

***Title: peginterferon alfa-2b (PEG-Intron), peginterferon alfa 2-a (Pegasys),
ribavirin (Copegus, Rebetrol)***

Origination: 04/29/02	Revised: 05/25/11	Annual Review: 12/15/11
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Purpose:

To provide guidelines and criteria for the review and decision determination of requests for medications that requires prior authorization.

Background Information:

Medication Summary

- **Peginterferon alpha** and **ribavirin** are used in this procedure as generic terms only and do not denote particular products.
- **Peg-Intron (peginterferon alfa-2b)** is indicated for use alone or in combination with Rebetol (ribavirin) for the treatment of chronic hepatitis C in Members with compensated liver disease.
- **Pegasys (peginterferon alfa-2a)** alone or in combination with ribavirin, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Members in whom efficacy was demonstrated included Members with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and Members with HIV disease that is clinically stable (e.g., antiretroviral therapy not required or receiving stable antiretroviral therapy).
- **Pegasys (peginterferon alfa-2b)** is also indicated for the treatment of adult Members with HBeAg positive and HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation.
- **Copegus/Rebetrol (ribavirin)** monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should NOT be used alone for this indication.
- **Copegus (ribavirin)** in combination with Pegasys, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Members in whom efficacy was demonstrated included Members with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and Members with HIV disease that is clinically stable (e.g., antiretroviral therapy not required or receiving stable antiretroviral therapy).

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Background Information, continued:

Medication Summary, continued

- **Rebetol** (ribavirin, USP) Capsules and Oral Solution are indicated in combination with Intron A (interferon alfa-2b recombinant), Peg-Intron (peginterferon alfa-2b, recombinant), or Pegasys (peginterferon alfa-2a, recombinant) injection for the treatment of chronic hepatitis C in Members with compensated liver disease.

Eligibility Criteria

- Member must be eligible for benefit coverage (i.e., self-injectable rider) within the specified date(s) of service.
- Prior authorization requests that do not meet clinical criteria in this Procedure will be forwarded to a Clinical Pharmacist for review.

Exclusions for Pegasys/Peg-Intron or ribavirin

- Member is less than 2 years of age.
- Member who is pregnant or unwilling to comply with adequate contraception.
- Member has advanced cirrhosis and is at risk for decompensation (Child-Pugh class B & C), which can be identified by any of the following:
 - a. Coagulopathy or elevated INR in absence of warfarin
 - b. Ascites
 - c. Encephalopathy
 - d. Hypoalbuminemia
 - e. Hyperbilirubinemia
- Member has persistently normal ALT levels in absence of biopsy documenting liver damage secondary to HCV or HBV.
- Member has diagnosis of major, uncontrolled depressive illness, or untreated thyroid disease.
- Member has severe, concurrent debilitating conditions, such as uncontrolled hypertension, advanced heart failure or coronary heart disease, uncontrolled diabetes, chronic obstructive pulmonary disease.
- Member has history of solid organ (renal, heart, lung) or bone marrow transplant; safety and efficacy has not been established.
- Member has a prescription for or is currently taking Epivir, Hepsera, Tyzeka, or Baraclude for the treatment of hepatitis B (no additional benefit when used in combination with peginterferon).
- Member has a diagnosis of autoimmune disease or hemoglobinopathy (e.g., thalassemia major, sickle-cell anemia).

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Background Information, continued:

Reference Statement

- Guidelines will be compiled from available US Food and Drug Administration (FDA) approved indications, general practice guidelines, and/or evidence-based uses established through phase III clinical studies without published conflicting data. Only clinical studies published in their entirety in reputable peer-reviewed journals will be evaluated.

Procedure (per Catalyst question/answer format):

1. Does the Member meet any exclusion criteria (Refer to exclusions listed above)?
 If yes = deny with the following: Based on the information provided this Member does not meet coverage criteria.
 No = continue to 2
2. For which diagnosis is this request being prescribed?
 For Hepatitis C, continue to 3
 For Hepatitis B, refer to Hepatitis B section V (end of procedure)
 Other, deny for any other diagnosis. The plan does not cover these medications for any other diagnosis.
3. Is this request for initial therapy, for continuation therapy after the initial 16 weeks, for continuation therapy after completion of a full course of treatment (after 24 or 48 weeks depending on the genotype), or retreatment for a relapser (HCV RNA viral load has returned 6 months after completion of a full course of treatment)?
 Initial = continue to section I.
 Continuation after the initial 16 weeks of therapy = continue to section II.
 Continuation after completing a full course of therapy (after 24 or 48 week depending on the genotype) – confirmed by authorization history & pharmacy claims = continue to section III.
 Retreatment for a relapser = continue to section IV.

