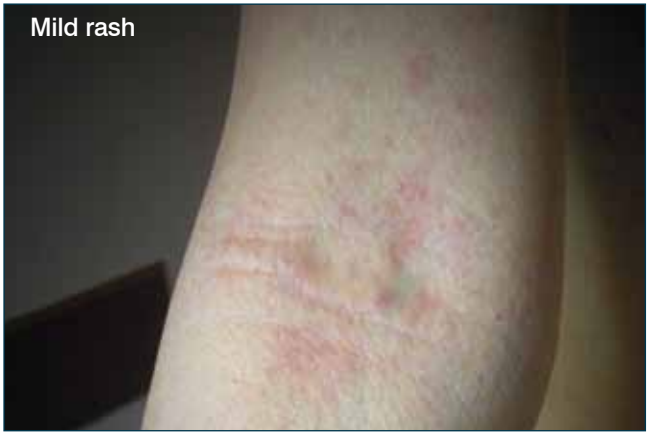


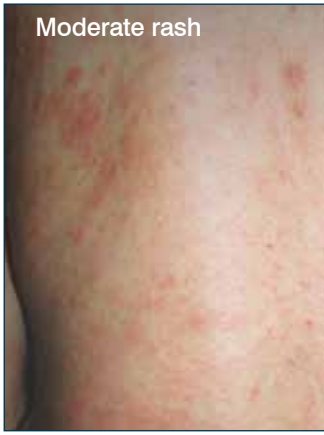
- Concomitant use of INCIVO® and systemic corticosteroids may result in loss of therapeutic effect of INCIVO®. Therefore this combination should be used with caution or alternatives should be considered.[1]
- Topical or systemic antihistaminic drugs may also be considered (note that astemizole and terfenadine are contraindicated with INCIVO®).[1]
- Follow up with the patient regularly until the rash has completely resolved.

Grading and management of rash[1]

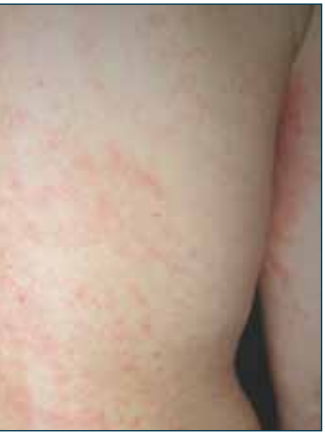
Severity[1]	Mild rash	Moderate rash
Description[1]	■ Localized skin eruption and/or a skin eruption with limited distribution (up to several isolated sites on the body)	■ Diffuse rash involving ≤50% of body surface area
Recommendation[1]	■ Monitor for progression or systemic symptoms until the rash is resolved	■ Monitor for progression or systemic symptoms until the rash is resolved ■ Consider consultation with a specialist in dermatology ■ For moderate rash that progresses to severe, permanently discontinue INCIVO®*
Proposed follow-up	■ Between days 2 and 4 after onset	

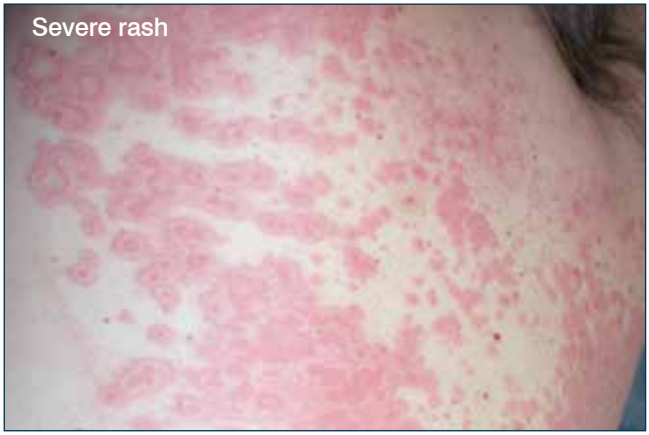
*For full recommendations, please refer to SmPC[1]





	Severe rash
	Extent of rash >50% of body surface area or associated with: ■ Significant systemic symptoms ■ Mucous membrane ulceration ■ Target lesions ■ Epidermal detachment
	■ **Permanently discontinue INCIVO® immediately** ■ Consultation with a specialist in dermatology is recommended ■ Monitor for progression or systemic symptoms until the rash is resolved ■ Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of INCIVO® discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered*
	■ Days 1, 3 and 7 after onset





Grading and management of rash.[1]

