EU Risk Management Plan for Pegasys (peginterferon alfa-2a)

RMP version to be assessed as part of this application:

RMP Version number: 10.2

Data lock point for this RMP: 11.07.2023

Date of final sign-off: 26.10.2023

Rationale for submitting an updated RMP:

- New EU RMP version prepared to support the extension of indications for
    - Pegasys is indicated as monotherapy in adults for the treatment of polycythaemia vera.
    - Pegasys is indicated as monotherapy in adults for the treatment of essential thrombocythaemia.

Summary of significant changes in this RMP:

- Part II Module SI.6 and SI.7: Update of epidemiology of the indication(s) and target population(s) with reference to the new indications

Details of the currently approved RMP:

Version number: 10.0

Approved with procedure: EMEA/H/C/000395/II/0112

Date of approval (opinion date): 29/09/2022

QPPV name: Pedro Jorge

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance **(INN or common name)**	Peginterferon alfa-2a
Pharmacotherapeutic group(s) (ATC Code)	L03AB11
Marketing Authorisation Holder	pharmaand GmbH (MA transfer from Roche Registration GmbH on 12 Aug 2021)
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Pegasys®
Marketing authorisation procedure	centralised
Brief description of the product	Chemical Class: Chemically modified interferon(IFN)
	Summary of mode of action: Peginterferon stimulates the production of effector proteins such as serum neopterin and 2',5'- oligoadenylate synthetase in a dose-dependent manner. In adults the stimulation of 2',5'- oligoadenylate synthetase is maximal after single doses of 135 to 180 micrograms (mcg) of PEG-IFNalfa-2a and stays maximal throughout the recommended once-weekly dosing interval. Peginterferon possesses the in vitro antiviral and antiproliferative activities of IFN alfa-2a. Interferons bind to specific receptors on the cell surface initiating a complex intracellular signaling pathway and rapid activation of gene transcription. IFN-stimulated genes modulate many biological effects including the inhibition of cell proliferation and immunomodulation.
	Important information about its composition The active substance, peginterferon alfa-2a, is a covalent conjugate of the protein interferon alfa-2aproduced by recombinant DNA technology in Escherichia coli with bis-[monomethoxy polyethylene glycol] Excipients are benzyl alcohol (10 mg/ 1 ml) sodium chloride, polysorbate 80, benzyl alcohol sodium acetate, acetic acid and water for injections.
Hyperlink to the Product Information	Please refer to proposed SmPC in module 1.3 – product information.

Indication(s) in the EEA	Current: **Chronic hepatitis B (CHB)** *Adult patients* 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 alanine aminotransferase (ALT) and histologically verified liver inflammation and/or fibrosis. *Paediatric patients 3 years of age and older* Pegasys is indicated for the treatment of HBeAg-positive CHB in non-cirrhotic children and adolescents 3 years of age and older with evidence of viral replication and persistently elevated serum ALT levels. With respect to the decision to initiate treatment in paediatric patients see sections 4.2, 4.4 and 5.1. **Chronic hepatitis C (CHC)** *Adult patients* Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease. *Paediatric patients 5 years of age and older* Pegasys in combination with ribavirin is indicated for the treatment of CHC in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA. When deciding to initiate treatment in childhood, it is important to consider growth inhibition induced by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case-by-case basis.
	Proposed: *Polycythaemia vera* • Pegasys is indicated as monotherapy in adults for the treatment of polycythaemia vera. *Essential thrombocythaemia* • Pegasys is indicated as monotherapy in adults for the treatment of essential thrombocythaemia.
Dosage in the EEA	Current: **Chronic hepatitis B**

Adult patients

The recommended dosage and duration of Pegasys® for both HBeAg-positive and HBeAg-negative CHB is 180 mcg once weekly for 48 weeks.

Pediatric patients (3 to 17 years of age)

For children and adolescents aged 3 to 17 years with HBeAg-positive CHB, and having a BSA greater than 0.54 m^2, the recommended doses for Pegasys® are as follows:

- For a BSA range of 0.54-0.74 m^2 the weekly dose is 65 mcg.
- For a BSA range of 0.75-1.08 m^2 the weekly dose is 90 mcg.
- For a BSA range of 1.09-1.51 m^2 the weekly dose is 135 mcg.
- For a BSA range of greater than 1.51 m^2 the weekly dose is 180 mcg.

The recommended duration of therapy is 48 weeks. Before initiating therapy for CHB, persistently elevated serum ALT levels should have been documented. The response rate was lower in patients with no to minimal increase in ALT level at baseline:

Chronic hepatitis C

Monotherapy for hepatitis C should only be considered in case of contraindication to other medicinal products.

Treatment-naïve adult patients

The recommended dose for Pegasys® is 180 mcg once weekly given in combination with oral ribavirin or as monotherapy.

The dose of ribavirin to be used in combination with Pegasys® is given in the table below. The ribavirin dose should be administered with food.

Dosing Recommendations for Combination Therapy for Adult Patients with Chronic Hepatitis C

Genotype	Pegasys® Dose	Ribavirin Dose	Duration
Genotype 1 LVL with RVR*	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks

	<table><tr><td>Genotype 2 or 3 without RVR**</td><td>180 mcg</td><td>800 mg</td><td>24 weeks</td></tr><tr><td>Genotype 2 or 3 LVL with RVR**</td><td>180 mcg</td><td>800 mg</td><td>16 weeks[a] or 24 weeks</td></tr><tr><td>Genotype 2 or 3 HVL with RVR**</td><td>180 mcg</td><td>800 mg</td><td>24 weeks</td></tr></table> *RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;**RVR = rapid viral response (HCV RNA negative) by week 4; LVL = low viral load ≤ 800,000 IU/mL; HVL = high viral load > 800,000 IU/mL; IU = international unit; kg = kilogram; mg= milligram [a] It is presently not clear whether a higher dose of ribavirin (e.g., 1000/1200 mg/day based on body weight) results in higher sustained virological response (SVR) rates than does the 800 mg/day, when treatment is shortened to 16 weeks. The recommended duration of Pegasys® monotherapy is 48 weeks. <u>*Treatment-experienced adult patients*</u> The recommended dose of Pegasys® in combination with ribavirin is 180 mcg once weekly by SC administration. For patients <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, and regardless of genotype, should be administered. <u>*Human Immunodeficiency Virus (HIV) – Hepatitis C Virus (HCV) co-infected adult patients*</u> The recommended dosage for Pegasys, alone or in combination with ribavirin, is 180 mcg once weekly by SC administration for 48 weeks <u>*Pediatric population (5 years of age and older)*</u> Pegasys® is to be given once weekly by sc administration in combination with ribavirin. The recommended doses for Pegasys® are based on body surface area (BSA) categories as follows: • For a BSA range of 0.71-0.74 m^2 the weekly dose is 65 mcg. • For a BSA range of 0.75-1.08 m^2 the weekly dose is 90 mcg. • For a BSA range of 1.09-1.51 m^2 the weekly dose is 135 mcg. • For a BSA range of greater than 1.51 m^2 the weekly dose is 180 mcg. The recommended dose of ribavirin is based on the patient's body weight, with a target dose of 15 mg/kg/day, divided in two daily doses.
	Proposed: *Polycythaemia vera* and e*ssential thrombocythaemia* The dose is titrated individually with a recommended starting dose of 45 µg s.c./week and titrated in 45 µg increments monthly to a maximum of 180 µg s.c./week.
Pharmaceutical form(s) and strengths	Current: Solution for injection. Pegasys is supplied as a sterile, ready-to-use liquid for sc injection as pre-filled pens, PFS and vials as follows:

	• 180 mcg Pegasys pre-filled pen: each single use pre-filled pen contains 0.5 mL with 180 mcg PEG-IFN alfa-2a • 135 mcg Pegasys pre-filled pen: each single use pre-filled pen contains 0.5 millilitres (mL) with 135 mcg PEG-IFN alfa-2a • 180 mcg Pegasys PFS: each single use syringe contains 0.5 mL with 180 mcg PEG- IFN alfa-2a. The syringe is labelled with graduations corresponding to doses of 180 mcg, 135 mcg and 90 mcg • 135 mcg Pegasys PFS: each single use syringe contains 0.5 mL with 135 mcg PEG- IFN alfa-2a. The syringe is labelled with graduations corresponding to doses of 135 mcg, 90 mcg and 45 mcg. • 90 mcg Pegasys PFS: each single use syringe contains 0.5 mL with 90 mcg PEG-IFN alfa-2a. The syringe is labelled with graduations corresponding to doses of 90 mcg, 65 mcg, 45 mcg, 30 mcg, 20 mcg and 10 mcg. • Single dose vials: each vial contains 1.0 mL with 180 mcg of PEG-IFN alfa-2a. Not all strengths and pharmaceutical forms may be marketed.
	Proposed – Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations

Abbreviations	Definition
BSA	Body Surface Area
CDS	Core Data Sheet
CHB	Chronic Hepatitis B
CHC	Chronic Hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
DSR	Drug Safety Report
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ET	Essential thrombocythaemia
EU	European Union
FBC	Full blood count
FT3	free triiodothyronine
FT4	free thyroxine
HBc	Hepatitis B core
HBeAg	Hepatitis B envelope Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCC	hepatocellular carcinoma
HCT	Haematocrit
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HU	Hydroxyurea
HVL	High Viral Load
IFN	Interferon
IU	International Unit
JAK	Janus kinase
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPN	Myeloproliferative neoplasms
NA	nucleos(t)ide analogue
PEG-IFN	Peginterferon
PFS	Pre-Filled Syringe(s)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term(s)
PV	Polycythaemia vera
RMP	Risk Management Plan
RNA	Ribonucleic Acid
SAE	Serious Adverse Event

Abbreviations	Definition
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SVR	sustained virological response
UK	United Kingdom
US	United States
WHO	World Health Organisation

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Chronic Hepatitis B Infection in Adults

Incidence:

The Hepatitis B surveillance report, 2015 European Centre for Disease Prevention and Control (ECDC) identified 15,595 newly diagnosed cases of chronic hepatitis B (CHB) for all ages from 17 European countries, representing a notification rate of 0.01% (9.9 per 100,000 population), ranging from <0.1 per 100,000 (<0.0001%) in Romania to 20.1 per 100,000 (0.02%) in Sweden (ECDC, 2015).

In Poland, 2695 cases of CHB were recorded in 2014, exhibiting an incidence of 0.007%(7.0 per 100,000 population). Among 2695 cases, 64 cases (2.4%) were in the 0-19 years-old age group (Stępień et al., 2016).

In 2016, a total of 14,847 new cases of confirmed CHB were reported to center for disease control and prevention (CDC) from 43 states of US (CDC, 2016). According to the Hepatitis B and C Annual Surveillance Report from Michigan Department of Health and Human Services (MDHHS, US), in 2016, 1230 new cases of CHB were reported in Michigan in adults aged ≥ 20 years, accounting for an incidence of 0.017% (16.53 per 100,000 population) (MDHHS, 2016).

Prevalence:

The World Health Organization (WHO) estimated worldwide prevalence of CHB was 3.5% (257 million) in 2015. Among different WHO regions, the prevalence was reportedto be highest in the African regions (6.1%) and Western Pacific regions (6.2%) while thelowest prevalence was in the region of Americas (0.7%) (WHO, 2017). The prevalence data of CHB in different WHO regions are presented in Table 1. According to National Health and Nutrition Examination Survey (NHANES), the overall prevalence of CHB infection in the US was 0.34% (approximately 0.86 million) from 2011 to 2014 (Kim et al., 2017).

A systematic review of literature published between 2005 to 2015 by ECDC, reported anoverall prevalence of 0.9% from 13 countries (ranging from 0.1% in Ireland to 4.4% in Romania) (ECDC, 2016). The prevalence data of CHB across European countries are presented in Table 2.

Table 1 - Prevalence of Chronic Hepatitis B infection in the generalpopulation by WHO region, 2015

WHO Region	Estimated number of persons with CHB (million)	Prevalence of CHB (%)
Worldwide	**257**	**3.5**
Western Pacific Region	115	6.2
African Region	60	6.1
South-East Asia Region	39	2.0
Eastern Mediterranean Region	21	3.3
European Region	15	1.6
Region of Americas	7	0.7

Source: Global Hepatitis Report 2017, WHO (WHO,2015)

Table 2 - Prevalence of Chronic Hepatitis B infection in the adult general population of EU/EEA, 2005-2015

Countries	Prevalence of CHB (%)
Belgium	0.7%; 95% CI (0.5-0.8)
Croatia	0.7%; 95% CI (0.4-1.2)
Czech Republic	0.6%
France	0.7%; 95% CI (0.5-0.9)
Germany	0.4%; 95% CI (0.3-0.5)
Greece	3.3%; 95% CI (2.2-4.7)
Hungary	0.4%; 95% CI (0.1-1.0)
Ireland	0.1%; 95% CI (0.0-0.4)
Italy	0.7%; 95% CI (0.4-1.0)
Netherlands	0.2%; 95% CI (0.1-0.4)
Romania	4.4%; 95% CI (4.0-4.8)
Slovakia	1.1%; 95% CI (0.7-1.6)
Spain	0.8%; 95% CI (0.6-1.1)

Source: Systematic review, ECDC (ECDC, 2016)

Demographics of the population in the authorised indication and risk factors for the disease:

The risk of developing CHB infection depends on the age at which people are infected, with 90% of infants infected at birth developing chronic infection, compared with 1-10% of those infected at an older age or as adults (WHO, 2017). According to ECDC, 2015, hepatitis B virus (HBV) infection was found to be more prevalent among males (8.4 per 100,000) than in females (5.2 per 100,000). The male-to-female ratio was higher amongchronic cases (1.5 to 1). In adults aged ≥ 20 years, the notification rate of CHB was highest among 25-44-years' group (~ 30.0 per 100,000 in the age group 25-34 yearsand 24.0 per 100,000 in the age group 35-44 years). The lowest cases of CHB was reported among population ≥55 years (< 10.0 per 100,000) (ECDC, 2017).