Section I. FOR INITIAL THERAPY with combination of Pegasys/Peg-Intron plus ribavirin: (Need the following supporting documentation from the requesting provider)

- Recent progress notes
- HCV RNA viral load (lab within that last 3 months)
- Viral Genotype (should be one of the following: 1a, 1b, 2, 3, 4, or 6)
- Liver enzymes, specifically ALT (need at least 2 different labs from last 6 months to 1 year)
- Liver Biopsy report for genotype 1 only
- INR lab
- Concurrent request for ribavirin or clinical documentation of a contraindication that prevents its use (Refer to question 9 for a list of contraindications)

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Procedure, continued:

4. Does the Member have a **detectable** (out of range) HCV RNA viral load (confirmed via quantitative measurement, labs usually 50,000 up to 5+ million IU/ml) **AND** a viral genotype (1 thru 6)?
- Yes = continue to 5.
- No = Deny: The plan requires a detectable HCV RNA viral load and the viral genotype. Based on the information provided, this Member does not meet coverage criteria.
5. Does the Member **have at least 2 persistently elevated ALT levels** (out of range, lab usually > 40 U/L) – need to review multiple labs from various dates of service?
- Yes = continue to 8
- No = continue to 6 for genotype 1 **OR** continue to 7 for genotypes 2, 3, 4 or 6
6. **For genotype 1 only:** does the Member have ALT level within normal limits (within range) and **BOTH** of the following (**A & B**)?
- A. A liver biopsy that indicates either portal or bridging fibrosis or at least moderate degrees of inflammation and necrosis; **AND**
- B. A current INR (within the past 30 days) within normal limits (range 0.9 – 1.2)
- Yes = continue to 8
- No = Deny: The plan requires elevated ALT levels or liver biopsy & INR within normal limits for this genotype. Based on the information provided, this Member does not meet coverage criteria.
7. **For genotypes 2, 3, 4, or 6:** does the Member have ALT level within normal limits (within range) and a current INR (within the past 30 days) within normal limits (range 0.9-1.2)?
- Yes = continue to 8
- No = Deny: The plan requires elevated ALT levels or INR within normal limits for these genotypes. Based on the information provided, this Member does not meet coverage criteria.
8. Does the Member have a request for concurrent ribavirin therapy?
- Yes = **For all genotypes**, authorize Pegasys/Peg-Intron **plus** ribavirin for 16 weeks for initial therapy only. **(Please note the authorization should be loaded for 16 weeks only versus 4 months)**
- No = continue to 9

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Procedure, continued:

9. Does the Member have one (1) or more of the following contraindications to ribavirin?

Contraindication for use of ribavirin:
Member has a drug allergy to ribavirin
Member is pregnant or unwilling to comply with adequate contraception
Member with renal impairment (CrCl < 50ml/min) or on dialysis
Member has a diagnosis of autoimmune disease or hemoglobinopathy (e.g., thalassemia major, sickle-cell anemia)
Member has a history of significant anemia or neutropenia due to ribavirin

- Yes = **For all genotypes**, authorize Pegasys/Peg-Intron **ONLY** for 16 weeks. **(Please note the authorization should be loaded for 16 weeks only verses 4 months)**
- No = Obtain a request for ribavirin. **Unless a Member has a contraindication to ribavirin, Pegasys/Peg-Intron plus ribavirin are the standard of treatment for Hepatitis C treatment in order to provide optimal response rate. Once new request is obtained go back to 8.**

Section II. FOR CONTINUATION OF THERAPY (after the initial 16 weeks): (Need the following supporting documentation from the requesting provider or from PBM pharmacy claim system).

