17 January 2013
EMA/CHMP/83314/2013
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Pegasys

### International non-proprietary name: PEGINTERFERON ALFA-2A

### Procedure No. EMEA/H/C/000395/X/0059/G

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Product information

| | |
|---|---|
| **Name of the medicinal product:** | Pegasys |
| **Applicant:** | Roche Registration Ltd.<br>6 Falcon Way<br>Shire Park<br>Welwyn Garden City AL7 1TW<br>United Kingdom |
| **Active substance:** | peginterferon alfa-2a |
| **International Nonproprietary Name/Common Name:** | peginterferon alfa-2a |
| **Pharmaco-therapeutic group (ATC Code):** | IMMUNOSTIMULANTS, Interferons (L03AB11) |
| **Therapeutic indications:** | <u>Chronic hepatitis B</u><br><br>Pegasys is indicated for the treatment of hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B (CHB) in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see sections 4.4 and 5.1).<br><br><u>Chronic hepatitis C</u><br><br>*Adult patients*<br>Pegasys is indicated for the treatment of chronic hepatitis C (CHC) in adult patients who are positive for serum hepatitis C virus ribonucleic acid (HCV-RNA). This includes patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).<br><br>The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. The combination of Pegasys and ribavirin is indicated in treatment naïve patients and in adult patients who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination therapy with ribavirin.<br><br>Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.<br><br>*Paediatric patients 5 years of age and older:*<br>Pegasys in combination with ribavirin is indicated for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older, who are positive for serum HCV-RNA.<br><br>When deciding to initiate treatment in childhood, it is important to consider growth inhibition induced |

| | |
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| | by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4). |
| **Pharmaceutical form:** | Solution for injection |
| **Strengths:** | 135 µg, 180 µg, 90 µg |
| **Routes of administration:** | Subcutaneous use |
| **Packaging:** | pre-filled pen, pre-filled syringe (glass), vial (glass) |
| **Package sizes:** | 1 pre-filled pen, 1 pre-filled syringe + 1 injection needle, 1 vial, 4 pre-filled pens, 4 pre-filled syringes + 4 injection needles, 4 vials, 12 pre-filled pens, 12 pre-filled syringes + 12 injection needles |

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# List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AR | Assessment report |
| AUC | Area under the serum concentration versus time curve |
| bid | Twice daily |
| BMI | Body mass index |
| BSA | Body surface area |
| CHC | Chronic Hepatitis C |
| CI | Confidence interval |
| EMA | European Medicines Agency |
| ERA | Environmental risk assessment |
| EU | European Union |
| GCP | Good Clinical Practice |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| IFN | Interferon |
| IU | International units |
| kg | Kilogram |
| lb | Pounds |
| LoQ | List of questions |
| MAH | Marketing Authorisation Holder |
| µg | Microgram |
| mg | Milligram |
| ml | Millilitre |
| PAC | Post-approval commitment |
| PD | Pharmacodynamic(s) |
| PDCO | Paediatric Committee |
| PEC | Predicted environmental concentration |
| PEG | Polyethylene glycol |
| PEG-IFN | Peginterferon |
| PIP | Paediatric investigation plan |
| PK | Pharmacokinetic(s) |
| po | By mouth, orally |
| qd | Once daily |
| RBV | Ribavirin |
| SAE | Serious adverse event |
| SC | Subcutaneously |
| SmPC | Summary of Product Characteristics |
| SVR | Sustained virological response |
| TSH | Thyroid stimulating hormone |
| US | United States |
| VL | Viral load |
| VR | Virological response |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Roche Registration Ltd. submitted on 01 December 2011 to the European Medicines Agency (EMA) through the centralised procedure an application for an extension of the Marketing Authorisation (MA) pursuant to Article 19 of Commission Regulation (EC) No 1234/2008. Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008 the application was grouped with a type II variation submitted pursuant to Article 16 of Commission Regulation (EC) No 1234/2008.

This grouped application includes:

- An application for an extension of the MA for a new strength (90 µg)
- A type II variation, extension of indication to include the treatment of chronic hepatitis C in paediatric patients aged 5 years and older

The application submitted is composed of administrative information, complete quality data and clinical data based on applicants' own tests and studies and/or bibliographic literature.

### *Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/274/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/274/2011 was not yet completed.

### *Information relating to orphan market exclusivity*

**Similarity**

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific Advice*

The applicant received Scientific Advice from the CHMP on 21 September 2000 and 23 April 2009. The Scientific Advice pertained to quality aspects of the dossier. In addition the applicant obtained scientific advice from National Competent Authorities.

### *Licensing status*

Pegasys has been given a Marketing Authorisation in the European Union (EU) on 20 June 2002.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Concepcion Prieto Yerro**

- The application was received by the EMA on 1 December 2011.
- The procedure started on 21 December 2011.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 March 2012 (Annex 2).
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 April 2012 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2012.
- The Rapporteurs circulated the Joint Updated Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 14 September 2012 (Annex 4).
- During the CHMP meeting on 20 September 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 December 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 January 2013 (Annex 6).
- During the meeting on 17 January 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pegasys on 17 January 2013.

# 2. Scientific discussion

## *2.1. Introduction*

Although vertical transmission from mother to child of hepatitis C virus (HCV) (also known as perinatal or mother-to-child transmission) is now the primary source of infection in children, the characteristics of HCV disease state are similar in the paediatric and adult population with a few exceptions. Most vertical transmission appears to occur either in uteri or intrapartum. Estimates of the risk of vertical transmission of HCV range from 3% to about 10% of pregnancies in anti-HCV-positive women, and the risk is known to be increased in HIV/HCV-coinfected mothers, probably as a result of higher HCV viral load because of maternal immunosuppression. The progression of HCV has been reported to be slower in children than in adults, and inflammation of liver tissue has usually been found to be mild at the time of diagnosis and to remain at a low level over more than 10 to 15 years. Evidence of advanced hepatic fibrosis is not common in paediatric subjects, particularly in younger subjects and Guido et al. (Am J Gastroenterol 2003) concluded that at least 10 years would be required for the development of severe fibrosis in children.

Despite treatment of chronic HCV with interferons (IFNs) being authorized in the European Union (EU) and US from the age of 3 years for the past several years, there remains a lack of consensus about the necessity to treat paediatric patients. However, the balance of opinion is shifting towards earlier treatment because of the perceived higher tolerability and comparable response rates to those observed in adults.

Roche Registration Ltd. (Roche) are submitting an application to support a new indication and line extension for the use of Pegasys (peginterferon alfa-2a, PEG-IFN alfa-2a) in combination with ribavirin (RBV) in treatment-naive children aged 5 to 17 years with chronic hepatitis C (CHC). The application is

based on findings from the post-approval commitment (PAC) study, NV17424, which evaluated treatment of CHC with PEG-IFN alfa-2a in combination with RBV, and PEG-IFN alfa-2a alone, in children aged 5 to 17 years.

## *2.2. Quality aspects*

### 2.2.1. Introduction

This is an application for a line extension to add a new strength related to a paediatric formulation (90 micrograms solution for injection in prefilled syringes) and for a type II variation to extend the indication to the paediatric population in children and adolescents aged 5 and older with chronic hepatitis C.

The newly developed PFS 90 µg/0.5 mL presentation contains the same drug product formulation of peginterferon alfa-2a in the same container closure system as the already globally approved 135 µg/0.5 mL and 180 µg/0.5 mL PFS and differs only in the amount of peginterferon alfa-2a used for formulation. The composition of the PEGASYS 90 µg/0.5 mL PFS is identical to that contained in the 180 µg/1.0 mL Vials. The presentation differs from the currently approved PFS only with regard to the labelling of the primary packaging (PFS): Six graduation marks are shown instead of three.

### 2.2.2. Active Substance

The peginterferon alfa-2a (Ro 025-8310) active substance used for the manufacture of the PEGASYS Pre-filled Syringes 90 µg/0.5 mL will be manufactured and tested according to the currently approved license.

### 2.2.3. Finished Medicinal Product

The concentration of active substance of the new PEGASYS 90 µg/0.5 mL PFS and the approved strengths of PEGASYS PFS and vials is presented in Table 1 below. All presentations have the same qualitative and quantitative composition for the excipients: sodium chloride, polysorbate 80, benzyl alcohol (10 mg / 1 mL), sodium acetate, acetic acid and water for injections at pH 6.0.

**Table 1.** Active substance concentrations of the new PEGASYS 90 µg/0.5 mL PFS and the approved 135 µg/0.5 mL PFS, 180 µg/0.5 mL PFS, 135 µg/1.0 mL and 180 µg/1.0 mL Vials

| ***Ingredient*** | ***Function*** | ***Quantity per mL*** | | | | |
|---|---|---|---|---|---|---|
| | *Dosage form* | ***90 µg/0.5 mL PFS*** | *135 µg/0.5 mL PFS** | *180 µg/0.5 mL PFS** | *180 µg/1.0 mL Vial** | *135 µg/1.0 mL Vial** |
| Peginterferon alfa-2a | active substance | **180µg** | 270µg | 360µg | 180µg | 135µg |

*approved in the EU and in many other countries

## *Pharmaceutical Development*

The pharmaceutical development of the PEGASYS 90 µg/0.5 mL PFS was focused to those aspects which are different to the currently marketed PEGASYS PFS. These aspects included:

- differences in the filling of the PEGASYS 90 µg/0.5 mL PFS compared to the marketed PEGASYS 135 µg/0.5 mL PFS and 180 µg/0.5 mL PFS as well as
- dose accuracy tests of the six graduation marks

*Components of the drug product / Drug product*

The newly developed PFS 90 µg/0.5 mL presentation contains the same drug product formulation of peginterferon alfa-2a in the same container closure system as the already globally approved 135 µg/0.5 mL and 180 µg/0.5 mL PFS and differs only in the amount of peginterferon alfa-2a used for formulation. The composition of the PEGASYS 90 µg/0.5 mL PFS is identical to that contained in the 180 µg/1.0 mL Vials. Therefore no additional formulation development work was performed.

*Manufacturing process development*

As in the case for the currently authorised drug product strengths, the manufacturing procedure consists of a standard manufacturing process routinely applied for sterile liquid parenteral products which cannot be terminally sterilized by heat.

*Container closure system*

The primary packaging components of the 90 µg/0.5 mL PFS presentation is identical to the approved PFS dosage strength. As established for the currently licensed syringe strengths, the 90 µg/0.5 mL PFSs have self-adhesive transparent labels with graduation marks to allow accurate dosing of smaller amounts of drug product. The presentation differs from the currently approved PFS only with regard to the labelling of the primary packaging (PFS): Six graduation marks (10 µg, 20 µg, 30 µg, 45 µg, 65 µg and 90 µg) are shown instead of three (45 µg, 90 µg, 135 µg or 90 µg, 135 µg and 180 µg, respectively).

A study was performed to determine the dose accuracy for these marks. Results, in terms of the mean and variations of the ejected amount correspond with the declared injection dose.

*Microbiological attributes*

Since the primary packaging components of the 90 µg/0.5 mL PFS presentation is identical to the approved PFS dosage strengths, no additional development has been conducted. This was accepted by the CHMP.

*Compatibility*

Based on the stability data available at submission, no alterations in the physical and biochemical properties of the product are observed for the 90 µg/0.5 mL PFS.

## *Manufacture of the product*

The manufacturing process is conducted according to the already established and authorised PFS strengths, employing the following steps: Preparation of the formulated bulk, Sterilization of primary packing material and equipment, Bioburden reduction filtration, Sterile filtration, Filling into syringes and insertion of plunger stopper, and finally Optical inspection of the syringes.

The manufacturing process and controls are acceptably described. Considering that sterilisation is made using dual filtrations, the limits set for bioburden control are considered acceptable.

*Process validation and/or evaluation*

The verification of process consistency has been acceptably verified by process validation. Process validation for the PEGASYS Pre-filled Syringes 90 µg/0.5 mL was performed at the manufacturing site Roche Kaiseraugst, Switzerland.

The same fundamental manufacturing process and process parameters are used for PEGASYS Pre-filled Syringes 90 µg/0.5 mL as already established for the currently marketed PEGASYS Pre-filled Syringes 135 µg/0.5 mL and 180 µg/0.5 mL. Therefore, the focus of the process validation design for the PEGASYS Pre-filled Syringes 90 µg/0.5 mL was on the sterile filtration and filling process.

### *Product specification*

The release and stability specifications and analytical procedures for 90 µg/0.5 mL PFS are identical to those approved for the currently authorised PFS, with exception of the amount of peginterferon alfa 2a in each syringe. The specifications contain tests for pharmacopoeial methods as well as specific methods.

Three registration batches of the 90 µg/0.5 mL PFS were tested according to the approved analytical procedures. The corresponding results were evaluated and found compliant with the proposed specifications.

The reference standards are the same as for the already approved PEGASYS PFS.