In the US, it is estimated that over 70% of new cases are imported chronic HBV cases. Per the estimates of NHANES 2011-2014 survey, in the US the prevalence of CHB was 0.27% (for age 20-39 years), 0.41% (for age 40-64 years), and 0.59% (for age ≥ 65 years). The prevalence of CHB in Asians, non-Hispanic blacks, and non-Asian non-blackrace groups was 2.74%, 0.64%, and 0.15%, respectively (Kim et al., 2017).

Males were found to be at higher risk for CHB based on several epidemiological data(ECDC, 2017; Stępień et al., 2016). History of intravenous drug use, blood/ blood product transfusion, surgical intervention are independent risk factors for HBV infection(Gheorghe et al., 2013). Other risk factors for hepatitis-B surface antigen (HBsAg) positivity include homosexuality in men and body piercing (Jagannathan et al., 2010).

The main existing treatment options:

The major international guidelines recommend the use of two different types of drugs for the treatment of CHB infection [EASL 2017 Clinical Practice Guidelines, AASL 2017, Liaw YF 2013], which differ in their mode of action, therapeutic effect, and therefore goal of treatment:

- Conventional IFN and PEG-IFN alfa have a dual immunomodulatory and antiviral effect, are used for a finite period (1 year) and provide sustained off-therapy response in a subset of patients. PEG-IFN, where available, has replaced standard IFN for the treatment of CHB infection, mainly because of its easier application and increased rates of response [EASL 2017 Clinical Practice Guidelines]. PEG-IFN alfa-2a is licensed globally, whereas PEG-IFN alfa-2b is licensed in a few countries for the treatment of CHB infection [Liaw YF 2013]. However, PEG-IFN alfa-2b is not more commercially available.
- Nucleos(t)ide analogue (NAs; e.g., lamivudine, adefovir, entecavir, tenofovir, and telbivudine) provide antiviral suppression, are administered long-term (potentially indefinitely) and are associated with clinical benefits as long as treatment is maintained. Of the five approved NAs, entecavir and tenofovir are generally considered to have the best profile with regards to efficacy, safety, and drug resistance.

PEG-IFN is recommended in these CHB infections treatment guidelines as first-line standard of care as is treatment with entecavir or tenofovir. The UK National Institute forHealth and Care Excellence (NICE) guidance [UK NICE guidelines 2017] has shown thatPEG-IFN alfa-2a is more cost-effective than life-long NA therapy and has recommended PEG-IFN alfa-2a as the first-line treatment option in both HBeAg-positive and HBeAg-negative patients with compensated liver disease, in first-line treatment in children and young people with CHB infection and compensated liver disease, and in first-line treatment for patients co-infected with hepatitis D. (Note: pharma& PEG-IFN alfa-2a is currently not approved for the treatment of patients with hepatitis D and any treatment decision should be made with the clinician’s best judgment.).

NAs are recommended for patients who are unlikely to achieve success with IFN therapy,have contraindications, or are intolerant [Mauss S et al 2017]. The advantages of NA therapy are good tolerability and oral administration, while the disadvantages are the indefinite duration because of the high risk of relapse after NA treatment is withdrawn, risk of resistance development, and the lack of long-term safety data to support chronic usage [EASL 2017 Clinical Practice Guidelines].

Natural history of the indicated condition in the untreated population:

The natural history of CHB is dynamic and complex and progresses nonlinearly through several recognizable phases. The phases are of variable duration, not necessarily sequential, and do not always relate directly to criteria and indications for antiviral therapy. In some people, CHB is inactive and does not lead to significant liver disease. In others, it may cause progressive liver fibrosis, leading to cirrhosis with end-stage liverdisease, and a markedly increased risk of hepatocellular carcinoma (HCC), independentof the presence of cirrhosis - usually many years after initial infection. Longitudinal studies of untreated CHB show an 8-20% cumulative risk of developing cirrhosis over five years. In those with cirrhosis, there is an approximately 20% annual risk of hepatic decompensation and the annual incidence of HBV-related HCC is high, ranging from <1% to 5%. Untreated patients with decompensated cirrhosis have a poor prognosis,with 15-40% survival at five years (WHO, 2015).

Worldwide, the majority of persons with CHB are infected at birth or in early childhood. According to WHO, it is estimated that around 650,000 people die each year from the complications of CHB (WHO, 2015). In the WHO European Region, approximately 36,000 deaths a year had accounted from HBV (WHO, 2013). In a study by Fedeli et al.in 2017, between 2011 and 2013, 0.2% of all deaths were due

to HBV among subjects aged ≥ 20 years in Italy. Mortality rates associated with HBV infection increased slowly with age and were always higher in the males (Fedeli et al., 2017).

Per CDC, in 2016, the overall HBV-related mortality rate was 0.45 deaths per 100,000 population. Asians/Pacific Islanders had the highest HBV-related mortality rate of 2.39 deaths per 100,000 population than other racial/ethnic populations. Persons aged 55-64years and 65-74 years had the highest age-specific mortality rates at 1.39 deaths per 100,000 population and 1.34 deaths per 100,000 population, respectively. Hepatitis B- related mortality rate in males was three times of mortality rate for females (0.69 deathsper 100,000 population vs. 0.23 deaths per 100,000 population) (CDC, 2016).

Important co-morbidities:

Results of 10-year longitudinal analysis of a large population-based cohort of 44,026 CHB patients in the US suggested that comorbidities such as diabetes, hypertension, and hyperlipidaemia increased significantly from 2006 to 2015. Hyperlipidaemia increased from 8.4% to 47.3% and hypertension from 43.0% to 75.9%. Non-alcoholic fatty liver disease and hepatic steatosis increased by almost 4-folds in CHB patients from 2006 to 2015, while there was a 2 to 4-fold increase in the prevalence of glomerulonephritis, proteinuria, nephrotic syndrome or nephropathy among the CHB population (Nguyen et al., 2017).