- Review previous pharmacy claims in PBM pharmacy claim system for Pegasys/Peg-Intron and ribavirin (Need to calculate how many weeks of therapy have been completed – actual processed claims. This will determine how many more weeks of therapy are to be approved.)
- Recent progress notes
- New HCV RNA viral load (drawn 12-weeks after initiation of treatment) - will need to compare to initial HCV RNA viral load
- Viral Genotype
- Concurrent request for continuation of ribavirin or clinical documentation of a contraindication that prevents it use (Refer to question 9 for contraindications if necessary)

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Procedure, continued:

10. Does the Member have a co-infection of HIV? (Can be determined by pharmacy claims for any HIV medication or from progress notes provided)

Yes = Authorize Pegasys/Peg-Intron **plus ribavirin** for 32 weeks or more depending on completion of the initial 16 weeks of therapy (duration of therapy should be up to a total of 48 weeks). **This quantity should have been calculated prior to question 10 based on how many weeks of therapy have already been completed – how many claims have processed - if all 16 weeks have been completed = 4 fills @ 28 days each - the new approval should be for 32 weeks only – again please load for 32 weeks only verses 8 months.**

No = continue to questions that corresponds to the Member's genotype below (Go to question 11 for Genotype 1, 4, 6 **OR** Go to question 12 for Genotype 2, 3)

For Genotype 1, 4, 6:

11. **For genotype 1 (1a or 1b), 4, or 6** - Is the **repeat** (drawn 12-weeks after initiation of therapy) HCV RNA viral load **undetectable** (lab usually < 50 IU/ml) **OR decreased at least 100-fold (2 log 10)** from pre-treatment HCV RNA viral load (as an example, if initial viral load was 5,910,000 IU/ml and new lab is 59,100 IU/ml – this is exactly a 2 log 10 drop, **basically just remove two zeros from the original number = a 2 log reduction**)?

Yes = Authorize Pegasys/Peg-Intron **plus ribavirin** for 32 weeks or possibly more depending on completion of the initial 16 weeks of therapy (duration of therapy should be up to a total of 48 weeks). **This quantity should have been calculated prior to question 10 based on how many weeks of therapy have already been completed – how many claims have processed - if all 16 weeks have been completed = 4 fills @ 28 days each - the new approval should be for 32 weeks – again please load for 32 weeks only verses 8 months.**

No = Deny: The plan requires the repeat HCV RNA viral load to be undetectable or at least a decrease by 100-fold (2 log reduction). Based on the information provided, this Member does not meet coverage criteria.

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Procedure, continued:

For Genotype 2, 3:

12. **For genotype 2, 3** - Is the **repeat** (drawn 12-weeks after initiation of therapy) HCV RNA viral load **undetectable** (lab usually < 50 IU/ml) **OR decreased at least 100-fold (2 log 10)** from pre-treatment HCV RNA viral load (as an example, if initial viral load was 5,910,000 IU/ml and new lab is 59,100 IU/ml – this is exactly a 2 log 10 drop, **basically just remove two zeros from the original number = a 2 log reduction**)?

Yes = Authorize Pegasys/Peg-Intron **plus ribavirin** for 8 weeks or possibly more depending on completion of the initial 16 weeks of therapy (duration of therapy should be up to a total of 24 weeks. **(This quantity should have been calculated prior to question 10 based on how many weeks of therapy have already been completed – how many claims have processed - if all 16 weeks have been completed = 4 fills @ 28 days each - the new approval should be for 8 weeks – again please load for 8 weeks only verses 2 months)**)

No = Deny: The plan requires the repeat HCV RNA viral load to be undetectable or at least a decrease by 100-fold (2 log reduction). Based on the information provided, this Member does not meet coverage criteria

Section III. REQUEST FOR CONTINUATION PAST 24 or 48 WEEKS depending on genotype: (Need the following supporting documentation from the requesting provider or from PBM pharmacy claim system).

