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Product name: **PEGINTRON**
Procedure No. **EMEA/H/C/280/II/45**

SCIENTIFIC DISCUSSION

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Introduction

The more common virus HCV genotypes in Europe are genotypes 1, 2 and 3. Previous studies with the combination therapy of Intron A (a non-pegylated interferon alfa) plus Rebetol (ribavirin) showed that patients infected with genotype 2 or 3 only require 6 months of treatment and do not benefit from a longer treatment period. Based on an extrapolation from these results, the initial recommended duration of therapy for PegIntron (peginterferon alfa-2b) plus Rebetol (ribavirin) was of at least 6 months for HCV genotype 2 and 3. The decision to further extend the treatment period to one year for some patients should be based on prognostic factors such as age> 40 years, male gender and/or bridging fibrosis.

Part of the MAH's commitments at the time of approval was to perform a study addressing the benefit of a 6-month duration of treatment with peginterferon alfa-2b/ribavirin in hepatitis C patients with genotype 2/3 and genotype 1/low viral load infection. Based on the results in patients with HCV genotype 2 and 3, the MAH has applied for a type II variation to update SPC sections 4.2 and 5.1 regarding the duration of therapy for patients infected with HCV genotype 2 or 3. Additional minor changes to sections 2 and 5.1 of the SPC and to the PL were included in order to comply with CPMP/463/00 and CPMP/BWP/3068/03 guidelines. The MAH took this opportunity to update the wording of the storage conditions in the SPC, PL and labelling in accordance with the latest templates.

Clinical aspects

Study P01882 - Duration of treatment for patients infected with genotype 2 or 3

This was a single arm, open label study that included 224 patients with genotype 2 or 3 who received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg – 1,400 mg p.o. for 6 months (based on body weight: 1,400 mg to patients weighing > 105 kg, only three patients were enrolled). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 µg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/mL	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6-month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Discussion

Clinical Efficacy

Genotype 1
Part of the commitments at the time of approval was to perform a study addressing the benefit of 6-month duration of treatment with peginterferon alfa-2b/ribavirin in hepatitis C patients with genotype 2/3 and genotype 1/low viral load infection. In this application only the results for the sub group of patients infected with genotype 2 and 3 were provided. The MAH has committed to submit the final report including data on patients infected with genotype 1 (low viral load) at a later stage.

Genotype 2
Despite the low number of patients (42/224) infected with HCV genotype 2, the overall results of Study P01882 support the fact that 6 months of treatment is sufficient in most patients: there were 100% responders at the end of the 24 weeks treatment with 93% of sustained virologic response 24 weeks after the end of treatment and 7% of relapse.

Genotype 3
The overall results of Study P01882 support the fact that 6 months of treatment is sufficient in most patients infected with genotype 3: 93% (169/182) responders at the end of 24 weeks of treatment, 79% of sustained virologic response and 14% of relapse. In this study patients infected with genotype 3 with a high viral load (>600 000 IU/ml) appeared as having a poorer response as compared to those with low viral load (≤600 000 IU/ml) (70% vs. 86% of sustained response).

Genotype 4, 5 or 6
The more common genotypes in Europe are genotypes 1, 2 and 3 and only these genotypes were included in Study P01882. However the historical study C98-580 was a worldwide study and open to all genotypes. Based on an analysis performed at the request of the CHMP, the MAH proposed that the duration of treatment for patients infected with genotype 4 is as long as for genotype 1 (i.e. 48 weeks). Not enough data were available for genotype 5 and 6, and the MAH could not provide any recommendations for patients infected with these genotypes.

Dose

The doses received in the study were PegIntron 1.5 microg/kg once weekly and Rebetol 800-1400 mg/day based on body weight. Whereas the currently maximum recommended dose for Rebetol is 1200mg/day (for patients >85 kg), the study protocol recommended 1400 mg/day for patients > 105Kg in order to give them the optimal dose of Rebetol (13 ± 2 mg/kg/day). However, since only 3 patients weighted more than 105 kg and received this increased dose, it was insufficient to adequately assess the safety and efficacy of the 1400mg/day dose. No revision of the posology Section 4.2 of the SPC was proposed by the MAH. The CHMP considered this acceptable, however, this should be reconsidered once the results of the ongoing clinical studies exploring the 1400 mg dose in patients >105 kg are submitted. The MAH was requested to submit these results as soon as they are available.

