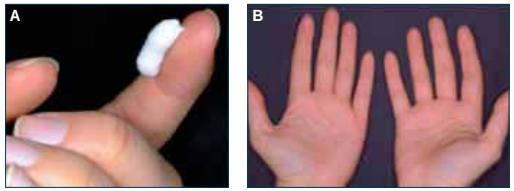
GENERAL GUIDANCE FOR MANAGING RASH

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.

- Consider using emollient cream or lipid-rich lotion (not aqueous lotion or ointment), and ensure the correct dose and amount of emollient is used.
- Consider using 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.

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

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



- 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.

DERMATOLOGICAL SIDE EFFECTS OF TELAPREVIR

In placebo-controlled Phase II and III studies, the incidence of rash during the 12-week INCIVO® dosing period was 55%, versus 33% with placebo plus peginterferon alfa/ribavirin alone. The majority (>90%) of rashes were mild or moderate and typically pruritic, eczematous and involving ≤30% of the body surface area.[1] Half the rashes started during the first 4 weeks, but rash can occur at any time during INCIVO® combination treatment.[1]

Discontinuation of INCIVO® combination treatment is not required for mild and moderate rash, but patients should be monitored for progression. 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% body surface area) was reported in 4.8% of patients treated with INCIVO® vs. 0.4% of patients treated with peginterferon/ribavirin alone.[1]

Improvement of rash occurs after INCIVO® dosing completion or discontinuation. However, rashes may take several weeks to resolve.[1]

In placebo controlled Phase II and III trials, 0.4% of patients had suspected Drug Rash with Eosinophilia and Systemic Symptoms (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]

INCIVO® must not be restarted if discontinued.

GUIDANCE ON SUSPICION AND IDENTIFICATION OF DRESS AND STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS[1,3–10]

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

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 naive 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-naive 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, hypokalaemeia, 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 CIs. 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.** Hettiaratchy S, et al. Br Med J 2004;329:101–103. **3.** Roujeau JC, et al. Dermatol Sinica 2009; 27:203–209. **4.** Walsh SA, et al. Clin Exp Dermatol 2011;36:6–11. **5.** Jeung Y-J, et al. Allergy Asthma Immunol Res 2010;2:123–126. **6.** French LE, et al. Allergol Int 2006;55:9–16. **7.** Roujeau JC. Toxicology 2005;209:123–129. **8.** Revuz J, et al. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. In: Life-threatening dermatoses and emergencies in dermatology. 2009, Springer. **9.** Wolf R, et al. Clinics in Dermatology 2005;23:171–181. **10.** Mockenhaupt M, et al. J Investig Dermatol 2008;128:35-44.

INC/HPC/EDL/4/2012/CY/MT157

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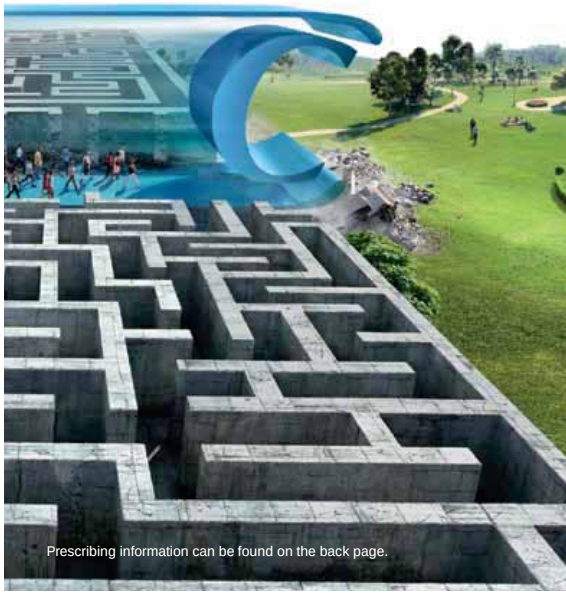
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

MANAGING DERMATOLOGICAL REACTIONS IN PATIENTS TREATED WITH INCIVO®

PLUS PEGINTERFERON ALFA AND RIBAVIRIN

INCIVO® telaprevir



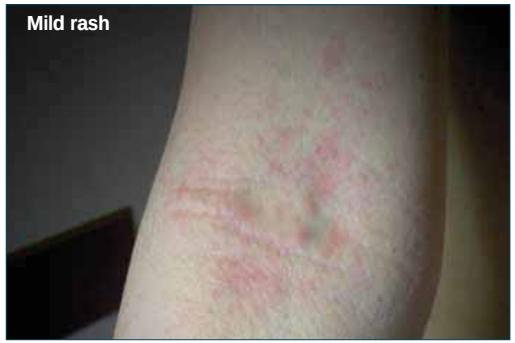
Prescribing information can be found on the back page.

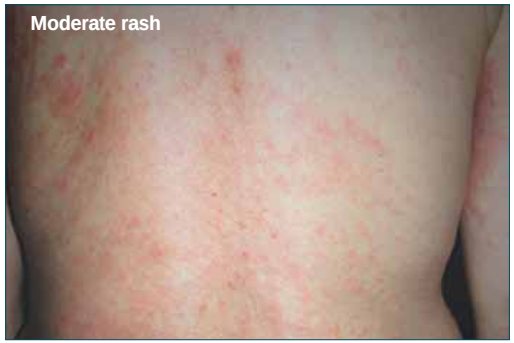
Grading and management of rash[1]

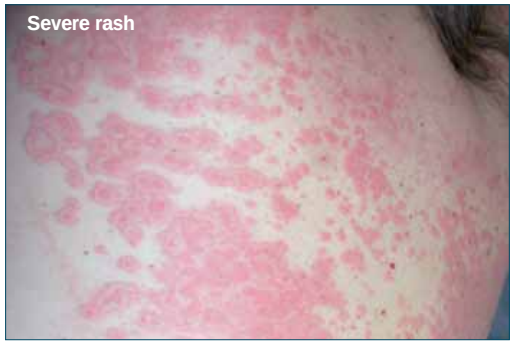
Severity[1]	Mild rash	Moderate rash	Severe rash
Description[1]	■ Localized skin eruption and/or a skin eruption with limited distribution (up to several isolated sites on the body)	■ Diffuse rash involving ≤50% of body surface area	Extent of rash >50% of body surface area or associated with: ■ Significant systemic symptoms ■ Mucous membrane ulceration ■ Target lesions ■ Epidermal detachment
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®[a]	■ **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[a]
Proposed follow-up	■ Between days 2 and 4 after onset		■ Days 1, 3 and 7 after onset

Severe Cutaneous Adverse Reactions

Description	■ 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)
Recommedation	If suspected or diagnosed: ■ **Permanent and immediate discontinuation of INCIVO®, peginterferon alfa and ribavirin** ■ Consult with a specialist in dermatology
Proposed follow-up	■ If diagnosis is confirmed, hospitalize the patient ■ Regular follow-up needed until resolution







[a] For full recommendations, please refer to EU SmPC[1]

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:[2]

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