SI.2 Chronic Hepatitis B Infection in Paediatric Population

Incidence:

According to WHO, in 2015 the global cumulated incidence of CHB in children under 5 years was 1.3%. The incidence of CHB in children under 5 years across different WHOregions was reported to be 0.4% in the European Region, 0.2% in the region of the Americas, 0.9% in the Western Pacific Region, 0.7% in the South-East Asia region, 1.6% in the Eastern Mediterranean region and 3.0% in the African region (WHO, 2017).

An annual epidemiological Hepatitis B surveillance report 2015 by ECDC (data available from 30 EU/EEA member states) reported that the notification rate of CHB was about 1.0, 2.0 and 10.0 cases per 100,000 population for <5 years, 5 to 14 years and 15 to 19 years' age groups respectively (ECDC, 2017).

A retrospective study of prospective data from 5 US-funded Perinatal Hepatitis B Prevention Programs was conducted. The analysis included data for mother-infant pairsfrom 2008 to 2013. The study included pregnant/postpartum women who were HBsAg-positive while perinatal HBV infection was defined as HBsAg positivity in an infant, 24 months of age born to an HBsAg-positive woman. Among the 9252 infants for whom HBsAg testing results were available, 100 acquired perinatal HBV infection. The incidence of perinatal HBV infection was 1.08% (Schillie et al., 2015).

According to the Annual Surveillance Report (2016) from MDHHS, 54 new cases of CHB was reported among Michigan residents aged between 0 to 19 years, accounting for an incidence of 0.0022% (2.18 per 100,000 population) (MDHHS, 2016).

Prevalence:

In the WHO South-East Asia Region (SEAR), the overall regional prevalence of CHB among 5-year-old children in 2015 was reported to be 1.1%. The highest rates of perinatal CHB were reported in Myanmar (16 per 1000 live births) and Bangladesh (15 per 1000 live births). Thailand had the lowest rate (0.48 per 1000 live births) followed by the Maldives (0.55 per 1000 live births) (Childs et al.,

2017). Data from the NHANES, US from 2011 to 2014 estimated that the prevalence of CHB in population aged between 6-19 years was found to be 0.13%; 95% CI (0.00 to 0.31) (Kim et al., 2017).

The Chinese Center for Disease Control and Prevention reported that CHB infection among Chinese population aged 1-4 years and 5-14 years in 2014 was 0.3% and 0.9% respectively (Cui et al., 2017). A review by Paganelli (2012) reported that HBsAg seroprevalence in children <16 years of age was found to be 1.8% in China, 0.9% in Korea, 3.1% in Colombia, 7.5% in Vietnam, 0.8% in Brazil, 12.4% in Nigeria and 2% to 14% in Combodia (Paganelli et al., 2012).

Demographics of the population in the authorised indication and risk factors for the disease:

In the US (2011-2014), NHANES survey, it was reported that the prevalence of CHB in children aged 6-19 years was found to be 0.86% in Asians population and 0.11% in non-Asian, non-black population. No cases were reported for non-Hispanic Blacks (Kim et al.,2017).

In highly endemic areas, CHB occurs mainly in infancy and early childhood, with mother-to-child transmission accounting for more than half of the chronic infections. After exposure, risk of developing CHB is higher for newborns (90%) than for infants and children <5 years of age (25-30%) (Paganelli et al., 2012). In children, vertical transmission is the primary route of transmission of viral hepatitis with the mean rate of 15.7% (from 11 published studies). The most prominent risk factors for vertical transmission are HBeAg positivity in mothers, high maternal viral load at the time of delivery, and vaginal delivery. Other risk factors include co-infection with human immunodeficiency virus (HIV), male sex of infants and HBV genotype B2 (Mavilia et al.,2017; Gentile et al., 2014)

The main existing treatment options

European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended that finite-duration IFN-a therapy remains the treatment strategy of choice for HBeAg-positive children with elevated ALT levels (A1), as in this patient population seroconversion to anti-HBs is the main aim. IFN-a is the only available treatment offering a chance of sustained off-treatment VR. NA used to be second-line therapies because of the high risk of emergence of resistant mutant strains. Nevertheless, the recent FDA approval of NA with higher genotypic barrier to resistance has opened the way for the use of such drugs as first-line treatment for adolescents. In patients older than 12 years of age, tenofovir (or entecavir for patients P16 years old) is the best choice, as response rate is high and resistance is less likely recommended dose for tenofovir is 300 mg once daily, and for entecavir is 0.5 mg once daily (for nucleoside-naïve patients). Lamivudine is the only NA currently approved for younger children. For children with cirrhosis, who need antiviral treatment to be continued, switch to tenofovir (if P12 years of age), alone or in combination with entecavir (if P16 years of age) or maintenance of lamivudine (if <12 years of age) despite an incomplete VR is recommended. Combination therapy with adefovir and lamivudine has been tried only in children not responding to adefovir monotherapy, and its efficacy has not been compared to monotherapy.

Natural history of the indicated condition in the untreated population:

Chronic hepatitis B in childhood is a mild disease, and infected children are mostly asymptomatic. It is marked by four phases: immune tolerant phase, immune active phase, low replication phase, and the reactivation phase. The immunotolerant phase is characterized by high viral replication and little liver damage, although in Italian children, after 7 years of disease, 7-10% of subjects showed severe hepatitis at liver biopsy and 1.7-4.5% had cirrhosis. Reactivation phase is found in 20 to 30% of patients in which HBeAg seroconversion occurs. A prospective follow-up study of children with CHB showed that only 4.3% of 140 HBeAg seroconverters had re-elevated ALT. Cirrhosis developed in 1-5% of HBeAg-positive children. Hepatocellular carcinoma developed in 2% to 5% of the children with CHB. Children developing HCC are more likely to be males (70%), with cirrhosis (80%) and undergoing early

seroconversion, suggesting that necroinflammation during seroconversion to anti-HBe may be severe and can lead to cirrhosis and HCC (Paganelli et al., 2012; Chen et al., 2010)

Important Co-morbidities

There is limited information on co-morbidities associated with HBV children. The Chronic Hepatitis in Children B (ChicB) Surveillance, England identified 325 HBV cases among children (born during 1988-2008 and were diagnosed during 1989-2009). Among them, information on co-morbidity was available for 21 (6%) children. The co-morbidities included neurodevelopmental delay (n=6), hemoglobinopathy (n=4), congenital heart disease (n=3), malignancy (n=3), epilepsy (n=2), primary immunodeficiency (n=2) and metabolic disorder (n=1) (Ladhani et al., 2014).