Severity	Description	Recommendation	Follow-up
Severe Cutaneous Adverse Reactions	■ Generalized bullous eruption ■ Drug rash with eosinophilia and systemic symptoms (DRESS) ■ Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) ■ Acute generalized exanthematous pustulosis (AGEP) ■ Erythema multiforme (EM)	If suspected or diagnosed: ■ **Permanent and immediate discontinuation of INCIVO®, peginterferon alfa and ribavirin** ■ Consult a specialist in dermatology	■ If diagnosis is confirmed, hospitalize the patient ■ Regular follow-up needed until resolution

GUIDANCE ON SUSPICION AND IDENTIFICATION OF DRESS AND STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS.[1,4–11]

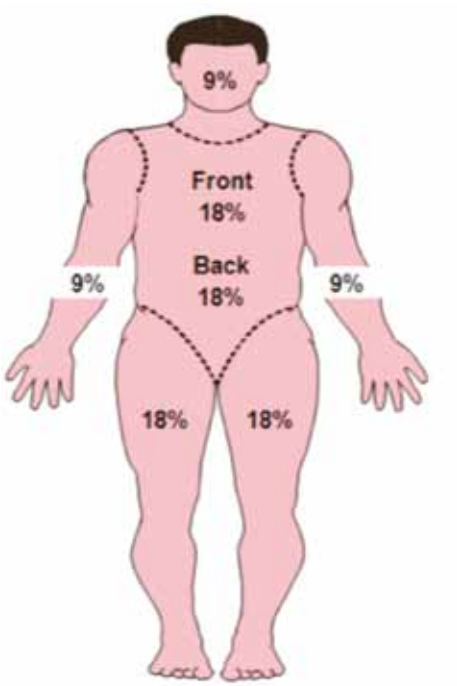
When to suspect DRESS – alert criteria:
Onset from 6–10 weeks after first dose
Rapidly progressing exanthema
Prolonged fever (>38.5°C)
Facial edema
If any DRESS alert criteria are found, the patient should be assessed for the following DRESS confirmation criteria:
Enlarged lymph nodes (at least 2 sites)
Eosinophilia (≥700/μL or ≥10%)
Atypical lymphocytes
Internal organ involved: a. liver: alanine aminotransferase, alkaline phosphatase ≥2 x upper limit of normal b. kidney: rise in creatinine ≥150% basal level

When to suspect Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis – alert criteria:
Rapidly progressing exanthema
Skin pain
Mucosal involvement at ≥2 sites
Blisters or epidermal detachment
Atypical/typical target lesions

What to do if DRESS or Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis is suspected:
Discontinue all drugs
Hospitalize the patient
Consult dermatologist

HOW TO CALCULATE BODY SURFACE AREA

Body surface area can be estimated using the guide below, showing body parts and the percentage of body surface area they cover:[3]



Adult body	Body surface area
Perineum	1%
Arm	9%
Head (front and back)	9%
Leg	18%
Chest	18%
Back	18%

ANEMIA

Anemia is a well-recognized adverse event in patients receiving peginterferon alfa/ribavirin, and INCIVO® has been shown to have an additive but reversible effect on the incidence and severity of anemia.[2]

Summary of anemia occurring during pooled placebo-controlled Phase II/III clinical studies of INCIVO® (INCIVO®/placebo treatment phase).[1]

Patients (%)	INCIVO® T12/PR* n=1346	Control Placebo/PR48 n=764
Anemia (all grades, SSC)	32.1	14.8
Hemoglobin <10 g/dL Hemoglobin <8.5 g/dL	34 8	14 2
Discontinuations due to anemia (SSC)		
INCIVO®/placebo alone All drugs	1.9 0.9	0.5 0.5
Ribavirin dose reduction	21.6	9.4
Transfusion	2.5	0.7

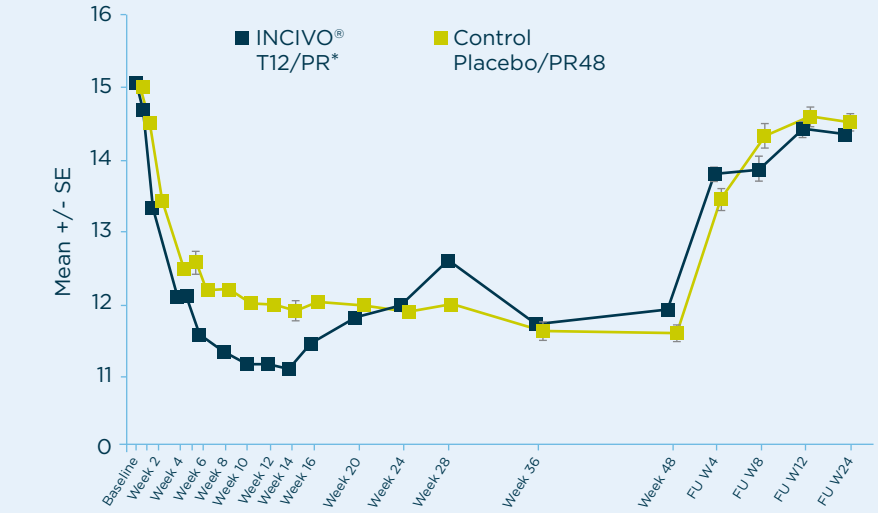
PR: peginterferon alfa-2a and ribavirin; SSC: special search category
* 12 weeks of INCIVO® in combination with any duration of PR