The specifications (types and materials) of the PEGASYS 90 µg/0.5 mL PFS are identical to the specifications of the already approved material.

### *Stability of the product*

All of the three registration batches were put on a formal stability study. The available results obtained allow the conclusion that the long-term stability of 90 µg/0.5 ml PFS shows consistent quality attributes.

In summary, the 90 µg/0.5 mL PFSs manufactured at Roche Kaiseraugst show the same stability characteristics as established for the already approved 180 µg/1.0 mL Vial presentation of the same concentration and composition. Therefore, the data support the same shelf life of 36 months at the recommended storage condition of 2 °C – 8 °C.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The newly developed PFS 90 µg/0.5 mL presentation contains the same drug product formulation of peginterferon alfa-2a in the same container closure system as the already approved 135 µg/0.5 mL and 180 µg/0.5 mL PFS and differs only in the amount of peginterferon alfa-2a used for formulation. The composition of the PEGASYS PFS 90 µg/0.5 mL PFS is identical to that contained in the 180 µg/1.0 mL Vials. The primary packaging components are identical to the approved PFS dosage strength. The presentation differs from the currently approved PFS only with regard to the labelling of the primary packaging (PFS): Six graduation marks (10 µg, 20 µg, 30 µg, 45 µg, 65 µg and 90 µg) are shown instead of three (45 µg, 90 µg, 135 µg or 90 µg, 135 µg and 180 µg, respectively). Dose accuracy has been acceptably shown.

Except for the batch formula, where the amount of peginterferon alfa-2a is adapted to the new strength and the batch size is smaller, the manufacturing process is identical to the currently approved process for the Pegasys 135 µg/0.5 mL and 180 µg/0.5 mL PFS presentations. Verification of the consistency of the process has been acceptably shown by process validation data in this line extension submission for the 90 µg/0.5ml PFS.

The release and stability specifications are identical, where applicable, to the currently approved vial and PFS specifications. Batch data for the three 90 µg/0.5ml validation batches are found compliant with the specifications. Furthermore, stability data is included and the stability profile is well

comparable with the currently approved 180 µg/1.0ml vial presentation of identical composition. Therefore, the claim that data support the same shelf life of 36 months at the recommended storage condition of 2 °C – 8 °C as currently approved, is considered acceptably justified.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of data on quality, the CHMP considers that the application for the additional strength of Pegasys (90 µg, solution for injection in pre-filled syringe) can be approved.

### 2.2.6. Recommendation(s) for future quality development

N/A

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

No new data on Pharmacology, Pharmacokinetics or Toxicology have been submitted by the applicant in this application.

### 2.3.2. Ecotoxicity/environmental risk assessment

The applicant argues that no new ERA is needed for the present paediatric indication by presenting the following justification:

Total average HCV prevalence in Europe is approximately 0.77-1.2% for adults and 0.13-0.6% for juveniles (children 0-14 years) (Anglemyer et al., Internal Epidemiology Report, Roche/Genentech South San Francisco 2011). The applicant acknowledges a potentially significant increase in usage for the intended paediatric indication compared to the previously approved adult indication. Romania has the highest prevalence in adults (3.5%) and the UK has the highest prevalence in children (2.8%) (Anglemyer et al., Internal Epidemiology Report, Roche/Genentech South San Francisco 2011). The maximum single dose of Pegasys is 180 µg of the active substance dosed at least 7 days apart. Hence, assuming both a highest theoretical prevalence, respectively penetration factor (Fpen) of 6.3% (3.5% plus 2.8%) of the whole population and an evenly spaced excretion of Pegasys over that week would result in an initial surface water predicted environmental concentration (PEC):

(0.18 mg/week÷7 days/week)x0.063/(2001x10) = 0.00081 µg Pegasys/L = 0.81 ng Pegasys/L

Hence, the worst-case European Pegasys surface water PEC for all potential HCV patients, including all age groups and all HCV subtypes is below the EMA threshold concentration of 0.01 µg/L by a factor of more than 10.

Moreover, during human metabolism the pharmacologically active interferon moiety is at least partly degraded through proteolytic mechanisms, with mostly only the PEG moiety being excreted whole. In addition, Pegasys has been tested for biodegradability in a closed-bottle test according to OECD test guideline 301D. While not achieving formal ready biodegradability, it was shown to degrade to a significant part. This partial degradation was likely achieved through proteolysis of the interferon moiety, while long-chained PEGs are known to be slowly degradable (Straub in K. Kuemmerer, M. Hempel (eds.) Green and Sustainable Pharmacy, Springer Verlag Berlin Heidelberg 2010). Hence, both human metabolism and biodegradation during sewage treatment further decrease the already low surface water PEC.

### 2.3.3. Discussion on non-clinical aspects

The toxicological profile of peginterferon alfa-2a is well known and thus no new non-clinical data are considered necessary for supporting the new strength and the paediatric indication.

The prevalence of HCV in juveniles in the EU is based on an internal study report. This report in turn uses references available in the general literature to estimate prevalence. It is the view of the CHMP that the presented prevalence report is valid and thus it is agreed that no new ERA is necessary for the increased usage of Pegasys by including paediatric patients in the indication.

### 2.3.4. Conclusion on the non-clinical aspects

No new non-clinical studies have been performed in support of this application and no further studies are considered necessary by the CHMP. The available non-clinical data are considered sufficient by the CHMP to support this application.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

#### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 2.** Overview of Pivotal and Supporting Clinical Studies Providing Main Efficacy Data

| | | | | | Efficacy Analysis Population | | |
|---|---|---|---|---|---|---|---|
| **Protocol No.** | **Study Design** | **No. of centers and Locations** | **Study Population** | **Treatment Regimen, Dose and Duration** | **Total No of Patients** | **Sex (M/F)** | **Age range, years** |
| **Supporting Study in Paediatric Patients** | | | | | | | |
| NR16141 | Phase 2, multicentre, open-label study of viral kinetics, PK, and safety in patients who received PEG-IFN alfa-2a subcutaneously (SC) once a week for 48 weeks with 24 weeks of treatment-free follow-up. | 5 centres in the United States | Children aged 2 to 8 years | Patients received an injection of PEG-IFN alfa-2a SC once a week for 48 weeks and continued to be evaluated throughout a 24-week treatment-free follow-up period.<br>The paediatric dose of PEG-IFN alfa-2a for this study was obtained by multiplying the BSA of a child in $m^2$ by the $\mu g/m^2$ dose for an average adult with a BSA of 1.73 $m^2$ (180 µg x BSA / 1.73 $m^2$). | 14 | 8/6 | 2-8 |

| | | | | | Efficacy Analysis Population | | |
|---|---|---|---|---|---|---|---|
| **Protocol No.** | **Study Design** | **No. of centers and Locations** | **Study Population** | **Treatment Regimen, Dose and Duration** | **Total No of Patients** | **Sex (M/F)** | **Age range, years** |
| **Pivotal Study in Paediatric Patients** | | | | | | | |
| NV17424 | Phase 3, multicentre, randomised, blinded (through at least Week 24 of treatment), placebo-controlled study | 11 centres in the United States | Children aged 5 to 18 years (screening must have been completed before the patient's 18th birthday) with chronic HCV infection and compensated liver disease | Patients were randomised in a 1:1 ratio to one of the following two initial treatment regimens:<br>Group 1: 180 µg x BSA / 1.73 $m^2$ of PEG-IFN alfa-2a once weekly, administered SC and 15 mg/kg body weight/day RBV, administered orally (po), twice daily (bid) (maximum dose of 1,200 mg/day for patients with body weight ≥75 kg or 1,000 mg/day for patients with body weight <75 kg).<br>Group 2: 180 µg x BSA / 1.73 $m^2$ of PEG-IFN alfa-2a once weekly, administered SC and placebo, administered po, bid.<br>Blinded treatment was administered for 24 weeks. At Week 24, those patients who exhibited a virological response (VR) (ie, undetectable HCV RNA in plasma) were kept on the same blinded treatment regimen for an additional 24 weeks. At Week 48, treatment was discontinued and the patients were followed untreated for 24 weeks (ie, to Week 72). Patients with detectable HCV RNA at Week 24 were unblinded. Those receiving PEG-IFN alfa-2a monotherapy were treated for an additional 48 weeks with PEG-IFN alfa-2a plus RBV combination therapy. | 114 | 63/51 | 5-17 |

## 2.4.2. Pharmacokinetics

***The proposed dose for PEG-IFN alfa-2a in Paediatric Patients with HCV***

The application concerns children in the age range 5 to 17 years inclusive. The MAH originally submitted pharmacokinetic data from 14 children in the age range 2 to 8 years (study NR16141). Six of the children in this group were 5 years of age or above. Unfortunately, no pharmacokinetic (PK) sampling was performed in the phase III study (study NV17424), resulting in a lack of pharmacokinetic data in older children, 9-17 years. This lack of characterisation of PK in the target population was raised as an Other Concern in the day 120 List of Questions.

In study NR16141, a dose of 180 µg x BSA/1.73 $m^2$ of PEG-IFN alfa-2a was administered subcutaneously once weekly. Roughly, the exposure in these children was 25% to 70% higher than that observed in adults receiving a weekly dose of 180 µg of PEG-IFN alfa-2a. In a population pharmacokinetic analysis it was shown that clearance of PEG-INF alfa-2a was related to Body Surface Area (BSA). Based on these facts the applicant proposed a different dosing regimen than used in the pivotal phase III study (Table 3). This proposed dosing guideline is based on BSA categories and, it was claimed by the MAH, should result in exposures that are within the same range shown to be safe and efficacious in adults. The CHMP noted that this proposed regimen suggested somewhat lower doses than the ones tested, especially for the smallest children (Table 3).

**Table 3.** Proposed, rejected, Paediatric BSA Dosing Category Regimen

| BSA Range ($m^2$) | Dose (µg) | Dose received as percentage of the dose used in the paediatric studies (180 µg x BSA/1.73 m2) |
|---|---|---|
| 0.54-0.70 | 45 | 80%-62% |
| 0.71-0.90 | 65 | 88%-69% |
| 0.91-1.15 | 90 | 95%-75% |
| 1.16-1.5 | 135 | 112%-87% |
| >1.5 | 180 | |

To use a model for the purpose of simulating the exposure following a non-studied dosing regimen, a high level of confidence in the model is required. Further work was requested by the applicant to provide this confidence.

By extending the initial PopPK model to include six adult studies, the applicant could show that the elimination of PEG-INF alfa-2a is indeed correlated to body size (BSA) in children aged 2 to 17 years as well as in adult patients. The paediatric/adult dataset was composed of 14 paediatric and 402 adult patients with a total of 143 and 4,021 PK observations respectively. The relation between clearance and BSA was confirmed in this analysis.

The model was qualified for the purpose of simulations in the two populations and was used to interpolate exposures for the 5 to 17 year-olds (NV17424) population where PK data was missing.

Neutrophil count is the most readily assessed pharmacodynamic effect of interferon alfa known to be exposure-dependent. As a way to increase the confidence in the modelling approach, the applicant was therefore encouraged to extend the model to describe the relation between exposure to PEG-INF alfa-2a and the response in neutrophil count and to externally validate this model by simulating the response in absolute neutrophil count seen in study NV17424. In an attempt to address this request,

the applicant used a relationship between PK exposure (AUC) and the risk of neutropenia (NTT), established by pooling data from the paediatric and adult populations and simulated the expected outcome in terms of neutropenia. There was a general agreement between the observed risk of neutropenia (27%) and the model predicted 90% CI [15% to 28%].

While the overall frequency of neutropenia in NV17424 was higher than in other trials, supporting the assumption that drug exposure has indeed been higher, it is notable that one would expect an inverse correlation between BSA and neutropenia, given the applicant's assumption that peginterferon alfa-2a exposure would have increased by up to 70% from the >1.5 $m^2$ category (roughly "adult size") to the lowest BSA categories. The table below illustrates that there was no such trend despite a, in this context, considerable number of patients (table 6). While the applicant's PK model predicted the highest drug exposures in the smallest children, these in fact had less observed neutropenia than did larger children, in whom the applicant's model predicted less elevated drug exposures compared to adults. Note, in relation to these data, that in adults, the proportion of patients with grade 3/4 neutropenia increased from 23.5% to 35% as the dose, and likely consequently exposure, increased by 50% from 180 µg to 270 µg/week (Cumulative Incidence of Neutrophil Count <1.0x$10^9$/L at week 4 from studies NV15489, NV15495, NV15496, NV15497 and NV15801).