SI.3 Chronic Hepatitis C Infection in Adults

Incidence

According to the WHO, 1.75 million new infection cases of hepatitis C virus (HCV) were reported in 2015 worldwide, with an overall incidence of 23.7 per 100,000 (0.023%) (WHO, 2017).

Hepatitis C surveillance report (2015) by ECDC reported 4394 newly diagnosed cases of chronic hepatitis C (CHC) from 12 European countries, representing a notification rate of 0.003% (3.2 per 100,000 population) ranging from <0.1 in Romania to 76.1 per 100,000 population in Latvia (ECDC, 2017).

In 2016, a total of 148,932 case reports of CHC were reported to CDC from 42 states (CDC, 2016). According to the Hepatitis B and C Annual Surveillance Report from MDHHS, in 2016, 11,734 new cases of CHC were reported in Michigan in adults (aged ≥ 20 years), accounting for an incidence of 0.16% (157.7 per 100,000 population) (MDHHS, 2016).

A systematic review in 2009 reported a 0.04% (40.79 per 100,000) incidence of HCV infection in Russia (Cornberg et al., 2011).

Prevalence

According to the WHO, worldwide 71 million persons were living with CHC infection in 2015, accounting for 1% of the total population. The WHO Eastern Mediterranean Region had the highest prevalence (2.3%) followed by the European Region (1.5%) (WHO, 2017). The prevalence of CHC in different WHO regions is presented in Table 3.

The ECDC conducted a systematic review of the literature published between the years 2005 to 2015 became available for a total of 13 countries under EU/EEA. Based on the evidence, a total of 5.6 million Europeans were found living with CHC, corresponding to an overall prevalence of 1.1% (ranging from 0.1% in Belgium to 5.9% in Italy) (ECDC, 2016). The prevalence data of CHC across European countries are presented in Table 4.

A retrospective study based on data from NHANES (2003-2010), estimated the prevalence of CHC infection in population aged ≥ 6 years to be 1.0%; 95% CI (0.8% to 1.2%), corresponding to 2.7 million chronically infected population in the U.S (Dennistonet al., 2014).

Table 3 - Prevalence of Chronic Hepatitis C infection in the general population by WHO region, 2015

WHO Region	Estimated number of persons with CHC (million)	Prevalence of CHC (%)
Worldwide	**71**	**1.0**
Western Pacific Region	14	0.7
African Region	11	1.0
South-East Asia Region	10	0.5
Eastern Mediterranean Region	15	2.3
European Region	14	1.5
Region of Americas	7	0.7

Source: Global Hepatitis Report 2017, WHO (WHO, 2017)

Table 4 - Prevalence of Chronic Hepatitis C infection in the general population of EU/EEA, 2005-2015

Countries	Prevalence of CHC (%)
Belgium	0.1%; 95% CI (0.0-0.4)
Croatia	0.9%; 95% CI (0.6-1.5)
France	0.8%; 95% CI (0.7-1.1)
Germany	0.4%; 95% CI (0.3-0.5)
Greece	2.2%; 95% CI (1.3-3.4)
Hungary	0.5%; 95% CI (0.2-1.1)
Ireland	0.1%; 95% CI (0.0-0.4)
Italy	5.9%; 95% CI (5.2-6.6)
Latvia	2.4%; 95% CI (1.7-3.3)
Netherlands	0.1%; 95% CI (0.0-0.2)
Romania	3.2%; 95% CI (2.9-3.6)
Slovakia	2.0%; 95% CI (1.4-2.7)
Spain	1.1%; 95% CI (0.3-2.8)

Source: Systematic review, ECDC (ECDC, 2016)

Demographics of the population in the authorised indication and risk factors for the disease:

According to the ECDC, 5.2% of CHC cases were found to be in the population under 25 years of age (ECDC, 2017). The most affected age group among males was between 35 and 44 years of age (23.6 cases per 100,000); among females, the age group between 25 and 34 years of age (10.3 cases per 100,000) was the most affected (ECDC, 2017). In Frankfurt (Germany), the highest prevalence of CHC in males was found among the age group 46 to 55 years (4.8%) while in women the highest prevalence was in the age group 66 to 75 years (2.97%). Higher prevalence was found in Whites (2.76%) as compared to 2.27% in other ethnicities (Oriental, African and Asian) (Bert et al., 2016).

In 2016, African Americans (155.46 per 100,000) had the highest incidence rate of CHC infection in Michigan compared with other racial groups (149.82 for American Indian,

73.36 for Caucasians, and 17.45 per 100,000 for Asians). In 2016, the rate of CHC reports was 1.46 times higher in males (142.42 per 100,000) than females (97.23 per 100,000) in Michigan (MDHHS, 2016). According to NHANES 2003-2010 survey in US, CHC were more likely to occur in 40-59 years, males, non-Hispanic blacks, and among those who fall under lower socio- economic status (Denniston et al., 2014).

Hepatitis C is most commonly associated with unsafe injection practices and procedures such as renal dialysis and unscreened blood transfusions. In middle and high-income countries, most HCV infections occur among people who use unsterile equipment to inject drugs and contaminated drug solutions. The risk of transmission of HCV from a mother to her child occurs in 4-8% of births to women with HCV infection, and in 10.8- 25% of births to women with HIV and HCV co-infection. Other routes of transmission of HCV include intranasal drug use and different modes of bloodborne transmission, such as cosmetic procedures (such as tattooing and body piercing), scarification and circumcision procedures. Prisoners and previously incarcerated persons also had high prevalence of HCV infection (WHO, 2016).

The main existing treatment options

The goal of treating CHC infection in a patient of any age is to achieve sustained elimination of HCV. The combination of PEG-IFN and ribavirin has been the mainstay of CHC infection treatment in adults for approximately a decade. The option of IFN monotherapy is mainly suitable for patients who cannot tolerate or have a contraindication to ribavirin or other medicinal products. Two PEG-IFNs are available: PEG-IFN alfa-2a (PEGASYS®, pharma&) and PEG-IFN alfa-2b (PegIntron®, Merck). In general, the two PEG-IFNs have shown similar SVR rates, but their pharmacokinetic profiles differ (Mauss S et al 2017, EMA guidelines 2011). Since the approval of sofosbuvir and simeprevir, PEG-IFN alfa-2a in combination with ribavirin, is no longer considered the standard of care, and the recommendations for treatment are dependent on the HCV genotype, including an IFN-free option (EASL recommendations 2017, World Cancer Research Fund International).