Transfusion rates over the whole study period were 4.6% and 1.6% respectively in patients receiving INCIVO® combination treatment or peginterferon alfa and ribavirin alone. Erythropoïesis-stimulating agents (ESAs) were generally not permitted and used in only 1% of patients in the Phase II and III clinical trials.[1]

A decrease in hemoglobin levels occurs during the first 4 weeks of treatment, with lowest values reached at the end of INCIVO® dosing. Hemoglobin values gradually improve after INCIVO® dosing completion.[1]

- In Phase III studies in treatment-naïve patients, the presence of anemia had no effect on SVR rates with INCIVO®-based treatment. SVR rates were also comparable between patients whose anemia was managed with or without ribavirin dose reduction.[12]

Hemoglobin shifts in pooled placebo-controlled Phase II/III studies of INCIVO®.[2]



No. of patients														
INCIVO®*	1345	1291	1248	1209	1074	1040	1016	498	544	525	251	100	276	250
Pbo/PR	764	742	721	677	625	584	565	459	399	379	109	84	123	114

PR: peginterferon alfa-2a and ribavirin; SE: standard error
* 12 weeks of INCIVO® in combination with any duration of PR

GUIDANCE FOR MANAGEMENT OF ANEMIA[1]

- Hemoglobin should be monitored at regular intervals prior to and during INCIVO® combination treatment: hemoglobin monitoring is recommended at Weeks 2, 4, 8 and 12 and as clinically appropriate thereafter.
- Baseline hemoglobin values of ≥12 g/dL (females) and ≥13 g/dL (males) are recommended prior to initiation of combination therapy in adults.
- For the management of anemia, refer to the Summary of Product Characteristics for ribavirin for its dose reduction guidelines.
- If ribavirin is permanently discontinued due to anemia, INCIVO® must also be stopped permanently. Treatment with peginterferon alfa and ribavirin may be continued if INCIVO® is discontinued due to anemia.
- **The dose of INCIVO® must not be reduced.**
- **INCIVO® must not be restarted if discontinued due to anemia.**

ANORECTAL SIGNS AND SYMPTOMS

- In placebo-controlled Phase II and III studies during the INCIVO®/placebo treatment phase, anorectal adverse events were reported in 26.2% of INCIVO®-treated patients versus 5.4% of patients treated with peginterferon alfa/ribavirin alone.[2]

Incidence of the most frequently reported terms within the anorectal adverse events special search category in pooled placebo-controlled Phase II/III studies during the INCIVO®/placebo treatment phase.[2]

Patients (%)	INCIVO® T12/PR* n=1346	Control Placebo/PR48 n=764
Hemorrhoids	12.2	2.6
Anorectal discomfort	7.9	2.1
Anal pruritus	6.2	0.9

PR: peginterferon alfa-2a and ribavirin

* 12 weeks of INCIVO® in combination with any duration of PR

Other anorectal special search category event preferred terms were reported in <5.0% of patients in the T12/PR group

- In clinical trials, the majority of these events (e.g. hemorrhoids, anorectal discomfort, anal pruritus and rectal burning) were mild to moderate. Very few led to treatment discontinuation and resolved after completion of INCIVO® dosing.[1]

- Onset was most common in the first 2 weeks of treatment.[2]

TREATMENTS THAT MAY HELP MANAGE SYMPTOMS

- Standard symptomatic care may be considered for the management of anorectal side effects, including short-term use of proprietary combination hemorrhoid preparations, topical corticosteroids, topical local anaesthetics and antihistamines, according to the nature of the adverse event.