**Table 4.** Neutropenia by BSA stratum

| BSA stratum ($m^2$) | n | Neutropenia (<0.75x$10^9$/L) | Dose reduction due to neutropenia | Serious adverse events within first 24 weeks | Discontinuations due to AE |
|---|---|---|---|---|---|
| <0.7 | 0 | - | - | - | - |
| 0.7-0.9 | 20 | 4 (20%) | 3 (15%) | 0 (0%) | 1 (5%) |
| >0.9-1.15 | 19 | 10 (53%) | 9 (47%) | 0 (0%) | 2 (10.5%) |
| >1.15-1.5 | 30 | 14 (47%) | 14 (47%) | 1(3.3%) | 1 (3.3%) |
| >1.5 | 45 | 12 (27%) | 11 (24%) | 1 (2.2%) | 7 (15.5%) |

This discrepancy could, in principle, be due either to a different PK/PD relation in children, or to an erroneous estimation of drug exposure, which was indirect. It is noted that this lack of a gradient of increasing neutropenia with decreasing BSA stands in contrast to the general, relatively high frequency of neutropenia within NV17424. A relationship between BSA and the effect on circulating neutrophils might theoretically be obscured if baseline neutrophils were considerably higher with decreasing BSA (and age). Such data, however, have not been found in the dossier.

The MAH was therefore requested to further analyse the absolute change in neutrophil count from base line to the first on-treatment measurement (at week 1; after which near-maximal decrease of neutrophils occurs, and before data are confounded by dose modifications), as well as absolute neutrophil count at week 1, and relate these variables to the individual predicted mean and cumulative exposure for the same period. In their response, the MAH have not provided data on absolute change from baseline, and have not plotted the neutrophil parameters for each individual patient as a function of model-predicted AUC or mean exposure during the first dosing interval for each patient, as had been requested. Thus, the data presented by the MAH failed to corroborate what the CHMP required in order to have full confidence in the applicant's PK model, on which the proposed posology is based - that, within the relevant BSA range higher predicted AUC is associated with a greater drop in neutrophil count from baseline, as would be expected.

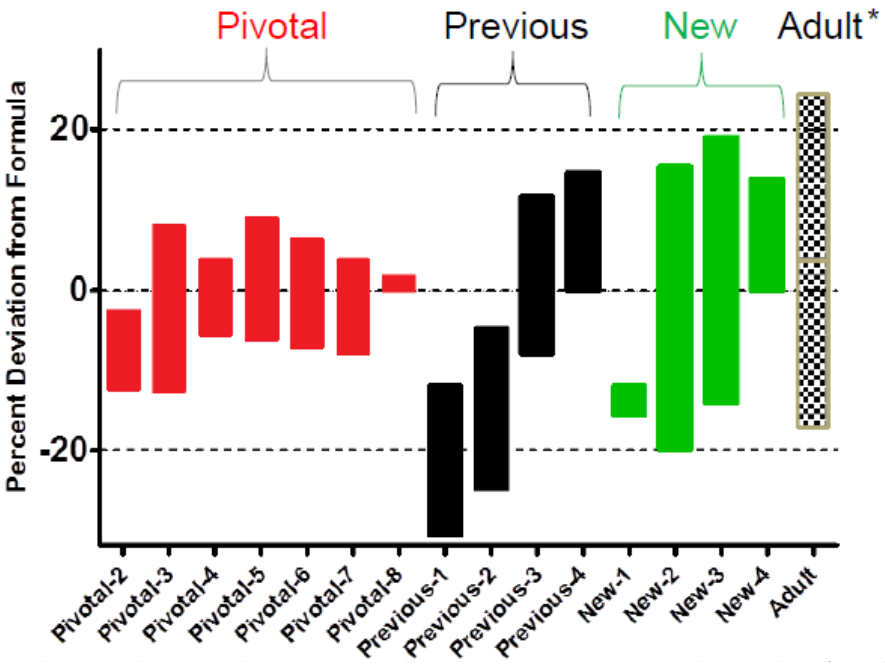
There was therefore insufficient confidence in the applicant's model to approve the proposed posology, which would prescribe up to 40% lower doses than those actually studied, and the CHMP requested that the posology must remain that studied in the pivotal trial as well as the PK trial. That said, the applicant was invited to use a BSA category dosing scheme, to help avoid dosing errors. However, the applicant was required to reasonably fit the BSA categories to the studied dose of 180 µg x BSA/1.73. This updated paediatric BSA-dosing category regimen is shown below in table 5.

**Table 5.** Updated Paediatric BSA Dosing Category Regimen

| BSA Range ($m^2$) | Dose (µg) |
|---|---|
| 0.71-0.74 | 65 |
| 0.75-1.08 | 90 |
| 1.09-1.51 | 135 |
| >1.51 | 180 |

Figure 1 compares the range of deviation from the formula-based dosing for the pivotal study; the previous, rejected, BSA category-based dosing regimen; the updated BSA category-based dosing regimen; and the adult dosing. The range of deviations in adults was computed by comparing the ratio of 180 µg dose per adult BSA of the 5$^{th}$ and 95$^{th}$ percentile adult BSA (from 6 adult studies, n=1940) to the reference (180/median adult BSA). Each bar represents an individual BSA category, from smaller to larger going from left to right (i.e previous 1 = 0.71-0.90, previous 2 = 0.91-1.15, etc; new 1 = 0.71-0.74, new 2 = 0.75-1.08, etc). These new BSA categories have deviations (-20% to +19%) that are similar to the adult deviations (-17% to +24%) (Figure 1).

**Figure 1.**




*

The CHMP considered that the MAH has complied with the request to adjust BSA categories to the doses generated by the formula, and considers that the present degree of deviation, within +/- 20% of the dose, is acceptable. As stated by the MAH, this is in a similar range to that accepted for the ribavirin dosing, and that seen given the BSA distribution in an adult population.

Due to the uncertainties about actual exposure in the smallest children, the CHMP requested a restriction to children with a BSA >0.7 $m^2$, as there was no experience of Pegasys use in children smaller than this, within the pivotal trial.

***Dose Modifications for PEG-IFN alfa-2a in Paediatric Patients with HCV***

Pharmacokinetic simulations have also been performed by the applicant to evaluate dose modification. The recommended dose modification scheme for PEG-IFN alfa-2a is provided in Table 6. These doses are predicted to provide PEG-IFN alfa-2a exposures in children, across the full range of BSA, which are similar to those in adults receiving each corresponding level of dose modification according to the currently approved dose modification scheme in adults (180 to 135 to 90 to 45 µg).

**Table 6.** Recommended Dose Modification in Paediatric Patients for PEG-IFN alfa-2a

| Starting Dose (µg) | 1 Level Reduction (µg) | 2 Level Reduction (µg) | 3 Level Reduction (µg) |
|---|---|---|---|
| 65 | 45 | 30 | 20 |
| 90 | 65 | 45 | 20 |
| 135 | 90 | 65 | 30 |
| 180 | 135 | 90 | 45 |

The CHMP noted that the dose reduction scheme for adults goes from 180 to 135 (75%), 90 (50%) and 45 (25%) of the initial dose. In the NV17424 study the same proportions of the original dose were used per step of dose reduction. This proposed dose reduction scheme allows for a 33% rather than 25% first step reduction, in the initial 135 µg/week categories. The second step dose reduction is in some dose categories up to 55% of the original dose. The applicant's dose reduction schemes was considered appropriate by the CHMP.

***Dose Recommendations for RBV in Combination with PEG-IFN alfa-2a in Paediatric Patients with HCV***

The dose of RBV used in study NV17424 was 15 mg/kg daily as a split dose. The proposed RBV dosing and administration directions in the Pegasys SmPC will follow the guidance established in the NV17424 protocol, ie, 15 mg/kg/day RBV divided into two doses administered orally to a maximum dose of 1,000 mg/day for patients with body weight < 75 kg or 1,200 mg/day for patients with body weight ≥ 75 kg. In study NV17424, a 100 mg tablet was used, however, this is not a commercially available dosage form, and therefore doses have to be rounded to the nearest 200 mg. The 200 mg tablet can be used to accurately dose children down to 23 kg and the degree of rounding is of the same magnitude as that used in study NV17424. Thus, the dose recommendations for RBV as outlined in Table 7 are consistent with those evaluated in study NV17424. For children who are below 23 kg, accurate doses cannot be rounded to the nearest 200 mg and so the applicant provides RBV dose recommendations only for children ≥ 23 kg (Table 7).

**Table 7.** Ribavirin Dosing Recommendations for Paediatric Patients

| Body weight kg (lbs) | Ribavirin Daily Dose | Ribavirin Number of Tablets |
|---|---|---|
| 23 – 33 (51-74) | 400 mg/day* | 1 x 200 mg tablets A.M.<br>1 x 200 mg tablets P.M. |
| 34 – 46 (75-102) | 600 mg/day* | 1 x 200 mg tablets A.M.<br>2 x 200 mg tablets P.M. |
| 47 – 59 (103-131) | 800 mg/day* | 2 x 200 mg tablets A.M.<br>2 x 200 mg tablets P.M. |
| 60 – 74 (132-164) | 1,000 mg/day* | 2 x 200 mg tablets A.M.<br>3 x 200 mg tablets P.M. |
| ≥75 (>165) | 1,200 mg/day* | 3 x 200 mg tablets A.M.<br>3 x 200 mg tablets P.M. |

** approximately 15 mg/kg/day*

The CHMP noted that in the 23-33 kg stratum, the proposed dosing scheme yields doses of 17.4-12.1 mg/kg. The 34-46 kg stratum will receive 17.6-13 mg/kg. The 47-59kg stratum will receive 17-13.6 mg/kg. The maximal deviation downwards from 15 mg/kg is 19.3%, and upwards is 17.3%. In comparison, the adult posology for ribavirin in combination with peginterferon alfa-2a is 1,000 mg/day in patients weighing <75kg and 1,200 mg/day in patients weighing >75kg. By this posology, a patient weighing 60 kg is delivered 16.6 mg/kg and a patient weighing 100 kg is delivered 12 mg/kg. Thus, with the dosing recommended in paediatric patients, the deviation from the target dose is less than 20% and approximately similar to that of the adult posology. The CHMP considers this acceptable.

The proposed dose modification for RBV is presented below in Table 8.

**Table 8.** Paediatric Dose Reduction Scheme for Ribavirin

| Full Dose | One Step Dose Modification | Ribavirin Number of Tablets |
|---|---|---|
| 400 mg/day | 200 mg/day | 1 x 200 mg tablets A.M. |
| 600 mg/day | 400 mg/day | 1 x 200 mg tablets A.M.<br>1 x 200 mg tablets P.M. |
| 800 mg/day | 400 mg/day | 1 x 200 mg tablets A.M.<br>1 x 200 mg tablets P.M. |
| 1,000 mg/day | 600 mg/day | 1 x 200 mg tablets A.M.<br>2 x 200 mg tablets P.M. |
| 1,200 mg/day | 600 mg/day | 1 x 200 mg tablets A.M.<br>2 x 200 mg tablets P.M. |

In the NV17424 study, the recommended downward dose adjustment for ribavirin was from 15 mg/kg/day (as a split dose [bid]) to 7.5 mg/kg/day qd or bid (based on dose). This proposed dosing scheme implies the same 50% reduction in all but the patients receiving an initial dose of 600 mg, who will receive a 33% reduction of ribavirin dose. The proposed dose reduction scheme is considered acceptable by the CHMP.

#### *2.4.2.1. Discussion on clinical pharmacokinetics*

The application as initially submitted included pharmacokinetic data of six children in the relevant age range, i.e. 5-17 years; all six were younger than 9 years (study NR16141). No pharmacokinetic sampling was performed in the phase III study (study NV17424), resulting in a lack of pharmacokinetic data in older children, 9-17 years. In the PK study NR16141 a weekly dose of 180 µg x BSA/1.73 ($m^2$) of PEG-IFN alfa-2a was administered, and it was observed that the exposure in these children was 25% to 70% higher than that seen in adults receiving a weekly dose of 180 µg of PEG-IFN alfa-2a. In a population pharmacokinetic analysis it was shown that clearance of PEG-INF alfa-2a was related to Body Surface Area (BSA).

Based on this model, the applicant initially proposed a different dosing regimen than the one used in the pivotal phase III study, which suggested lower doses than the ones tested. The greatest difference in administered dose according to this initially proposed dosing regimen would have been an approximately 40% decrease for children with low BSA (~0.5 $m^2$). The desired reduction in exposure following dose reduction rests on the assumption that the pharmacokinetics of PEG-INF alfa-2a is linear in the dose range under consideration. As previously assessed in the Pegasys MAA, Peginterferon alfa-2a pharmacokinetics in adults is considered dose-linear within the therapeutic range after single and multiple doses with a comparable pharmacokinetic profile between healthy volunteers and the target population. This indicates that, at least in adult patients, a dose reduction would lead to a predictable reduction in exposure.