An analysis, which included trials in children and adolescents of either PEG-IFN alfa-2a plus ribavirin or PEG-IFN alfa-2b plus ribavirin, demonstrated that both combinations are effective for treating CHC infection in children and adolescents (Druyts E at al 2013).

Natural history of the indicated condition in the untreated population

Chronic infection with HCV is usually clinically silent and is very rarely associated with life-threatening disease. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15-45% of the infected individuals in the absence of any treatment. Almost all the remaining 55-85% of persons harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC. Of those

with chronic HCV infection, the risk of cirrhosis of the liver is 15-30% within 20 years. The risk of HCC in persons with cirrhosis is approximately 2-4% per year (WHO, 2016).

The WHO estimated that around 704,000 people died worldwide from the complications related to CHC in 2013 (WHO, 2016). In the WHO European Region, around 15 million people are living with HCV (i.e., 2.0% of adults), and approximately 86,000 deaths per year were reported due to HCV complications (WHO, 2018). Fedeli et al (2017) analysed mortality associated with HCV in Italy for the year 2011-2013, and reported that 27,730 (1.6%) of all deaths were due to HCV among population aged ≥20 years (Fedeli et al., 2017).

According to the CDC, the overall CHC-related mortality rate was estimated to be 4.5 deaths per 100,000 population in 2016 in US. Persons aged 55-64 years had the highest HCV-related mortality rate (21.8 deaths/100,000 population) compared with other age groups, accounting for 49.8% of HCV-related deaths in 2016. American Indians/Alaska Natives had the highest HCV-related mortality rate compared with other racial/ethnic populations, at 10.8 deaths/100,000 population. Non-Hispanic whites accounted for 63.5% of the 17,986 HCV-related deaths that included race/ethnicity information in 2016. The HCV-related mortality rate in males was approximately 2.6 times the rate in females (CDC, 2016).

Important co-morbidities

Persons infected with HCV often have other comorbidities such as HBV, HIV, TB and substance use (WHO, 2016). The most important comorbidities affecting the course of CHC include HBV co-infection, metabolic syndrome, and intestinal bacterial overgrowth. Comorbidities affecting the course and response to therapy include schistosomiasis, iron overload, alcohol abuse, and excessive smoking. Comorbidities affecting response to antiviral therapy include depression, anaemia, cardiovascular disease, and renal failure (El-Zayadi, 2009). In a cross-sectional retrospective review of data from 800 patients with HCV was evaluated between the years 1998 to 2007 in California (US). Diabetes and obesity was reported in 12.5% and 23.9% of HCV affected population, respectively. End-stage renal disease was found in 4.5% and HIV in 5.3% of population. Hypertension occurred in 26.9% and hyperlipidemia in 12.3% of HCV patients (Basseri et al., 2010). In the US, a retrospective observational study conducted in adult CHC patients between 2006 and 2010, the comorbid conditions with prevalence ≥5% of patients were hypertension, lipid metabolism disorders, compensated cirrhosis, advanced liver disease, type 2 diabetes, depression, non-alcoholic fatty liver disease, and chronic obstructive pulmonary disease/asthma. Average rates of liver transplant and HIV/AIDS in the cohort were 3.9% and 2.8%, respectively (Lauffenburger et al., 2014). In another retrospective study conducted (1998 to 2006) in US, the most frequent comorbidities in CHC patients were liver disease (37.5%), connective tissue disease (37.5%), abdominal pain (36.1%), upper respiratory infections (35.6%), and lower respiratory disease (33.7%), benign neoplasms (24.3%), genitourinary symptoms & ill-defined conditions (14.8%), and viral infections (13.8%) (Louie et al., 2012). A prospective, multicenter, observational study was carried out in France involving 1860 CHC patients aged ≥18 years initiating combination therapy with peginterferon a-2b and ribavirin. The frequent comorbidities present in the population were psychiatric patients (22%), drug users (44%) and HIV-co-infected patients (3%). Other comorbid chronic diseases were hypertension (36%), diabetes mellitus (22%) and asthma (9%) (Marcellin et al., 2011).

SI.4 Chronic Hepatitis C Infection in Paediatric Population

Incidence:

According to the ECDC Surveillance Atlas for Hepatitis C, 2016, the notification rate of CHC was reported to be 0.00017% (0.17 per 100,000) among children aged 0-14 years and 0.00008%

(0.08 per 100,000) in children aged 5-14 years (ECDC, 2017). An Annual Surveillance Report (2016) from MDHHS, US reported 149 new cases of CHC among Michigan residents aged between 0 to 19 years, accounting for an incidence of 0.006 % (6.0 per 100,000 population) (MDHHS, 2016).

The risk of transmission of HCV from a mother to child occurs in 4-8% of births (WHO, 2016). The estimated risk of transmitting HCV infection from mother to child is 1.7% per pregnancy if the mother has detectable anti-HCV antibodies, 4.3% if the mother has detectable HCV-RNA, and 7.1% if the mother tested positive for HCV-RNA at least twice during pregnancy or around the time of delivery (Mack et al.,2012). Hepatitis C mother- to-child-transmission occurs at an overall rate of 5% to 15% with 3% to 5% progressing to chronic infection (AASLD, 2017). The incidence of vertical HCV infection to children from HCV-positive and RNA-positive women from a systematic review of 17 studies (1997 to 2012) ranged from 1.1% to 10.7%. Meta-analysis showed that the pooled incidence of vertical HCV infection among children born to HIV-negative women was 5.8% (Benova et al., 2014).

Prevalence:

The prevalence of CHC is lower in children than adults; an estimated 5 million children worldwide have active HCV infection (AASLD, 2017).

Hepatitis C virus infection is estimated to affect 0.1% to 2% of children in the US (Macket al.,2012). From 2011 to 2014, Quest Diagnostics Health Trends National Database, US performed 86,783 HCV tests in 57,136 children aged between 2 and 13 years.

Children having current HCV infection during this period were 0.76% (Ly et al., 2017).Data from the NHANES collected between 2003 and 2010 indicates that 0.2% of 6 to 11-year-olds (31,000 children) and 0.4% of 12 to 19-year-olds (101,000 adolescents) in the US are chronically infected with HCV (AASLD, 2017).

Demographics of the population in the authorised indication and risk factors for the disease:

From a large population based study in US, HCV infection rate was 3.2-fold higher among children in the youngest than the oldest age: 1.62% in those aged 2 to 3 years and 0.50% in those aged 12 to 13 years. The prevalence of HCV was found to be higher in females (0.83%) than in males (0.68%) (Ly et al., 2017).