PRESCRIBING INFORMATION

INCIVO® ▼ 375mg film-coated tablets
ACTIVE INGREDIENT(S): Telaprevir
Please refer to Summary of Product Characteristics (SmPC) before prescribing.
INDICATION(S): Only in combination with peginterferon alfa and ribavirin, for treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis): treatment naïve or previously treated with interferon alfa (pegylated or non-pegylated) alone or combination with ribavirin, including relapsers, partial and null responders.
DOSAGE & ADMINISTRATION: *Adults:* Two 375 mg tablets, orally every 8 hours with food, swallowed whole (total daily dose: 6 tablets) for 12 weeks, in combination with peginterferon alfa-2a or -2b and ribavirin. Refer to peginterferon alfa and ribavirin SmPCs for specific dosage instructions. Total treatment duration of peginterferon alfa and ribavirin either 24 or 48 weeks refer to INCIVO SmPC. *All patients:* Patients with HCV RNA > 1,000 IU/ml at week 4 or 12 should discontinue all therapy. In case of 48 weeks treatment, discontinue peginterferon alfa and ribavirin if HCV RNA detectable at week 24 or 36. Do not reduce or interrupt INCIVO treatment. Do not restart INCIVO treatment if discontinued for ADRs or insufficient virologic response. Missed dose can be taken within 4 hours; otherwise skip dose. *Children:* <18 years old - no data available. *Elderly:* Limited data ≥ 65 years old. *Renal impairment:* No dose adjustment . No data on moderate/severe renal impairment (CrCl ≤ 50 ml/min) or haemodialysis. *Hepatic impairment:* Dose modifications not required in mild hepatic impairment (Child-Pugh A, score 5-6). Not recommended in moderate to severe impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. Peginterferon alfa and ribavirin are contraindicated in ChildPugh score ≥ 6.
CONTRAINDICATIONS: Hypersensitivity to INCIVO tablets. Combinations with strong inducers of CYP3A and active substances highly dependent on CYP3A for clearance where resulting elevated plasma concentrations associated with serious and/or life-threatening events. Do not use with medicines such as: alfuzosin, amiodarone, bepridil, quinidine, astemizole, terfenadine, cisapride, pimozide, ergot derivatives, lovastatin, simvastatin, atorvastatin, sildenafil or tadalafil (only when used for treatment of pulmonary arterial hypertension), oral midazolam and triazolam, rifampicin, St. John's wort, carbamazepine, phenytoin, phenobarbital. Concomitant Class Ia or III antiarrhythmics, except IV lidocaine. Refer to SmPCs for peginterferon alfa and ribavirin for their contraindications
SPECIAL WARNINGS & PRECAUTIONS: *Rashes:* Severe rashes reported with INCIVO combination treatment; inform patients. Monitor all rashes for progression. Consider consultation with dermatology specialist for moderate rash (≤ 50% of body surface area). If rash severe (> 50% of body surface area), discontinue INCIVO immediately; consult dermatology specialist; peginterferon alfa and ribavirin may need to be discontinued. Discontinue INCIVO, peginterferon alfa and ribavirin if generalised bullous eruption, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome/toxic epidermal necrolysis, acute generalised exanthematous pustulosis, erythema multiforme suspected/diagnosed; consult dermatology specialist. Do not restart INCIVO if discontinued. *Anaemia:* Incidence and severity of anaemia increased with INCIVO combination treatment. Regularly monitor haemoglobin prior to and during treatment. Management of anaemia, see SmPC for ribavirin. If ribavirin permanently discontinued, INCIVO must also be permanently discontinued. If INCIVO discontinued for anaemia, may continue treatment with peginterferon alfa and ribavirin. Do not reduce dose of INCIVO or restart if discontinued. *Pregnancy and contraception:* see 'Pregnancy' below, . see also SmPC for ribavirin. *Cardiovascular:* Significance of modest increase in QTcF interval uncertain. Use with caution with Class Ic antiarrhythmics propafenone and flecainide and other QT prolonging medicines. Avoid in patients with congenital QT prolongation, or family history of congenital QT prolongation or sudden death. Caution in patients with: history of acquired QT prolongation; persistent heart rate < 50 bpm; history of heart failure with reduced left-ventricular ejection fraction; with medicinal products known to prolong QT interval. Clinical and ECG monitoring required. Monitor and correct electrolyte disturbances. *Laboratory tests:* Monitor