The CHMP considered that this approach was not unreasonable due to the relatively high number of dose reductions and dose-dependent side effects seen in study NV17424. It is in principal considered beneficial to avoid unnecessary over-exposure in children. Also, in the field of antivirals, mimicking adult exposure is generally considered a valid basis for an efficacy imputation. From this point of view, the proposed reduced dosing algorithm could have been accepted. However, to use a model for the purpose of simulating the exposure following a non-studied dosing regimen, a high level of confidence in the model is required, to ensure that the projected exposure throughout the BSA range was indeed correct, and that underexposure (in relation to the adult range) was avoided.

In response the applicant extended the initial PopPK model to include six adult studies. Although the number of children included in the NR16141 study was limited, the relation between clearance and BSA was consistent when adding adult data, giving further assurance that the relation is valid for children as well as adult patients. The applicant has also extended the model to describe the relation between exposure to PEG-INF alfa-2a and the response in neutrophil count, which is the most readily assessed exposure-dependent pharmacodynamic effect of interferon alfa. While the PK modelling data provided by the applicant are considered robust, the MAH could not fully explain the discrepancy between the model and the results from study NV17424, which did not clearly indicate an increased risk of neutropenia with decreasing BSA as would be expected from the model.

Without sufficient confidence in the model supporting the proposed dosing scheme, the MAH was requested to propose a BSA category-based posology, which is reasonably well-aligned with the actual dose used in the two clinical studies underlying this application. This new dosing regimen minimises the deviation from the formula-based doses studied in the pivotal trial to within 20%, and was considered acceptable by the CHMP. Of note, this deviation is similar to the deviations achieved in adults receiving a fixed dose of 180 µg. Finally, this dosing regimen allows for use of the currently available 90 µg PFS, which has been specifically developed for paediatric patients and will accommodate for dose reduction as needed.

#### *2.4.2.2. Conclusions on clinical pharmacokinetics*

The updated, BSA category-based posology, with a restriction to children with a BSA >0.7 $m^2$, was considered acceptable by the CHMP.

## 2.4.3. Clinical efficacy

The clinical documentation submitted by the applicant consists of one PK trial in which a single dosing scheme, 180 µg x BSA/1.73 $m^2$, was investigated (study NR16141), and one efficacy trial in which peginterferon alfa-2a at the abovementioned dose with and without ribavirin 15 mg/kg, was investigated (study NV17424). The paediatric ribavirin dose has previously been established.

**PK and pilot trial**

Study NR16141 was a Phase 2, multicentre, open-label study of viral kinetics, PK, and safety conducted at five centres in the United States. Fourteen patients aged 2 to 8 years with CHC were enrolled into the study and received an injection of PEG-IFN alfa-2a SC once a week for 48 weeks (Peginterferon alfa-2a monotherapy). Sustained virological response (SVR) is shown below in Table 9.

**Table 9.** SVR at Week 72, Standard Population in Study NR16141

| | **Pegasys 180 µg x BSA /1.73 $m^2$ N = 14** | |
|---|---|---|
| | N | SVR |
| All patients | 14 | 6 (43%) |
| Genotype 1 | | |
| ≤ 800,000 IU/ml | 10 | 5 (50%) |
| >800,000 IU/ml | 3 | 1 |
| Genotype 3 | | |
| > 800,000 IU/ml | 1 | 0 |

Note: Percentages are not calculated if n < 10.

It is the understanding of the CHMP that the outcomes of this small study prompted the hypothesis that peginterferon alfa-2a monotherapy rather than combination therapy with ribavirin, might be appropriate in children, and thus informed the design of the pivotal trial. Of note, 5 of the 6 patients achieving SVR in this monotherapy study had low baseline viral load.

**Pivotal trial**

Study NV17424 (PEDS-C) was a Phase 3, multicentre, randomised, blinded (through at least Week 24 of treatment), placebo-controlled study that compared the efficacy and safety of PEG-IFN alfa-2a in combination with RBV and PEG-IFN alfa-2a monotherapy in treatment-naïve children aged 5 to 18 years (screening must have been completed before the patient's 18$^{th}$ birthday) with chronic HCV infection and compensated liver disease.

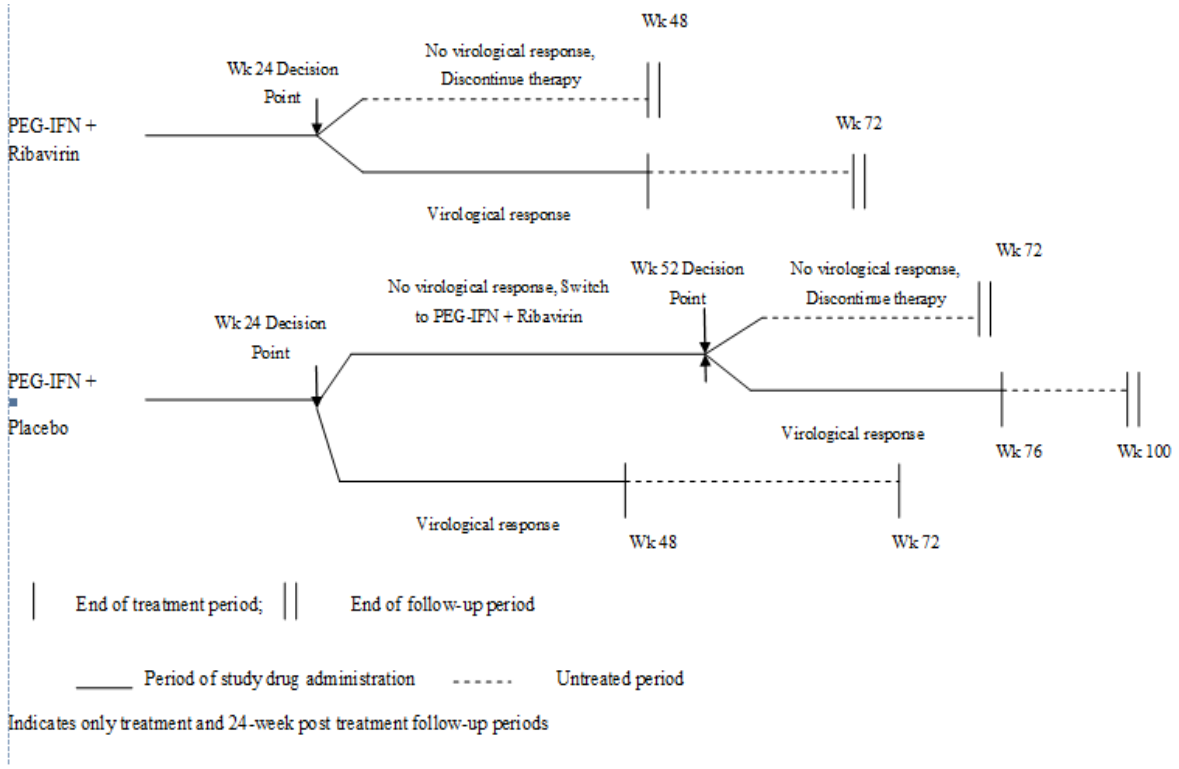
The reason for restricting inclusion to ≥ 5 years of age, rather than from 3 years of age and upwards, as discussed in the PIP, appears to have been that there was no liquid formulation of Copegus (ribavirin), and there was a concern about swallowing capsules in small children. Of note, there is such a ribavirin formulation of Rebetol.

Patients were randomly assigned in a 1:1 ratio to one of two treatment groups:

- Group 1: 180 µg x BSA / 1.73 $m^2$ of PEG-IFN alfa-2a once weekly, administered SC and 15 mg/kg body weight/day RBV, administered po bid (maximum dose of 1,200 mg/day for patients with body weight ≥ 75 kg or 1,000 mg/day for patients with body weight < 75 kg).
- Group 2: 180 µg x BSA / 1.73 $m^2$ of PEG-IFN alfa-2a once weekly, administered SC, and placebo, administered po bid.

Patients with detectable HCV RNA at Week 24 were considered non-responders and treatment was unblinded at Week 28. Non-responders who were receiving RBV in combination with PEG-IFN alfa-2a discontinued treatment. Non-responders in the PEG-IFN alfa-2a monotherapy group, however, could begin taking open-label RBV at Week 28 (Figure 2).

**Figure 2.** Overall Design of Study NV17424




The primary measure of efficacy was sustained virological response (SVR) according to the scheduled treatment period, defined as the percentage of patients with undetectable HCV RNA as measured by the HPS/COBAS TaqMan HCV Test (lower limit of detection is 10 IU/ml) at or after week 68 (ie, a single last HCV RNA <10 IU/ml measured ≥ study day 477 [time window for Week 72 assessment]).

**Baseline characteristics of the study population**

The mean age of the population was 10.8 years with a range from 5-17. There were slightly more males than females and 80% of the population was Caucasian. BSA ranged from 0.71-2.18 $m^2$. Eighty (80) % of patients had genotype 1 infection, and only 20% of patients, about 10 patients in each group, had genotype 2/3. Mean baseline HCV-RNA was approximately 5 million IU/ml. All but one patient did not have cirrhosis.

**Summary of Main Efficacy Results**

SVR rates in the respective treatment groups were as follows (Table 10). Note that this represents a mix of genotypes:

**Table 10.** Sustained Virological Response (COBAS TaqMan HCV Test <10 IU/ml) According to Scheduled Treatment Period, Intent-to-Treat Population

| PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N=55 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N=59 | Odds Ratio (95% CI) (a) | Relative Risk (95% CI) (b) | P Value (c) | Interaction P Value (d) | Pearson Chi-Square P Value |
|---|---|---|---|---|---|---|
| 27 (49%) | 12 (20%) | 5.14 (1.88, 14.00) | 2.44 (1.40, 4.24) | 0.0012 | 0.8704 | 0.0012 |

Sustained virological response (SVR) according to scheduled treatment period is defined as a single last HCV RNA measurement that is not detectable (HPS/COBAS TaqMan HCV Test <10 IU/mL) >= week 68 (>= study day 477).
HCV RNA measurements after switch from monotherapy to combination therapy were not used to determine SVR.
Patients without measurements in the relevant time window are considered non-responders in the analysis.
(a) The odds ratio is the ratio of the odds of a response in combination therapy group to the odds of a response in monotherapy group.
(b) The relative risk is the ratio of the probability of a response in combination therapy group to the probability of a response in monotherapy group.
(c) Assessed by Cochran-Mantel-Haenszel test stratified by center, HCV genotype (1 vs non-1).
(d) Breslow and Day's test for homogeneity of the odds ratio across strata.

Just as in adults, the superior efficacy of combination therapy over monotherapy is very evident, and arguably repeating this comparison in a paediatric population was in no way mandated.

A subgroup analysis of SVR is presented in Table 11 below. The point estimate for SVR in patients with genotype 1 in the combination arm was 42% (19/45). This is in the range seen when treating adult patients, but about 10% or so lower than reported in paediatric cohorts, where the prevalence of negative prognostic factors is generally lower than in adult populations, and SVR rates subsequently higher. It is also lower than that seen in the PegIntron pivotal paediatric trial (53%).

The point estimate for SVR for the 10 patients with genotype 2/3 was 80%, which is within the expected range.

Furthermore, as expected, baseline viral load (VL) had a considerable impact on the probability of SVR, with 71% of patient with VL <800,000 reaching SVR. Here no evident advantage of combination therapy was seen, but note that the sample is far too small to draw any conclusions. In general, it is anticipated that combination therapy will be more effective also in this subgroup.

There was no clear difference in response rates among patients > or < 11 years of age, and no clear trend related to BSA.

Of note, two different assays were used in the PEDS-C trial in parallel to assess virological response, the COBAS TaqMan HCV Test, which was the pre-defined primary endpoint for which results are shown in Tables 10 and 11, and the Amplicor Test. Two patients infected with genotype 1 had no measurement by COBAS TaqMan HCV Test in the relevant time window and therefore were considered non-responders in the analysis (Table 10 and 11). Both patients had data from the Amplicor test which showed that they achieved SVR. Therefore the SVR rates in the PEG-IFN alfa-2a plus RBV combination therapy group based on the Amplicor test are 29/55 (53%) for all HCV genotypes and 21/45 (47%) for HCV genotype 1. These data are reflected in the SmPC.