Prognostic factors

The virological response (2 log viral load decrease or undetectable level of HCV RNA) observed at week 12 has been shown to be predictive for a sustained response. It has been shown that the negative predictive value of the week 12 response was 100% for genotype 1 only (with PegIntron 1.5 + ribavirin (> 10.6 mg/kg)) and not for genotype 2 and 3 (with PegIntron 1.5 + ribavirin 800-1400 mg) since one patient had a sustained response without having an early virologic response at week 12.

Predictability of sustained response by viral response at week 12 and genotype*				
Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50%

*reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

Based on the results provided as part of this application, predictors of sustained response identified by single variation logistic regression were: sex, genotype, viral load, treatment duration and steatosis. Weight was not considered predictive in the analysis of this study where the ribavirin dose received was based on subject weight.

Although the patients infected with genotype 2 appeared to be better responders than those infected with genotype 3, after stepwise regression, viral load, treatment duration > 16 weeks and steatosis remained the only significant predictors of outcome. Age and sex do not appear as negative prognostic factors in this analysis. These findings justify the rediscussion of the negative prognostic factors that could lead to one year of treatment as currently stated in the SPC.

A logistic regression meta-analysis of genotype 2 and 3 patients treated with Intron A or PegIntron plus ribavirin did not identify any subset, based on prognostic factors, that would benefit from a duration of treatment greater than 24 weeks. Especially patients infected with HCV genotype 3 with high viral load do not appear to benefit from the longer treatment duration.

In the absence of reliable data on pronostic factors to support a longer treatment, the CHMP considered that a treatment of 24 weeks is recommended for all patients infected with genotype 2 or 3. However the CHMP requested the applicant to closely monitor the rate of relapse observed following the introduction of this new recommendation in order to detect any increase. The MAH was requested to keep the CHMP regularly informed of the results. In addition, considering that retrospective analysis have limitations, the MAH was recommended to prospectively investigate pronostic factors in future studies.

Clinical Safety

The nature of the adverse drug reactions observed in this study was consistent with the known safety profile of the medicinal products and no new adverse drug reactions were identified. As expected, the treatment was better tolerated when halving the treatment duration (discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %). This further supports a duration of treatment of 24 weeks.

Amendments to the Product Information

It was agreed to include the details of Study P01882 in section 5.1 of the SPC.
Further, the following recommendations on the duration of treatment was added in section 4.2 of the SPC:

"Genotype 1: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of ~~one year~~ 48 weeks)."

"Genotypes 2 or 3: It is recommended that all patients be treated for 24 weeks."

"Genotype 4: In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1."

With reference to predictability of sustained virological response, it was agreed to amend section 4.2 as follows:
"*Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders ~~(negative predictive value 100 % for combination therapy, 98 % for monotherapy). Virological response is defined as at least a 2 log decrease or absence of detectable HCV-RNA at Week 12. With combination therapy all patients with genotypes 2 or 3 achieved virological response at Week 12~~ (see also section 5.1)".*

In addition, it was agreed to include the detailed results described in the above table in section 5.1.

Additional minor changes to sections 2 and 5.1 of the SPC and to the PL were included in order to comply with CPMP/463/00 and CPMP/BWP/3068/03 guidelines. The MAH also took this opportunity to update the wording of the storage conditions in the SPC, PL and labelling in accordance with the latest templates.

Benefit/risk

Considering the safety profile of the combination therapy Pegintron plus Rebetol, the quite comparable efficacy data achieved in genotype 2 and 3 with a treatment of 24 weeks as compared to 48 weeks and the absence of reliable negative prognostic factors supporting a longer duration, it seems reasonable to recommend a duration of treatment of 24 weeks for all patients infected with genotype 2 or 3.

CONCLUSION

The CHMP considered this type II variation to be acceptable and agreed on the proposed wordings to be introduced into the SPC and reflected into the PL, based on the observations and the appropriate conclusions.

The CHMP adopted on 20 June 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.