HCV RNA levels at least at weeks 4 and 12. Prior to treatment, monitor complete blood count with white blood cell differential counts, electrolytes, serum creatinine, liver function tests, TSH, uric acid and at least at weeks 2, 4, 8 and 12. *Combination with peginterferon alfa-2b:* No clinical data on treatment-experienced patients and limited data in treatment-naïve patients. *Thyroid disease:* Risk of increased TSH. Monitor TSH levels before and during treatment. Possible dose adjustment of thyroid replacement therapy. No clinical data on re-treating patients who have failed HCV NS3-4A protease inhibitor-based therapy; in pre/peri/post-liver or other transplants; with HCV/HBV co-infection. Limited data in HIV/HCV co-infection. Tablets contain sodium.
SIDE EFFECTS: Very common (≥ 1/10): anaemia, nausea, diarrhoea, vomiting, haemorrhoids, proctalgia, pruritus, rash. Common (≥ 1/100 to < 1/10): oral candidiasis, thrombocytopenia, lymphopenia, hypothyroidism, hyperuricaemia, hypokalaemia, dysgeusia, syncope, anal pruritus, rectal haemorrhage, anal fissure, hyperbilirubinaemia, eczema, swelling face, exfoliative rash, oedema peripheral, product taste abnormal. Serious side effects: DRESS, Stevens-Johnson syndrome, retinopathy. **Refer to INCIVO SmPC for other side effects. Refer to peginterferon alfa and ribavarin SmPCs for associated side effects.**
PREGNANCY: Not recommended. Males and females (of childbearing potential) and their partners must use 2 effective non-hormonal contraceptives during treatment and for 2 months after INCIVO treatment ended. Refer to peginterferon alfa and ribavirin SmPC.
LACTATION: Discontinue breast-feeding prior to therapy.
INTERACTIONS: Co-administration with CYP3A and/or P-gp inducers may decrease INCIVO plasma concentrations; avoid use with mild/moderate CYP3A inducers. CYP3A and/or P-gp inhibitors may increase telaprevir plasma concentrations. INCIVO may increase systemic exposure to substrates of CYP3A or P-gp. Refer to C/Is. Avoid domperidone. Rifabutin, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, salmeterol, vardenafil not recommended. Inhaled/nasal fluticasone/budesonide not recommended unless benefit/risk positive. Avoid colchicine in renal or hepatic impairment. Caution with: Class Ic antiarrhythmics propafenone and flecainide, IV lidocaine, digoxin, clarithromycin, erythromycin, telithromycin, troleandomycin, warfarin, dabigatran, trazodone, ketoconazole, itraconazole, posaconazole, voriconazole, parenteral midazolam, amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil, systemic dexamethasone, bosentan, atazanavir/ritonavir, tenofovir disoproxil fumarate, abacavir, zidovudine, ethinylestradiol/norethindrone, cyclosporine, tacrolimus, sirolimus, methadone, tadalafil (for erectile dysfunction). Use telaprevir 1,125 mg q8h with efavirenz. Clinical relevance of changes unknown for alprazolam, escitalopram, zolpidem.
LEGAL CATEGORY: POM
MARKETING AUTHORISATION HOLDER: JANSSEN-CILAG INTERNATIONAL NV, Turnhoutseweg 30, B-2340 Beerse, Belgium. For full prescribing information, contact:
Cyprus Varnavas Hadjipanayis Ltd, Yiannou Kranidioti Avenue 226, Latsia 2234 Nicosia-Cyprus. PO BOX 21229, 1504 Nicosia. Tel. 00 357 22 207 700.
Malta A.M. Mangion LTD, Mangion Buildings, New Street in Valletta Road, Luqa LQA 6000, Malta. Tel. 00 356 2397 6000.
Prescribing information last revised: February 2012.

FOR Malta: Any suspected adverse drug reactions can be reported to: Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: http://www.medicinesauthority.gov.mt/pub/adr.doc

References: 1. INCIVO® SmPC, February 2012. 2. FDA Antiviral Drugs Advisory Committee. Telaprevir Briefing Document April 28, 2011. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterialsDrugsAntiviralDrugsAdvisoryCommittee/UCM252562.pdf 3. Hettiaratchy S, et al. Br Med J 2004;329:101–103. 4. Roujeau JC, et al. Dermatol Sinica 2009; 27:203–209. 5. Walsh SA, et al. Clin Exp Dermatol 2011;36:6–11. 6. Jeung Y-J, et al. Allergy Asthma Immunol Res 2010;2:123–126. 7. French LE, et al. Allergol Int 2006;55:9–16. 8. Roujeau JC. Toxicology 2005;209:123–129. 9. Revuz J, et al. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. In: Life-threatening dermatoses and emergencies in dermatology. 2009, Springer. 10. Wolf R, et al. Clinics in Dermatology 2005;23:171–181. 11. Mockenhaupt M, et al. J Investig Dermatol 2008;128:35–44. 12. Sulkowski MS, et al. J Hepatol 2011;54(Suppl. 1):S195.