**Table 11.** Subgroup analysis of Sustained Virological Response (HPS/COBAS TaqMan HCV Test <10 IU/ml) According to Scheduled Treatment Period, Intent-to-Treat Population

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N=55 | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N=59 | |
|---|---|---|---|---|
| | N | SVR | N | SVR |
| All Patients | 55 | 27 ( 49%) | 59 | 12 ( 20%) |
| HCV genotype | | | | |
| 1 | 45 | 19 ( 42%) | 47 | 8 ( 17%) |
| Non-1 | 10 | 8 ( 80%) | 12 | 4 ( 33%) |
| HCV genotype | | | | |
| 1 | 45 | 19 ( 42%) | 47 | 8 ( 17%) |
| 2 | 4 | 3 ( 75%) | 3 | 1 ( 33%) |
| 3 | 6 | 5 ( 83%) | 7 | 2 ( 29%) |
| Other | | | 2 | 1 ( 50%) |
| HCV RNA (COBAS TaqMan HCV Test) at baseline | | | | |
| <= 400,000 IU/mL | 10 | 8 ( 80%) | 7 | 5 ( 71%) |
| > 400,000 IU/mL | 41 | 17 ( 41%) | 52 | 7 ( 13%) |
| HCV RNA (COBAS TaqMan HCV Test) at baseline | | | | |
| <= 600,000 IU/mL | 15 | 10 ( 67%) | 10 | 7 ( 70%) |
| > 600,000 IU/mL | 36 | 15 ( 42%) | 49 | 5 ( 10%) |
| HCV RNA (COBAS TaqMan HCV Test) at baseline | | | | |
| <= 800,000 IU/mL | 17 | 12 ( 71%) | 12 | 9 ( 75%) |
| > 800,000 IU/mL | 34 | 13 ( 38%) | 47 | 3 ( 6%) |
| Geographical region (census regions) | | | | |
| Northeast | 13 | 7 ( 54%) | 14 | 4 ( 29%) |
| Midwest | 10 | 3 ( 30%) | 10 | 1 ( 10%) |
| South | 18 | 9 ( 50%) | 18 | 2 ( 11%) |
| West | 14 | 8 ( 57%) | 17 | 5 ( 29%) |
| Age | | | | |
| <= 11 years | 30 | 13 ( 43%) | 30 | 7 ( 23%) |
| >= 12 years | 25 | 14 ( 56%) | 29 | 5 ( 17%) |

Sustained virological response (SVR) according to scheduled treatment period is defined as a single last HCV RNA measurement that is not detectable (HPS/COBAS TaqMan HCV Test <10 IU/mL) >= week 68 (>= study day 477).
HCV RNA measurements after switch from monotherapy to combination therapy were not used to determine SVR.
Patients without measurements in the relevant time window are considered non-responders in the analysis.

**Proposed treatment duration for paediatric patients with genotype 2 / 3**

In study NV17424, patients infected with HCV genotype 2 or 3 were treated for 48 weeks with PEG-IFN alfa-2a in combination with RBV.

Combination therapy with PEG-IFN alfa-2a and RBV has also been studied in 65 children and adolescents with CHC by Sokal and coworkers in an international, multicentre, non-randomised trial (the CHIPS study) in which children and adolescents aged 6 to 18 years with CHC were treated with PEG-IFN alfa-2a plus RBV for either 24 weeks or 48 weeks depending on HCV genotype (Sokal et al, J Hepatol 2010). A weekly dose of PEG-IFN alfa-2a 100 µg/$m^2$ x BSA (maximum of 180 µg) was given SC. SVR was achieved by 57% of children with genotype 1, 4, 5 or 6 infection (48 weeks of treatment) and 89% of children with genotype 2 or 3 infection (24 weeks of treatment), which is consistent with the SVR rates seen in paediatric study NV17424 for genotype 2 or 3 (48 weeks of treatment).

Although the design of study NV17424 did not include a comparison of 48 versus 24 weeks of therapy in genotype 2/3 disease, the current treatment paradigm in adult disease is 24 weeks for genotype 2/3. The available data suggest that SVR rates achieved in paediatric subjects with genotype 2/3 disease treated with PEG-IFN alfa-2a or -2b for 24 weeks are as good or better than in adults. Therefore putting together all the available adult and paediatric data which have examined 24 weeks therapy in genotype 2/3, and taking into account the current PegIntron label in paediatrics, it was suggested by the MAH that this subset of paediatric patients would best be treated for 24 weeks, rather than 48 weeks. This argument was accepted by the CHMP.

## Summary of main study

The following table summarisea the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

**Table 12.** Summary of Efficacy for trial NV17424

| **Title: Peginterferon alfa-2a with or without ribavirin for children with chronic hepatitis C (PEDS-C)** | | |
|---|---|---|
| Study identifier | NV17424 | |
| Design | Study NV17424 was a phase III, multicentre, randomised, blinded (through at least week 24 of treatment), placebo-controlled study that compared the efficacy and safety of PEG-IFN alfa-2a in combination with ribavirin and PEG-IFN alfa-2a monotherapy in children 5 to 18 years of age with chronic HCV infection and compensated liver disease. | |
| | Duration of main phase:<br><br><br><br>Duration of Run-in phase:<br><br>Duration of Extension phase: | 48 weeks - 76 weeks of study treatment (dependent on treatment group and response; see below for details) + close monitoring for 24 weeks after discontinuation of study medications<br>Screening began 35 days prior to the first dose of study treatment<br>Two annual visits at 1 year and 2 years after the end of treatment (EOT) during the long-term follow-up period; additional protocol for long-term follow-up at approximately 5 years and 6 years post-treatment |
| Hypothesis | Exploratory: Study NV17424 was undertaken<br>• to prospectively investigate in a controlled, blinded fashion whether the addition of ribavirin to PEG-IFN alfa-2a therapy results in improved efficacy in the treatment of chronic hepatitis C among children 5 to 18 years of age compared with PEG-IFN alfa-2a monotherapy<br>• to provide a comprehensive evaluation of the safety of PEG-IFN alfa-2a, with or without the addition of ribavirin, in a paediatric population<br>• to compare short- and long-term outcomes, including health-related quality of life, cognitive, developmental, and psychological functioning, and behaviour in children treated with PEG-IFN alfa-2a with or without concomitant ribavirin | |
| Treatments groups | Combination arm | 180 µg x Body Surface Area (BSA)/1.73 $m^2$ of PEG-IFN alfa-2a once weekly, administered subcutaneously (sc) and 15 mg/kg body weight/day ribavirin, administered orally (po) twice daily (bid) (maximum dose of 1200 mg/day for patients with body weight ≥75 kg or 1000 mg/day for patients with body weight <75 kg); dose modifications as needed for safety reasons; 48 weeks; 55 patients randomised |

| | | |
|---|---|---|
| | Monotherapy arm | 180 µg x BSA/1.73 $m^2$ of PEG-IFN alfa-2a once weekly, administered sc and placebo, administered po bid; dose modifications as needed for safety reasons; 48 weeks; 59 patients randomised |
| | "Compassionate" combination treatment arm | Non-responders (patients with detectable HCV RNA at week 24) in the Monotherapy arm continued PEG-IFN alfa-2a and in addition at week 28 started taking open-label ribavirin (dose based on body weight as in Combination arm above) for at least an additional 24 weeks (i.e. to week 52); treatment was to be continued for 24 weeks beyond week 52 if the virus was undetectable at week 52, otherwise both study drugs were stopped at week 56; 28 patients switched |
| Selected endpoints and definitions | Primary endpoint: Sustained virological response (SVR) according to scheduled treatment period | Percentage of patients with undetectable HCV RNA as measured by the HPS/COBAS TaqMan HCV Test (lower limit of detection is 10 IU/ml) at or after week 68 (i.e. a single last HCV RNA <10 IU/ml measured ≥ study day 477) |
| | Secondary endpoint: Virological responses over time | Percentage of patients with undetectable HCV RNA (<10 IU/ml for the HPS/COBAS TaqMan HCV test, and <50 IU/ml for the AMPLICOR HCV RNA test) at defined time points |
| | Exploratory endpoint: Subgroup analysis | SVR according to scheduled treatment period by defined baseline factors |

**Results and Analysis**

| **Analysis description** | **Primary Analysis - SVR** | | |
|---|---|---|---|
| Analysis population and time point description | Intent-to-treat<br>At or after week 68 | | |
| Descriptive statistics and estimate variability | Treatment group | Combination arm (PEG-IFN alfa-2a + Ribavirin) | Monotherapy arm (PEG-IFN alfa-2a + Placebo) |
| | Number of subjects | 55 | 59 |
| | Patients with SVR according to scheduled treatment period | 27 (49%) | 12 (20%) |
| **Analysis description** | **Secondary Analysis – Virological response over time** | | |
| Analysis population and time point description | Intent-to-treat<br>Virological response over time was assessed at weeks 1, 3, 5, 12, 24, 48 (= scheduled EOT; EOT[S]), 60 and actual EOT (EOT[A]). Shown below are week 12 and EOT[S] for the HPS/COBAS TaqMan HCV Test (results for Amplicor HCV Test were consistent and are not shown). | | |
| Descriptive statistics and estimate variability | Treatment group | Combination arm (PEG-IFN alfa-2a + Ribavirin) | Monotherapy arm (PEG-IFN alfa-2a + Placebo) |
| | Number of subjects | 55 | 59 |
| | Patients with virological response at week 12 | 29 (53%) | 11 (19%) |
| | Patients with virological response at EOT[S] | 35 (64%) | 22 (37%) |
| **Analysis description** | **Exploratory Analysis – Subgroup analysis by HCV genotype** | | |
| Analysis population and time point description | Intent-to-treat<br>At or after week 68 | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | Combination arm (PEG-IFN alfa-2a + Ribavirin) | Monotherapy arm (PEG-IFN alfa-2a + Placebo) |
| | SVR in patients with HCV genotype 1 | 19/45 (42%) | 8/47 (17%) |
| | SVR in patients with HCV genotype Non-1 (includes genotypes 2, 3 and other) | 8/10 (80%) | 4/12 (33%) |
| Notes | Patients with detectable HCV RNA at week 24 stopped their treatment (in the combination arm) or switched to compassionate combination treatment (in the monotherapy arm) and were considered nonresponders, as were those without measurements at or after week 68. | | |

#### *2.4.3.1. Discussion on clinical efficacy*

## Design and conduct of clinical studies

Based on findings in the small PK study NR16141, NV17424 was designed as a randomised comparative trial of peginterferon alfa-2a monotherapy and standard combination therapy with ribavirin, notwithstanding the fact that the superiority of combination therapy has since long been firmly established in adults, and was standard of care at the time of initiation of NV17424. Indeed, this study convincingly showed the superiority of combination therapy compared to monotherapy also in children. While it is recognised that SVR rates on the whole are higher in children than in adults, most likely due to fewer negative prognostic factors, perhaps lower baseline HCV-RNA on average and less liver disease at baseline, it is unclear to the CHMP why it was considered necessary to conduct the formal comparison in children, as the a priori hypothesis that adding ribavirin would add efficacy also in children must have been very strong. In this respect, the general outcome of this study supports the extrapolation of antiviral treatment strategies from adults to children, indicating that studies in the latter should mainly focus on dose-finding and paediatric-specific safety issues.

Of note, in this study a 48-week treatment duration was used for patients with genotype 2/3 infection, of whom only 10 were studied with the relevant combination regimen. Based largely on the outcomes of study NV15942 in adults, a 24-week treatment regimen has since long been standard in patients with genotype 2/3 infection, which are more responsive to interferon therapy, and where a longer duration does not yield higher SVR rates in an unselected population. Of note, both the pivotal paediatric PegIntron study, as well as an investigator-initiated study of peginterferon alfa-2a 100 µg/ $m^2$ (a dose which is roughly similar to the (180/1.73) µg/$m^2$ of the present development program) have demonstrated response rates with 24 weeks of therapy in paediatric patients with genotype 2/3 which are on par with or higher than the responses seen in adults with this regimen (PegIntron EPAR and Sokal et al, J Hepatol 2010).

## Efficacy data and additional analyses

The paediatric development program presented by Roche includes 55 patients treated from the start with the relevant combination regimen. Among these, 45 patients had genotype 1 and 10 patients genotype 2/3. Point estimates for SVR was 42% in the former group and 80% in the latter group. While the study would be considered too small as a specific efficacy demonstration in the absence of supporting data, the CHMP considers that the studied combination regimen indeed yields an efficacy that is at least comparable to that seen in adults. Firstly, the PK study NR16141 demonstrated that the selected dose of peginterferon alfa-2a yields an exposure that is 25-70% higher than that seen in adults. Available data do not support that the PK/PD relation for interferon effect in children and adults

would fundamentally differ, given the same other relevant baseline characteristics. In view of this, based on the general paradigm for antiviral drug development in children, the outcomes of the NV17424 may mainly be viewed as a corroboration of what is fundamentally an extrapolation of efficacy from adults to children, given a drug exposure that is not lower than that in adults.

Furthermore, there is supportive evidence of efficacy in paediatrics. The abovementioned study by Sokal et al (J Hepatol 2010) in patients aged 6-17, using a roughly similar regimen, reported SVR rates of 57% in 47 patients with mainly genotype 1 (including 2 patients with genotype 4 and 5) treated for 48 weeks, and 89% in 18 patients with genotype 2/3, treated for 24 weeks. Furthermore, the pivotal paediatric study of PegIntron (peginterferon alfa-2b), conducted with a dose yielding an exposure 58% higher than that observed in adults, showed response rates of 53% in 72 patients with genotype 1 treated for 48 weeks, and 96% of 27 patients with genotype 2/3 treated for 24 weeks. The comparative efficacy of peginterferon alfa-2a and peginterferon alfa-2b has been studied in adults in the IDEAL study, and is more or less similar. In the light of this study, the CHMP concluded that the efficacy data can be extrapolated between the two medicinal products.