A French prospective study reported that when the viral load was greater than or equal to 6 log copies/mL, the neonatal transmission of HCV was 14.3%, representing a risk of transmission four times higher than for women with a lower viral load (OR: 4.0) (Benova et al., 2014). From a meta-analysis, maternal HIV co-infection was the most important determinant of risk of vertical HCV transmission (OR: 2.56). Other risk factors included presence of maternal HCV viremia and maternal history of injecting drug use. There is some evidence that prolonged rupture of membranes may increase vertical transmission risk of HCV (Benova et al., 2014).

The main existing treatment options:

The drugs currently approved by the European Medicines Agency (EMA) and the US FDA for treatment of children with chronic HCV infection, include IFNα-2b, Peg-IFNα-2a or -2b, ribavirin, sofosbuvir and ledipasvir/ sofosbuvir. The fixed-dose combination of ledipasvir/ sofosbuvir and the combination of sofosbuvir and ribavirin have been recently approved by EMA in 2017, for treatment of children 12 years or older with CHC virus genotype 1, 4, 5, and 6 and genotype 2 and 3 infection, respectively. Children younger than 12 years in Europe can be treated with the dual therapy of Peg-IFNα-2a or -2b and ribavirin. Children with HCV genotypes 1 or 4 infection should be treated for 48 weeks, whereas those with genotypes 2 or 3 should be treated for 24 weeks (Indolfi G et al 2018).

Natural history of the indicated condition in the (untreated) population

Hepatitis C infection acquired in infants can have several different patterns of outcome. Spontaneous resolution of infection is an important outcome, although it remains unclear whether children are more likely than adults to clear HCV infection. Some infants appear to acquire HCV infection from their chronically infected mother, but they lose all evidence of infection during early infancy (Mack et al.,2012).

About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV-RNA) by 3 years of age. Some may have spontaneous resolution as late as 7 years after vertical infection. Approximately 6% to 12% of older children experience spontaneous resolution with a few reports of strikingly higher proportions. The long-term course for those who do not have spontaneous resolution of CHC from infancy has been reported as mild: children are clinically well with normal or near-normal serum aminotransferases and little inflammation on liver biopsy. In a large European study, only 14% were mildly symptomatic. All the children had mild CHC on liver biopsy and only a single child from the total of 224 children developed cirrhosis.

Cirrhosis has been reported in 1% to 2% of children with CHC. Development of advanced liver disease in children is infrequent until more than 30 years of infection. Hepatocellular carcinoma is rarely encountered among children and has been reported almost exclusively in children with cirrhosis (AASLD, 2017).

Important co-morbidities:

Development of advanced liver disease is infrequent in HCV infected children. Like in adults, children with comorbid diseases such as obesity with nonalcoholic fatty liver disease, congenital heart disease with elevated right heart pressures and those receiving hepatotoxic drugs should be monitored carefully for disease progression.

Children with chronic HCV and a history of childhood leukemia may be at increased risk of developing HCC, but evidence is limited (AASLD, 2017).

SI.5 HIV/HCV Co-Infection

Incidence:

The incidence of acute HCV infection in HIV men who have sex with men varies from 2- 5 per 100 PY (Bichoupan et al., 2014). In a Swiss cohort, incidence of HCV was 7.4 per 100 person-years in IDU, 0.7 per 100 person-years in non-IDU practicing unsafe sex, and 0.2 per 100 person-years in those who did not report unsafe sex. A meta-analysis showed that the risk of vertical HCV infection to children of anti-HCV positive and HCV- RNA positive mothers was 10.8% for children of HIV-positive women (Benova et al., 2014).

Sun et al. (2012) examined the incidence of HIV/HCV co-infection in a cohort of 892 HIV-infected patients in Taiwan and reported an overall incidence rate of 0.70 per 100 PY. The rate increased from 0 in 1994 to 2000 and 0.23 in 2001 to 2005 to 1.0 per 100 PY in 2006 to 2010 (Sun et al., 2012).

Prevalence:

According to the WHO, among all HIV-infected persons, the prevalence of anti-HCV was 6.2%. This accounts for about 2.3 million people of the estimated 36.7 million living with HIV globally have serological evidence of past or present HCV infection (anti-HCV positive) (WHO, 2017).

The prevalence of HCV infection in individuals infected with HIV in the WHO European Region is very high, averaging 40% and reaching 50-90% in urban areas. Data from a EuroSIDA study (a prospective

observational cohort study covering 34 European countries along with Argentina and Israel) shows the prevalence is higher in the eastern (47.7%) and southern (44.9%) EuroSIDA regions than in the northern (24.5%) EuroSIDA region. This is due to the high rates of drug injection use in the two former regions. The prevalence of anti-HCV also varies widely among HIV transmission groups, ranging from 7-8% in men who have sex with men to 60-70% in hemophiliacs and 80-90% in injecting drug users (IDUs) (WHO).

According to the CDC factsheet 2017, in the US among HIV patients, about 25% are co- infected with HCV (CDC, 2018).

Demographics and risk factors:

According to WHO, eastern Europe and central Asia account for the largest proportion of HIV-infected persons who have serological evidence of past or present HCV infection (27%), because of injection drug use (WHO, 2017). From the EuroSIDA study revealed that the median age (interquartile range) of HIV-HCV antibody positive patients was 44 years (36 to 50 years) with male predominance of 67% (Peters et al., 2014).

The major risk factors associated with HIV-HCV antibody positivity are IDUs, heterosexual and homosexual contacts. Since HCV is more transmissible than HIV through blood contact, most PWID are already HCV-infected by the time they are diagnosed with HIV (Peters and Klein, 2015).

According to the WHO, among HIV-infected population, the prevalence of anti-HCV was highest in persons who inject drugs (82.4%), followed by men who have sex with men (6.4%), and was much lower in HIV infected persons without higher risk behaviors (2.4%). Globally, Eastern Europe and central Asia account for the largest proportion of HIV-infected persons who have serological evidence of past or present HCV infection (27%), because of injection drug use (WHO, 2017).

The main existing treatment options:

PEG-IFN alfa in combination with ribavirin is an alternative treatment for CHC infection in these co-infected patients. Since the approval of the direct acting antivirals (DAAs), PEG-IFN alfa in combination with ribavirin is no longer considered the standard of care, and the recommendations for treatment are identical to those for HCV mono-infected patients, dependent on the HCV genotype, stage of cirrhosis and naïve/treatment failure status and include mainly IFN-free options (EASL recommendations 2017, American asso. of study of Liver 2017).

Combination therapies DAAs (simeprevir, sofosbuvir) have demonstrated a considerable benefit with statistically significantly higher SVR rates including patients with and without cirrhosis, treatment-naïve patients, and patients who have not responded to previous therapy. In settings where none of these options is available, the combination of PEG-IFN alfa and ribavirin remains acceptable.