- Review previous pharmacy claims in PBM pharmacy claim system for Pegasys/Peg-Intron and ribavirin (Need to calculate how many weeks of therapy have been completed – actual processed claims.)
- Recent progress notes
- New HCV RNA viral load (drawn 24-weeks after initiation of treatment) - will need to compare to 12-week HCV RNA viral load (Obtain 12-week HCV RNA viral load from previous request in Stellant)
- Viral Genotype
- Concurrent request for continuation of ribavirin or clinical documentation of a contraindication that prevents its use (Refer to question 9 for contraindications if necessary)

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Procedure, continued:

13. Based on previous pharmacy claims, did the Member maintain adherence and complete the previously prescribed regimen (either 48 weeks for genotypes 1, 4, 6 **OR** 24 weeks for genotypes 2, 3)?
- Yes = **For genotype 1 only:** continue to 14 (Only genotype that should be considered for extended therapy)
- Yes = **For all other genotypes:** Deny: The plan does not allow for continuation of therapy for any genotype other than genotype 1. Based on the information provided, this Member does not meet coverage criteria.
- No = Extend current authorization only for the quantity required to complete the previously established duration of therapy (up to a total of 48 weeks for genotypes 1, 4, 6 **OR** 24 weeks for genotypes 2, 3) – **Will have to calculate how many weeks of therapy have already been completed – how many claims in SXC have processed since the initial approval period.**
14. **For genotype 1 only**, did the Member have delayed virus clearance (HCV RNA viral load became negative or undetectable between weeks 12 and 24)? (Will need to compare actual lab values - **drawn 12-weeks & 24-weeks after initiation of treatment**)
- Yes = continue to 15 for **genotype 1 only**
- No = Deny: For extension of therapy past 48 weeks, the plan requires the Member to have delayed virus clearance, where repeat HCV RNA viral load became negative or undetectable between weeks 12 and 24. Based on the information provided, this Member does not meet coverage criteria.
15. **For genotype 1 only**, did the Member achieve an undetectable (lab usually < 50 IU/ml) HCV RNA viral load **by at least week 24**? (Will need actual lab values - **drawn 24-weeks after initiation of treatment**)
- Yes = Authorize Pegasys/Peg-Intron **plus ribavirin for an additional 24 weeks**. This will allow for a total of 72 weeks of treatment. (**Please load for 24 weeks only verses 6 months**)
- No = Deny: For extension of therapy past 48 weeks, the plan requires the Member to have achieved a complete EVR (early virological response), where HCV RNA viral load is undetectable by week 24. Based on the information provided, this Member does not meet coverage criteria.

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Procedure, continued:

Section IV. RETREATMENT REQUEST for Relapsers (For Members who HCV RNA viral load returns within the first 12 to 24 weeks after completing a full course of Hep C therapy):

(Need the following supporting documentation from the requesting provider or from PBM pharmacy claim system).

- Review previous pharmacy claims in PBM pharmacy claim system for Pegasys/Peg-Intron and Ribavirin OR non-pegylated interferon (Intron-A, Infergen) – will need to calculate how many weeks of therapy have been completed – actual processed claims.)
- Recent progress notes
- New HCV RNA viral load (drawn 24-weeks after discontinuation of previous treatment)
- New liver enzymes, specifically ALT (need at least 2 different labs from last 6 months)
- New INR lab
- Liver Biopsy report for genotype 1 only
- Viral Genotype
- Concurrent request for continuation of ribavirin or clinical documentation of a contraindication that prevents its use (Refer to question 9 for contraindications if necessary)

16. Did the Member previously complete a full course of therapy with Pegasys/Peg-Intron and ribavirin (48 weeks for genotypes 1, 4, 6 **OR** 24 weeks for genotypes 2, 3)?

Yes = Deny: Retreatment is not recommended for Members who did not achieve an SVR (sustained virological response), which is the absence of HCV RNA from the serum 24 weeks after a prior full course of peginterferon (Pegasys/Peg-Intron) plus ribavirin. Based on the information provided, this Member does not meet coverage criteria.

No = continue to 17

17. Did the Member previously complete a full course of therapy (48 weeks for genotypes 1,4, 6 **OR** 24 weeks for genotypes 2, 3) **with non-pegylated interferon (Intron-A, Infergen) with or without ribavirin?**

Yes = Approve an additional course of therapy - return to the beginning of the procedure (Section I – For Initial Treatment) to begin steps for approval.

No = continue to 18

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Procedure, continued:

18. Did the Member previously complete a full course of therapy (48 weeks for genotypes 1,4, 6 **OR** 24 weeks for genotypes 2, 3) **with Pegasys/Peg-Intron monotherapy (w/o ribavirin)?**
- Yes = Approve an additional course of therapy - return to the beginning of the procedure (Section I – For Initial Treatment) to begin steps for approval.
- No = Deny, Retreatment is only recommended for Members who completed a full course of therapy with **non-pegylated** interferon (Intron-A, Infergen) with or without ribavirin **OR** with Pegasys/Peg-Intron monotherapy. Based on the information provided, this Member does not meet coverage criteria.