Finally, it is noted that the applicant originally applied for labelling for a lower dose of peginterferon alfa-2a than that studied in NV17424. This was not accepted by the CHMP as discussed in the Pharmacokinetics section above, and a BSA category-based posology that is aligned with the dosing studied in the trial was eventually agreed upon.

#### *2.4.3.2. Conclusions on the clinical efficacy*

Despite the reservations on the design of the pivotal trial, and the relatively small number of patients treated with the relevant combination regimen, the results of the studies presented by the applicant, together with other corroborative evidence, are considered indicative of at least equal efficacy of peginterferon alfa-2a and ribavirin at the studied doses in paediatric patients, compared to the efficacy seen in adults.

## 2.4.4. Clinical safety

## Patient exposure

The full safety population includes 114 patients from NV17424, aged 5-17 years, 55 of whom were initially treated with the relevant combination of peginterferon alfa-2a and ribavirin. Fifty-nine patients in NV17424 and 14 patients from the PK study NV16141 were treated with peginterferon alfa-2a monotherapy. Twenty-eight of these patients from NV17424 subsequently received peginterferon alfa-2a in combination with ribavirin.

## Adverse events

As expected, all patients experienced adverse events (AEs) (Table 13). There were no deaths in the study. Rates of serious AEs were below 5%, as opposed to approximately 10% in the adult IDEAL study. Of note, also in the pivotal study of PegIntron in paediatric patients, the rate of serious AEs was lower than in adults, and in the same range as the present study (3%).

**Table 13.** Overview of Adverse Events during Treatment and 24 Weeks Follow-up in Study NV17424 by Actual Treatment Group

| | PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ RBV 15 mg/kg N = 55 | PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ Placebo Only N = 31 | PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ Plac./RBV 15 mg/kg N = 28 |
|---|---|---|---|
| Any AE | 55 (100%) | 31 (100%) | 28 (100%) |
| Severe AEs | 10 (18%) | 10 (32%) | 1 (4%) |
| Life-threatening AEs | 0 (0%) | 1 (3%) | 0 (0%) |
| Related AEs (a) | 55 (100%) | 31 (100%) | 27 (96%) |
| Serious AEs | 2 (4%) | 1 (3%) | 0 (0%) |
| Related serious AEs (a) | 2 (4%) | 1 (3%) | 0 (0%) |
| Deaths | 0 (0%) | 0 (0%) | 0 (0%) |
| Dose modification for AEs or lab abnormalities (b) | | | |
| PEG-IFN alfa-2a | 20 (36%) | 11 (35%) | 12 (43%) |
| AE | 5 (9%) | 2 (6%) | 3 (11%) |
| Lab abnormality | 19 (35%) | 10 (32%) | 11 (39%) |
| RBV/Placebo | 14 (25%) | 10 (32%) | 10 (36%) |
| AE | 10 (18%) | 9 (29%) | 8 (29%) |
| Lab abnormality | 6 (11%) | 1 (3%) | 4 (14%) |
| Premature withdrawals for safety reasons | 7 (13%) | 5 (16%) | 1 (4%) |

*Note:* Values in this table represent the number and percentage of patients who experienced the event.
(a) Events judged by the investigator to be unlikely, possibly, probably, or definitely related to study treatment and expected non-serious adverse events.
(b) Dose modification was defined as at least one dose of study drug reduced or withheld. Patients who had their dose of study treatment modified for adverse events or laboratory abnormalities before being prematurely withdrawn for an adverse event or laboratory abnormality were included. Patients who had study drugs prematurely discontinued without first having the dose of study drug modified were not considered as having a dose modification in this analysis.

The general side effects profile was as expected with a pegylated interferon, including influenza-like symptoms with pyrexia and myalgia, gastrointestinal and cutaneous symptoms as well as neuropsychiatric symptomatology such as fatigue, irritability and depression.

## Serious adverse event/deaths/other significant events

No apparent differences in the frequency or types of treatment-related SAEs were observed among the three different treatment groups. Only three patients reported SAEs during the treatment and 24-week follow-up periods: two patients (4%) in the PEG-IFN alfa-2a plus RBV therapy group, one patient (1%) in the PEG-IFN alfa-2a plus placebo (monotherapy) group, and no patients in the PEG-IFN alfa-2a monotherapy non-responder/compassionate combination therapy group.

Two of the three SAEs (suicidal behavior in the PEG-IFN alfa-2a plus placebo (monotherapy) group and hyperglycaemia in the PEG-IFN alfa-2a plus RBV combination therapy group) were assessed by the investigator as being possibly related to study treatment. The third SAE (cholecystectomy in the PEG-IFN alfa-2a plus RBV therapy group) was assessed as unlikely related to study treatment.

New onset diabetes mellitus, as well as psychiatric symptoms such as abnormal/suicidal behaviour and depression, and on-treatment alanine aminotransferase (ALT) increases, are within the range of the well-described safety profile of alfa-interferons.

Furthermore, three of 114 patients (2.6%) developed possibly or probably related eye complications, including one case of ischaemic retinopathy and one case of uveitis. Retinopathy by ophthalmoscopic investigation during peginterferon alfa treatment has been reported in 10-34% of patients in different studies. Ophthalmic side effects are common, and include ischaemic retinopathy, which occurs with a frequency of between 1/1,000 and 1/10,000 according to the Pegasys SmPC. In this study, the frequency of ischaemic retinopathy was 1/114. Ocular AEs are part of the RMP.

## Laboratory findings

Neutropenia

Neutropenia is an important exposure-dependent side effect of interferons, and perhaps the most sensitive pharmacodynamic parameter by which to judge exposure within the presently relevant range. Of note, the pivotal NV17424 study lacked any PK assessment. All events of neutropenia were well tolerated and clinically managed by dose modifications of PEG-IFN alfa-2a. No patient had a neutrophil count less than 0.25 × $10^9$ cells/L during the study (Table 14).

**Table 14.** Overview of Neutropenia during Treatment and 24 Weeks Follow-up in Study NV17424

| | **PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ RBV 15 mg/kg N = 55** | **PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ Placebo Only N = 31** | **PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ Placebo/RBV 15 mg/kg N = 28** |
|---|---|---|---|
| Neutrophil Counts | | | |
| <0.75 x $10^9$/L | 20 (36%) | 8 (26%) | 12 (43%) |
| <0.5 x $10^9$/L | 4 (7%) | 1 (3%) | 5 (18%) |
| Neutropenia as | | | |
| Clinical adverse event | 0 (0%) | 0 (0%) | 0 (0%) |
| Serious adverse event (a) | 0 (0%) | 0 (0%) | 0 (0%) |
| Premature withdrawal from treatment for neutropenia | | | |
| PEG-IFN alfa-2a | 0 (0%) | 0 (0%) | 0 (0%) |
| RBV/Placebo | 0 (0%) | 0 (0%) | 0 (0%) |
| Dose modification of study treatment for neutropenia (b) | | | |
| PEG-IFN alfa-2a | 19 (35%) | 7 (23%) | 11 (39%) |
| RBV/Placebo | 0 (0%) | 0 (0%) | 0 (0%) |
| Treatment for Neutropenia | | | |
| Colony stimulating growth factors | 0 (0%) | 0 (0%) | 0 (0%) |

Note: Values in this table represent the number and percentage of patients who experienced the event.
(a) Neutropenia that met the definition of a serious adverse event.
(b) Dose modification is defined as at least one dose of study drug reduced or withheld. Patients who had their dose of study treatment modified for neutropenia before being prematurely withdrawn for neutropenia are included. Patients who had study drugs prematurely discontinued for neutropenia without first having the dose of study drug modified were not considered as having a dose modification in this analysis.

While data are not exactly comparable due to a more intense dose reduction scheme in NV17424 (see above), it is of some interest to compare these results with those seen in paediatric studies of peginterferon alfa-2b, as well as in adult studies with the peginterferons (Table 15).

**Table 15.** Between-study comparison of neutropenia

| | **Pegasys paediatric (PEG-IFN+ ribavirin)** | **PegIntron paediatric** | **Pegasys IDEAL** | **PegIntron IDEAL** |
|---|---|---|---|---|
| Patients with dose reduction due to neutropenia (%) | 19/55 (35%) | 13/107 (12%) | 203/1035 (19.6%) | 175/1019 (17.2%) |
| Patients with neutrophil count of 0.5-0.75 x $10^9$/L (%) | 16/55 (29%) | 14/107 (13%) | 218/1034 (21%) | 194/1000 (19%) |
| Patients with neutrophil count of <0.5 x $10^9$/L (%) | 4/55 (7%) | 3/107 (3%) | 61/1034 (5.9%) | 28/1000 (2.8%) |

Notwithstanding the differences mentioned above, these figures do seem to indicate that the pharmacodynamic effect of peginterferon alfa on neutrophils was greater in NV17424, likely due to higher exposure. On the other hand it is noted that neutropenia was well monitored and safely handled with dose reductions, as no patients had any clinical adverse events associated with neutropenia, nor needed permanent withdrawal of treatment. Thus, neutropenia per se does not appear to support the argument to label an untested dose of peginterferon alfa-2a for paediatric use, as originally proposed by the MAH.

Thrombocytopenia

Thrombocytopenia is another well-known haematological side effect of peginterferon alfa-2a. Thrombocytopenia was not considered to be a clinically relevant AE in any patient in the NV17424 study because no case of thrombocytopenia was serious, led to premature discontinuation of study drug, or required concomitant treatment or modification of ongoing concomitant treatment. No patient had a platelet count <50x$10^9$/L. This is not unexpected, as thrombocytopenia is mainly a problem in patients with hypersplenism, and only one patient in this study had cirrhosis.

Anaemia

Anaemia is the most important side effect of ribavirin, and a significant side effect of treatment. Anaemia findings are summarised in the table below (Table 16).

Ribavirin-associated anaemia is generally less troublesome in children than in adults. As a comparison, in the IDEAL study, almost 30% of patients treated with peginterferon alfa-2a+ribavirin reported haemoglobin levels below 10 g/dl.

**Table 16.** Overview of Anaemia during Treatment and 24 Weeks Follow-up

| | PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ RBV 15 mg/kg N = 55 | PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ Placebo Only N = 31 | PEG-IFN alfa-2a 180 µg x BSA /1.73 $m^2$ Plac./RBV 15 mg/kg N = 28 |
|---|---|---|---|
| Haemoglobin | | | |
| <100 g/L | 7 (13%) | 4 (13%) | 4 (14%) |
| <85 g/L | 0 (0%) | 0 (0%) | 0 (0%) |
| Anaemia as | | | |
| Clinical adverse event | 1 (2%) | 0 (0%) | 0 (0%) |
| Serious adverse event (a) | 0 (0%) | 0 (0%) | 0 (0%) |
| Premature withdrawal from treatment for anaemia | | | |
| PEG-IFN alfa-2a | 1 (2%) | 0 (0%) | 0 (0%) |
| RBV/Placebo | 1 (2%) | 0 (0%) | 0 (0%) |
| Dose modification of study treatment for anaemia (b) | | | |
| PEG-IFN alfa-2a | 0 (0%) | 0 (0%) | 0 (0%) |
| RBV/Placebo | 6 (11%) | 1 (3%) | 4 (14%) |
| Treatment for anaemia | | | |
| Haematopoietic stimulants | 0 (0%) | 0 (0%) | 0 (0%) |
| Transfusions | 0 (0%) | 0 (0%) | 0 (0%) |

Note: Values in this table represent the number and percentage of patients who experienced the event.
(a) Anaemia that met the definition of a serious adverse event.
(b) Dose modification is defined as at least one dose of study drug reduced or withheld. Patients who had their dose of study treatment modified for anaemia before being prematurely withdrawn for anaemia are included. Patients who had study drugs prematurely discontinued for anaemia without first having the dose of study drug modified were not considered as having a dose modification in this analysis.

ALT increases

Two patients in the pilot monotherapy trial and and 2 patients receiving monotherapy in the NV17424 study had treatment withdrawn due to ALT increases. It does not appear that any of these had significant concomitant bilirubin increases. ALT increases are known to occur in adults with peginterferon alfa-2a therapy.

Hypothyroidism

There were two patients with clinical AEs of hypothyroidism reported in the PEG-IFN alfa-2a plus placebo (monotherapy) group; both patients were treated with levothyroxine. The frequency of incident hypothyroidism in adults treated with peginterferon alfa-2a and ribavirin is about 5%. In the PegIntron pivotal paediatric trial, hypothyroidism was reported in 3% of patients. Data from the present study indicate a similar frequency, with a total of 5/114 patients reporting any low TSH value.

## Safety in special populations

Growth and development

In Study NV17424, the patient's weight, height, and body mass index (BMI) expressed as percentiles of the US normative population growth curves decreased during treatment in all three treatment groups. These lags in growth gain during treatment were compensated post-treatment and the percentiles were close to baseline data within 24 weeks to 2 years post-treatment.

The mean decrease from baseline for the last on-treatment assessment was -9.0%, -8.6%, and -6.0%, for the PEG-IFN alfa-2a plus RBV combination therapy group, the PEG-IFN alfa-2a plus placebo (monotherapy) group, and the PEG-IFN alfa-2a monotherapy non-responder/compassionate combination therapy group respectively. Height percentile changes by ages and gender are shown in Tables 17 and 18.

For height, 25% of the patients treated with combination PEG-IFN alfa-2a plus RBV had a >15% percentile decrease from baseline to the end of treatment, while at the end of 2 years post-treatment 11% of the patients in this group still showed a percentile decrease >15% from baseline (Tables 17 and 18).

**Table 17.** Summary of Height Percentile Changes

| **Male Percentiles for Height Means Change from Baseline at Follow-up Year 2** | **PEG-IFN alfa-2a plus RBV combination therapy group (n)** | **PEG-IFN alfa-2a plus placebo (monotherapy) group (n)** | **PEG-IFN alfa-2a monotherapy non-responder/compassionate combination therapy group (n)** |
|---|---|---|---|
| Age 5-10 years | -0.5 (4) | -5.5 (2) | -7.6 (3) |
| Age 11-14 years | -3.7 (13) | -8.6 (4) | +5.1 (5) |
| Age >14 years | +1.0 (3) | -13.6 (1) | -3.7 (2) |
| **Female Percentiles for Height Means Change from Baseline at Follow-up Year 2** | **PEG-IFN alfa-2a plus RBV combination therapy group (n)** | **PEG-IFN alfa-2a plus placebo (monotherapy) group (n)** | **PEG-IFN alfa-2a monotherapy non-responder/compassionate combination therapy group (n)** |
| Age 5-10 years | +6.1 (8) | -5.0 (6) | -17.5 (2) |
| Age 11-14 years | +11.9 (8) | +10.3 (2) | -1.6 (6) |
| Age >14 years | -3.3 (2) | -6.6 (1) | n/a (0) |

**Table 18.** Number of Patients with Significant Height Changes at the End of Follow-up Year 2

| **Males with a decrease in height percentiles from Baseline >15 at Follow-up Year 2** | **PEG-IFN alfa-2a plus RBV combination therapy group** | **PEG-IFN alfa-2a plus placebo (monotherapy) group** | **PEG-IFN alfa-2a monotherapy non-responder/compassionate combination therapy group** |
|---|---|---|---|
| Age 5-10 years | 0/4 | 0/2 | 1/3 |
| Age 11-14 years | 3/13 | 3/4 | 0/5 |
| Age >14 years | 0/3 | 0/1 | 0/2 |
| **Females with a decrease in height percentiles from Baseline >15 at Follow-up Year 2** | **PEG-IFN alfa-2a plus RBV combination therapy group** | **PEG-IFN alfa-2a plus placebo (monotherapy) group** | **PEG-IFN alfa-2a monotherapy non-responder/compassionate combination therapy group** |
| Age 5-10 years | 1/8 | 1/6 | 1/2 |
| Age 11-14 years | 0/8 | 0/2 | 0/6 |
| Age >14 years | 0/2 | 0/1 | 0/0 |

The impact of peginterferon + ribavirin treatment on height has been investigated in a long-term follow-up study after treatment with peginterferon alfa-2b and ribavirin, and the preliminary conclusion is that 48 weeks of therapy likely causes a loss of adult stature in some patients. The extent of this may depend on factors such as the age distribution of patients, the gender, and the relation of treatment to the onset of puberty. Therefore, the absolute values on on-treatment loss of height percentile are not entirely comparable between the pivotal studies for the respective peginterferons. In general, it appears that the outcomes of the respective studies are compatible with the a priori hypothesis that this would be roughly similar, and the concerns on growth relevant for treatment with the one peginterferon are considered equally relevant for the other.

#### *2.4.4.1. Discussion on clinical safety*

As expected, the safety profile that emerged in the paediatric studies is similar to that in adults. The frequency of serious adverse events, however, was numerically lower than typical in adults - 5% versus 10% in the largest adult study performed to date (IDEAL). Other studies with other interferons have also implied that interferon + ribavirin combination therapy may on average be better tolerated in children. A specific paediatric safety concern of interferon therapy is on-treatment growth retardation and the possibility that this may result in a permanent loss of adult stature. Upon CHMP request the applicant has supplemented the application with evaluable data concerning on-treatment and post-treatment growth, and particularly height. Overall a similar picture to that known for other interferons emerges, as would be expected. The applicant will perform a long term follow-up study on growth as detailed in the RMP.

The applicant was initially claiming a dose for peginterferon alfa-2a which was lower than that tested in the study. The rationale for this was that the dosing regimen used in the paediatric development program (180 µg x BSA/1.73 $m^2$) s expected to result in a 25-70% higher exposure than that seen with adults. However, it was also recognised by the applicant that the pivotal study did not show any trend to more symptomatic adverse events despite the higher estimated exposure.

The most sensitive pharmacodynamics effect of peginterferons by which to evaluate exposure in the relevant range is probably the effect on neutrophils. Cross-study comparisons, hampered by differing dose reduction schemes, indicate that neutropenia may be more common with the present dose in paediatric patients than it is in adults. However, this was managed by dose reduction according to specific guidelines, and was not associated with impaired efficacy, treatment discontinuations or SAEs.

The pharmacokinetic model provided as a basis for adjusting the doses to aim at an exposure more similar to that in the adult population is considered robust. However, the MAH could not fully explain the absence of a gradient with a higher frequency of neutropenia in patients with lower BSA, and therefore the CHMP remained concerned that the initially proposed dosing regimen could cause insufficient exposure compared to the studied regimen (see PK discussion above) remained. Therefore, a modified BSA category-based posology that reasonably agrees with the formula-based dosing studied in the trial (180 µg x BSA/1.73 $m^2$) was eventually agreed upon. Conclusions on the safety of this dose, over the entire dose range, however, is marred by the fact that there were only 20 patients with a BSA <0.9 and no patients with a BSA below 0.7 in the study and the CHMP therefore requested a restriction to BSA >0.7 $m^2$.

Within NV17424 there were two serious eye complications – one ischaemic retinopathy and one uveitis. Both of these conditions can be understood in relation to the known side effects profile of peginterferon alfa-2a. However, the study is too small to draw conclusions whether the relative frequency of such events is greater than in adults. A supplementary analysis of published data and the Roche safety database has not provided any further indications of a differential ophthalmic safety profile in children and adults.

Whereas the PDCO had recommended that peginterferon alfa-2a be studied in patients from 3 years of age, this study had a lower age limit of 5 years, which was justified by the lack of a liquid formulation of Copegus (ribavirin). The CHMP noted that a liquid formulation of ribavirin is marketed (Rebetol), which is labelled for paediatric use against hepatitis C. The applicant has further discussed whether a positive benefit-risk could not be inferred also for patients aged 3-5, with consequent labelling from the age of 3 years old. However, due to the lack of data and uncertainties about drug exposure in small patients, the CHMP concluded to restrict the indication from 5 years and upward.

Finally, upon CHMP request, a contraindication is added in the product information in paediatric patients with the presence of or history of severe psychiatric conditions, particulary severe depression, suicidal ideation or suicidal attempt (as present in the PegIntron SmPC). While the data presented by the MAH have not shown an increased risk of Pegasys in these patients compared to adult patients with existing or previous severe psychiatric disease (for which the SmPC includes a warning statement in section 4.4), the CHMP requested this contraindication in the absence of evidence to rule out this risk.

#### *2.4.4.2. Conclusions on the clinical safety*

The safety profile of peginterferon alfa-2a in a paediatric population was similar to that seen in adults. On the particular concern of the applicant, that the dose may be inappropriately high, data do not clearly indicate that this would be a major concern. Still, as the safety database in patients with low BSA is limited, the CHMP requested that the extent of the indication was limited to patients with a BSA >0.7.

The CHMP considers the following measures necessary to address issues related to safety:

Regarding the identified risk height and weight impairment in paediatric patients the MAH has committed to the long-term follow-up from paediatric study NV17424, as detailed in the RMP. The planned date for submission of final data is Q4 2013 (see below).

## *2.5. Pharmacovigilance*

### Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

### Risk Management Plan

The applicant submitted a risk management plan (Version 3.1, 26 November 2012). Based on the analysis of the safety profile, the applicant proposes the following risk management activities for the important identified and potential risks, as well as for important missing information:

**Table 19.** Summary of the Risk management plan

| Safety Concern | Agreed Pharmacovigilance Activities | Agreed Risk Minimisation Activities |
|---|---|---|
| Psychiatric and CNS reactions including depression, suicidal ideation, suicide attempt, suicide, aggression, nervousness, confusion, concentration impairment | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describing the spectrum of such events.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Haematological events including neutropenia, thrombocytopenia, anaemia, aplastic anaemia, and pancytopenia | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Instructions in Section 4.2 of the SPC discuss the occurrence of the haematological events, and provide recommendations for risk management by dose modification in the presence of decreased ANC, decreased platelet count, and treatment-emergent anaemia.<br><br>Warning in Section 4.4 of the SPC informs of recommended dose modifications in individuals with posttreatment haematological abnormalities.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Endocrine System Disorder AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of such events.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Cardiovascular AEs | Routine pharmacovigilence activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of such events. In addition, adverse events are listed in SPC Section 4.8 (undesirable effects) |
| Ischemic cardiac events in setting of ribavirin-induced anaemia | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Contraindication in Section 4.3 of the SPC indicates not starting or stopping treatment in patients with history of severe cardiac disease or uncontrolled disease in previous six months.<br><br>Warning in Section 4.4 of the Copegus SPC describes the ischemic cardiac events as a result of anaemia, and provides recommendations for risk management by modifying ribavirin dose.<br><br>Instructions in Section 4.2 of the SPC regarding treatment-emergent anaemia. |
| Hepatic decompensation AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Contraindication in Section 4.3 of the SPC indicates not starting therapy or stopping in those who develop autoimmune hepatitis, severe hepatic dysfunction or decompensated cirrhosis, as well as HIV / HCV co-infected patients with cirrhosis and a Child-Pugh score ≥6 except if due to drugs that cause indirect hyper-bilirubinemia<br><br>Warning in Section 4.4 of the SPC detailing the spectrum of occurrence of the hepatic decompensation and providing recommendations for management.<br><br>Instructions in Section 4.2 of the SPC discuss the occurrence of the event and provide recommendations for dose management based upon liver function parameters. |

| Safety Concern | Agreed Pharmacovigilance Activities | Agreed Risk Minimisation Activities |
|---|---|---|
| | | In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Hypersensitivity reaction AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of hypersensitivity reactions and provides recommendations for managing the events.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Autoimmune Disorder AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC discusses the possibility of development of auto-antibodies and autoimmune disorder during therapy and provides recommendations for continuation of therapy based on benefit-risk assessment.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Serious and severe infection (bacterial, viral, fungal) | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of occurrence of the event and recommendations for management.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Ocular AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of occurrence of ocular events and provides recommendations for management.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Pulmonary AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of such events.<br><br>In addition, adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Pregnancy and teratogencity AEs | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Contraindication in Section 4.3 not to use ribavirin in pregnant or lactating females.<br><br>Warning in Section 4.4 of the SPC discussing the need of using contraception during treatment with ribavirin.<br><br>Statement in Section 4.6 regarding the use of ribavirin in pregnancy and lactation. |
| Skin Disorders | Routine pharmacovigilance activities<br>Additional actions:<br>None. | Warning in Section 4.4 of the SPC describes the spectrum of skin disorder and provides recommendation for managing psoriasis.<br><br>In addition, skin adverse events are listed in SPC Section 4.8 (Undesirable effects). |
| Growth and weight impairment in paediatric and adolescent patients | Routine pharmacovigilance activities<br>Additional actions:<br>Assess safety profile from paediatric studies ((NV17424, NV25361, YV25718) including 5 year follow up | The Pegasys USPI has been updated with the information on growth impairment in pediatric population.<br>In addition, a proposed boxed warning regarding height and weight impairment in paediatric patients treated with Pegasys is proposed to be added to the SPC. |
| Potential Safety Concern Psychiatric/CNS Events in Paediatric Patients | Routine pharmacovigilance activities<br>Additional actions:<br>Assess new onset and possible persistence in paediatric studies (NV17424, NV25361, YV25718). | Will assess need for risk minimisation based on safety findings from pharmacovigilance activities.<br><br>Proposed wording regarding Psychiatric events in paediatric patients treated with Pegasys in Section 4.4 and 4.8 of the SPC. |
| Potential Safety Concern Thyroid Dysfunction | Routine pharmacovigilance activities<br>Additional actions: | Will assess need for risk minimisation based on safety findins from pharmacovigilance activities. |