Section V. FOR HEPATITIS B Treatment: (Need the following supporting documentation from the requesting provider).

- Recent progress notes
- HBV Markers, to include HBV DNA level, HBsAg, HBeAg
- Current liver enzymes, specifically ALT (need at least 2 different labs from last 6 months)
- Liver Biopsy (if treatment being requested for lower DNA levels (2,000 to 20,000 IU/ml) and borderline or minimally elevated ALT levels)

19. Has the Member been HBsAg positive for at least 6 months?

- Yes = continue to 20
- No = Deny: Treatment is only recommended for chronic Hepatitis B infection. Based on the information provided, this Member does not meet coverage criteria.

20. **For Commercial Members only-** Does the Member (HBeAg-positive **or** HBeAg-negative) have a quantitative HBV DNA greater than 20,000 IU/mL **AND** liver enzyme ALT greater than 2 times the upper limit of normal?

- Yes = Approve Pegasys 180mcg weekly for 48 weeks
- No = continue to 21 for HBeAg negative or 22 for HBeAg positive

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Procedure, continued:

21. **For Commercial Members only-** Is the Member HBeAg-negative with a quantitative HBV DNA greater than 2,000 IU/mL **AND** liver enzyme ALT less than 2 times the upper limit of normal with **BOTH** of the following (**A & B**)?

A. A liver biopsy that indicates moderate to severe inflammation or significant fibrosis and necrosis; **AND**

B. A current INR (within the past 30 days) within normal limits (range 0.9 – 1.2)

Yes = Approve Pegasys180mcg weekly for 48 weeks

No = Deny: Based on treatment guidelines, HBeAg-negative Members with lower HBV DNA levels (2,000 to 20,000 IU/ml) with borderline or minimally elevated ALT levels should have a liver biopsy to determine severity of hepatic involvement. Treatment should only occur with moderate to severe inflammation or significant fibrosis on biopsy. Based on the information provided, this Member does not meet coverage criteria.

22. **For commercial Members only-**Is the Member HBeAg-positive above 40 years of age with a quantitative HBV DNA greater than 20,000 IU/mL **AND** liver enzyme ALT normal or minimally elevated with **BOTH** of the following (**A & B**)?

A. A liver biopsy that indicates moderate to severe necroinflammation or significant fibrosis; **AND**

B. A current INR (within the past 30 days) within normal limits (range 0.9 – 1.2)

Yes = Approve Pegasys180mcg weekly for 48 weeks

No = Deny: Based on treatment guidelines, HBeAg-positive Members with elevated HBV DNA levels greater than 20,000 IU/mL with borderline or minimally elevated ALT levels should have a liver biopsy if above the age of 40 to determine severity of hepatic involvement. Treatment should only occur with moderate to severe necroinflammation or significant fibrosis on biopsy. Based on the information provided, this Member does not meet coverage criteria.

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References:

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14. Kaymakoglu S, Oguz D, Gur G, et al. Pegylated interferon Alfa-2b monotherapy and pegylated interferon Alfa-2b plus lamivudine combination therapy for Members with hepatitis B virus E antigen-negative chronic hepatitis B. *Antimicrob Agents Chemother*. 2007 Aug;51(8):3020-2.

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Disclaimer Information:

Prior Authorization criteria are developed to determine coverage for AvMed Health Plans' benefits, and are published to provide a better understanding of the basis upon which coverage decisions are made. AvMed Health Plans makes coverage decisions based on the Member's benefit plan contract and these criteria. This guideline sets forth concise clinical coverage criteria which have been developed from a review of current literature, policies of the FDA and other government agencies, and other appropriate references, in consultation and with approval from practicing physicians who are members of AvMed's Pharmacy and Therapeutic committee. Treating providers are solely responsible for the medical advice and treatment of Members. This guideline may be updated and therefore is subject to change. The use of these criteria is neither a guarantee of payment nor a final prediction of how specific claim(s) will be adjudicated.