| Safety Concern | Agreed Pharmacovigilance Activities | Agreed Risk Minimisation Activities |
|---|---|---|
| | Assess new onset and possible persistence in paediatric studies (NV17424, NV25361, YV25718). | |
| Potential of medication error in paediatric patients | Routine pharmacovigilance activities.<br>Additional actions:<br>None. | Dosing by BSA category and dosing graph proposed for SPC to also be added to Patient Leaflet to minimise risk of medication error. |
| Missing Safety Concern Safety of extending treatment to 72 weeks in adult HCV patients | Routine pharmacovigilance activities<br>Additional actions:<br>Assess safety in adult HCV previously non-reponding patients receiving Pegasys/ ribavirin for greater than 48 weeks in GUARD-C trial. | Will assess need for risk minimization based on safety results from GUARD-C trial |
| Missing Safety Concern Efficacy and Safety of Pegasys/ribavirin in paediatric HCV patients 3 to 5 years old | .Routine pharmacovigilance activities<br>Additional actions:<br>Paediatric studies (BV28334) | Proposed change to the Pegasys SPC that would indicate that limited information is available in this population in order to minimize the possibility of off-label use. In addition, information on safety and efficacy of Pegasys in this age group will be collected from a HCV paediatric study (BV28334), which is being conducted in the US. |
| Missing Safety Concern Efficacy and Safety of Pegasys/ribavirin in paediatric HIV/HCV | Routine pharmacovigilance<br><br>Additional actions:<br>None | Proposed change to the Pegasys SPC that would indicate that no information is available in this population in order to minimize the possibility of off-label use. |
| Missing Safety Concern Efficacy and Safety of Pegasys/ribavirin in paediatric HCV patients previous treatment failure | Routine pharmacovigilance<br><br>Additional actions:<br>None. | Proposed change to the Pegasys SPC that would indicate that limited information is available in this population in order to minimize the possibility of off-label use. |
| Missing Safety Concern Efficacy and Safety of Pegasys in immunoactive and immunotolerant paediatric HBV patients | Routine pharmacovigilance<br>Additional actions:<br>Assess the safety and efficacy of Pegasys based on prospective paediatric HBV studies (NV25361 and YV25718). | Will assess need for risk minimisation based on safety and efficacy findings from pharmacovigilance activities. |
| Missing Safety Concern Use of Pegasys in paediatric patients with renal impairment | Routine pharmacovigilance<br><br>Additional actions:<br>None. | Proposed change to the Pegasys SPC that would indicate that no information is available in this population in order to minimize the possibility of off-label use |

This RMP has been written in accordance with recommended guidelines.

Overall, the safety concerns for the paediatric indication reflect the known safety profile for the adult indication. In the safety specification the applicant has presented relevant information relating to the use of Pegasys for the paediatric indication in clinical trials. The total number of subjects included in trials is limited, and the number of paediatric patients in postmarketing reports is not clear. There are many identified safety concerns for Pegasys which are well-known and well documented given its extensive use in the adult population up to the present time. The applicant has adequately addressed each of the known safety concerns that were observed in the paediatric trials. Additionally, the applicant has included growth and weight impairment as an identified risk specific to the paediatric population. Furthermore, the applicant has included as potential risks of persistence/de novo development after treatment in paediatric subjects: neuropsychiatric events and thyroid dysfunction. The applicant has also included “medication errors” as a potential risk specific for the paediatric population, as that they may occur in children given the variable dose of Pegasys administered based on BSA. The applicant also reflected the limited information regarding HIV/HCV-coinfected paediatric

patients, paediatric nonresponders and paediatric HBV-infected subjects by inclusion into the RMP under the section of “Missing Information”; mention of the lack of data from these populations has been included in the SmPC as a risk minimisation measure.

The proposed pharmacovigilance plan includes routine pharmacovigilance for each of the safety concerns included in the safety specification, as well as four studies which are designed to collect additional information regarding paediatric-specific concerns. The primary safety concerns for which additional information is required relate to growth impairment and thyroid dysfunction. Data regarding these concerns is to be collected in the extension portion of the pivotal trial study NV17424. Retention in the study is reportedly high, and a review of study assessments has provided assurance of the collection of required data. Two additional studies in Hepatitis B subjects (NV25361 and YV25718) will provide information on an additional 135 children undergoing therapy. Regarding the safety concern of missing information in HCV-infected subjects 3-5 years old, the applicant has proposed an additional study BV28334 with a primary focus on collection of long term safety data for up to 3 years post treatment. However, no additional studies are proposed for HCV/HIV-coinfected patients, or those with previous treatment failure. This was considered acceptable by the CHMP. A previously planned registry study designed to further investigate these specific populations was not endorsed by the CHMP and has been removed from the RMP. The last study included in the pharmacovigilance plan is GUARD-C which is being performed in adults to address the safety of extending treatment to 72 weeks. A study protocol and update of the status of this study was included with the submitted data.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

| Description | Due date |
|---|---|
| Long-term follow-up from paediatric study NV17424 | Q4 2013 |
| GUARD-C (MV22255); SAEs reports of adult patients receiving more than 48 weeks Peggasys to be analyzed | Q1 2013 |
| HBV immune-tolerant long-term follow-up (Vergani) (NV25361) | Q4 2019 |
| HBV immune active (YV25718) | Q2 2016 |
| HCV Paediatric Study Ages 3-5 years (BV28334) | Q1 2023 |

No additional risk minimisation activities were required beyond those included in the product information.

## *2.6. Significance of paediatric studies*

The CHMP is of the opinion that study NV17424 (PEDS-C), which is contained in the agreed Paediatric Investigation Plan, EMA Decision P/274/2011 and has been completed after 26 January 2007, is considered as significant.

## *2.7. User consultation*

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant.

The changes to the currently approved package leaflet related to this grouped line extension and type II variation are considered to be not significant and therefore the CHMP concluded that an user consultation with target patient groups on the package leaflet is not necessary.

# 3. Benefit-Risk Balance

## *Benefits*

### Beneficial effects

Peginterferon alfa-2a, in combination with ribavirin provides SVR rates in children at rates at least similar to what is seen with the same regimen in adults. In the 55 paediatric patients treated with peginterferon alfa-2a and ribavirin combination therapy in the NV17424 study, SVR was achieved in 53% (29 patients). Eighty (80) % of patients infected with HCV genotype 2/3 achieved SVR (8/10 patients), while 47% of patients infected with HCV genotype 1 were successfully treated.

### Uncertainty in the knowledge about the beneficial effects

The paediatric development program presented by the MAH includes only 55 patients treated from the start with the relevant combination regime, i.e. peginterferon alfa-2a + ribavirin. Due to this small sample size, the SVR rates are an estimate. However, extrapolation from adult trials decreases the level of such uncertainty.

## *Risks*

### Unfavourable effects

The general safety profile of peginterferon alfa-2a in children, as observed in study NV17424, is similar to that in adults, and includes, among other effects, considerable haematological, psychiatric, autoimmune and endocrine risks.

Furthermore, there is a paediatric-specific effect of peginterferon alfa-2a and ribavirin on growth. There is a clear on-treatment growth retardation and, depending on at what age treatment is initiated, treatment may lead to a permanent loss of adult stature.

### Uncertainty in the knowledge about the unfavourable effects

The extent of paediatric exposure is not large enough to definitely rule out relative differences in the safety profile compared to treatment in adults. In particular, data in patients with a BSA <0.9 are scarce, and there are no data on patients with a BSA <0.7. This is important, not least due to the applicant's PK modelling, indicating an increasing drug exposure with decreasing BSA, up to at least 70% higher than adult exposure.

Furthermore, the precise extent of growth retardation, as well as the optimal time to conduct therapy in this respect, is unclear.

### Benefit-risk balance

The general aim of anti-HCV therapy is to achieve SVR, which, in the great majority of cases, is equivalent to cure of HCV infection and therefore ends the progression of HCV-related hepatic injury. The SVR results from study NV17424 indicate that peginterferon alfa-2a and ribavirin at the studied doses have at least equal efficacy in paediatric patients, compared to the efficacy seen in adults. This is also supported by other corroborative evidence, notably the PK study (NR16141), the investigator-

sponsored CHIPS study (Sokal et al, J Hepatol 2010) in patients aged 6-17, and also the paediatric experience with PegIntron (peginterferon alfa-2b), given that the IDEAL study has shown comparative efficacy of peginterferon alfa-2a and peginterferon alfa-2b (see Discussion on Clinical Efficacy above).

The safety profile of peginterferon alfa-2a observed in paediatric patients was similar to that seen in adults. The frequency of serious adverse events, however, was lower than typical in adults, confirming previous observations with other interferons that have also implied that interferon + ribavirin combination therapy may on average be better tolerated in children. That said, a specific paediatric safety concern of interferon therapy is on-treatment growth retardation and the possibility that this may result in a permanent loss of adult stature. A statement reminding the prescriber of the importance to consider this - potentially irreversible - growth inhibition when deciding to initiate treatment in paediatric patients has been included in section 4.1 of the SmPC, and a boxed warning in section 4.4. The applicant will also perform a long term follow-up study on growth, as detailed in the RMP.

Importantly, the applicant was initially requesting a dose of peginterferon alfa-2a which was lower than that tested in the study. The rationale for this was that the dosing regimen used in the paediatric development program (180 µg x BSA/1.73 $m^2$) was expected to result in a 25-70% higher exposure than that seen with adults. The proposed dose adjustment aimed to more closely mimic adult AUC and was based on the premise that PK/PD for efficacy in paediatric patients is similar to that in adults. While it is recognised that data are not sufficient to positively ascertain that this is so, it is also recognised that this assumption tacitly underlies the acceptance of NV17424 as principally sufficient for an approval; indeed, 55 patients with varying genotypes treated with peginterferon alfa-2a+ribavirin combination therapy would not be considered a large enough sample without an assumption of roughly similar PK/PD.

The CHMP considered that this approach was not unreasonable due to the relatively high number of dose reductions and dose-dependent side effects seen in study NV17424, although – importantly – the pivotal study did not show any trend towards more serious AEs despite the higher estimated exposure. It is considered beneficial to avoid unnecessary over-exposure in children, and, in the field of antivirals, mimicking adult exposure is generally considered a valid basis for extrapolating efficacy. However, the CHMP noted that to use a model for the purpose of simulating the exposure following a non-studied dosing regimen, a high level of confidence in the model is required.

Of note, while the pharmacokinetic model provided by the MAH as a basis for the dose adjustment was considered robust, the MAH could not entirely explain the absence of a gradient with a higher frequency of neutropenia in patients with lower BSA. Therefore the CHMP remained concerned that the initially proposed, lower, dosing regimen could cause insufficient exposure compared to the studied regimen (see discussion on clinical pharmacology above), and requested a modification of the proposed posology.

To reduce the risk of dosing errors the CHMP agreed to maintain a BSA category-based posology rather than the formula-based regimen used in the PK and the pivotal studies. However, the MAH was requested to adjust the BSA category-based dosing regimen to provide a reasonable fit with the doses generated by the algorithm used in the PK and the pivotal trial (180 µg x BSA/1.73 $m^2$). Of note there were only 20 patients with a BSA <0.9 $m^2$ and no patients with a BSA below 0.7 $m^2$ included in the pivotal study. Due to the lack of safety data and uncertainties about drug exposure in these smallest children, the CHMP therefore restricted the use to patients with a BSA >0.7 $m^2$. This updated BSA category-based dosing regimen is shown in table 5. The CHMP concluded that this posology prescribes a safe and effective dose over the full range of ages and body sizes in which peginterferon alfa-2a is to be indicated.

In conclusion, the benefit-risk balance of Pegasys, in combination with ribavirin for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older, who are positive for serum HCV-RNA, is positive.

# 4. Recommendations

## *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk/benefit balance of the extension of marketing authorisation for Pegasys 90 µg solution for injection is favourable and therefore recommends the granting of the marketing authorisation subject to the current conditions below.

In addition, the CHMP considers by consensus the following variation acceptable and recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variations requested** | | **Type** |
|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

Extension of the indication to include the treatment of chronic hepatitis C in paediatric patients aged 5 years and older with consequential changes to the SmPC and PL.

The MAH further took the opportunity to update the PI in line with the latest QRD template (version 8 revision 2) and to remove from Annex II the Nutley manufacturing site, which was withdrawn in a previous variation.

## *Conditions or restrictions regarding supply and use*

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

## *Other conditions and requirements of the Marketing Authorisation*

### Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines webportal.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

### Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted every three years.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

• At the request of the European Medicines Agency;

• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## *Paediatric Data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA Decision P/274/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/274/2011 have been completed after the entry into force of that Regulation.