Natural history of the condition in the (untreated) population:

Due to shared routes of transmission, 25-30% of HIV-infected patients are infected with HCV. Inversely, 8% of HCV infected patients are infected with HIV (Bichoupan et al., 2014). The natural history of HCV infection is exacerbated by the presence of HIV infection. HIV-infected patients are less likely to clear HCV following acute infection, and therefore have higher HCV-RNA loads leading to more rapid progression of HCV-related liver disease than those without HIV infection (Sulkowski MS, 2008). Human immunodeficiency virus infection has been associated with persistent HCV viremia, higher HCV viral load, and with reduced response to interferon-based HCV therapy. The increased risk of CHC infection and higher HCV-RNA levels are seen in HIV infected patients, and it is believed to be in part related to a decline in CD4 and CD8 T-cell response to HCV infection (Hernandez et al., 2011).

Certain factors, such as co-infection with HIV or the HBV and prevalent coexistent liver diseases such as nonalcoholic steatohepatitis, are well-recognized contributors to accelerated fibrosis progression. Immunosuppression leads to more rapid fibrosis progression, particularly in the settings of HIV/HCV co-infection (AASLD, 2017).

According to CDC, HIV/HCV co-infection more than triples the risk for liver disease, liver failure, and liver-related death (CDC, 2018). According to EuroSIDA database, the mortality of non-liver related deaths and liver-related deaths were 0.10% and 0.03% respectively, among HIV patients with anti-HCV positive serostatus (Rockstroh et al., 2013). In Canadian HIV/ HCV co-infection cohort study (2003 to 2014) it was reported that the mortality rate was 3.65/100 person-years where the standardized mortality ratio (SMR) was 9.3 for men and 19.4 for women. The main causes for death were liver related deaths (28%), drug overdose (18%), AIDS-related deaths (4%) and deaths due to unknown causes (26%) (Peters et al., 2014).

Important co-morbidities:

Risk of AIDS was reported to be increased 2-folds among co-infected patients as compared to HIV mono-infected. An Italian cohort study showed increases in bacterial and mycotic infections among co-infected population. The Women's Interagency HIV Study found increased bacterial pneumonia, HIV encephalopathy, and wasting syndrome among co-infected patients (Operskalski et al., 2011).

Hepatitis C-associated liver disease, including fibrosis, cirrhosis, and end-stage liver disease, is accelerated in HIV-HCV co-infected individuals. Progression to cirrhosis is threefold higher in co-infected than mono-infected patients, and approximately 33% progress to cirrhosis in less than 20 years (Operskalski et al., 2011).

Kidney diseases such as proteinuria and acute renal failure, diabetes mellitus, neurocognitive-motor dysfunction and bone complications like osteonecrosis or osteoporosis are significantly higher in HIV/HCV patients as compared to mono-infected patients. HIV/HCV co-infection is also associated with a higher prevalence of cardiovascular disease than HIV mono-infection individuals (Operskalski et al., 2011).

SI.6 Polycythaemia vera (PV)

Incidence:

The overall incidence of PV in the European Union (EU) EU is estimated to be 0.4–2.8 per 100,000 patients per year. (Nurgat, Lawrence, 2022, Vannucchi et al., 2015)

Prevalence:

In 2021, the overall prevalence of PV in the EU was approximately 3 in 10,000 people. (EMA, 2021)

Demographics and risk factors:

The median age at PV diagnosis ranges from 61 to 65 years. (Shallis et al., 2021)

The main existing treatment options:

Current treatments in PV are directed at reducing the risk of thrombosis and haemorrhage, and transformation to acute myeloid leukaemia and myelofibrosis (MF), and at the palliation of symptoms. (How, Hobbs, 2022, Thiele et al., 2022)

To prevent thrombo-haemorrhagic complications, all patients require phlebotomies. Phlebotomy can be initiated as an emergency treatment at diagnosis in patients with very high haematocrit (HCT) levels and clinical signs of hyperviscosity, and also as a longer-term maintenance treatment to keep HCT

levels below 45 % to effectively reduce the risk of thrombotic events .(Thiele et al., 2022, Tremblay, Mascarenhas, 2020, Tefferi, Barbui, 2023)

In addition, daily low dose aspirin (81-100 mg) is recommended in all PV patients, in the absence of contraindications. (Gerds et al., 2021, Thiele et al., 2022, Vannucchi et al., 2015, Tefferi, Barbui, 2023)

Cytoreductive therapy is dictated by individual risk for thrombosis, which considers 2 major risk factors: age >60 years and history of thrombosis. The presence of either one of these 2 risk factors defines high-risk for thrombosis and their absence low-risk. (Thiele et al., 2022)

First-line cytoreductive treatment in PV is hydroxyurea (HU)-based antiplatelet therapy. The exact mechanism of action of HU is unknown, its most important effect appears to be in blocking the ribonucleotide reductase system resulting in the inhibition of deoxyribonucleic acid (DNA) synthesis. Dosing depends on the clinical response and the effect on the full blood count (FBC); the recommended dose of HU is initially 15-20 mg/kg, adjusted according to response on HCT and platelet count; a usual daily dose being 500-1000 mg given orally. PV patients treated with HU may develop resistance to the drug or intolerance. Symptoms of intolerance may also include gastrointestinal symptoms, pneumonitis, and fever at any dose of HU. (Nurgat, Lawrence, 2022) Additionally, skin ulcers, a reduction in blood cells, gastrointestinal problems, oral ulcers, stomatitis, hyperkeratosis, or actinic keratosis have been reported as symptoms of HU intolerance (Griesshammer et al., 2015). HU presents a potential genotoxic risk that contraindicates conception during treatment for both, men and women. In addition, patients who have received or are receiving HU for long periods have developed secondary leukaemia, with no established link to HU treatment or the primary disease itself, or skin cancer. (Bristol-Myers Squibb, 2021, Cheplapharm, 2023) Consequently, younger patients, who may have had longer exposure to HU, potentially have an increased carcinogenic risk (Tremblay, Mascarenhas, 2020). Of note, although assumed in multiple publications, neither prospective nor well-designed retrospective studies in PV patients implicate HU as amplifying the intrinsic vulnerability of PV patients for leukaemic transformation (Tefferi, Barbui, 2023).

Another PEG-formulation of IFN-α (ropegIFN-α-2b, Besremi) is authorised as first-line monotherapy in adults for the treatment of PV without symptomatic splenomegaly since 2019. (EMA, 2022a)

In second-line treatment, ruxolitinib is indicated in cases of resistance or intolerance to HU at a dose of 10 mg given orally twice daily. Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. (EMA, 2023). Furthermore, Barbui et al found that patients treated with ruxolitinib have a 2 fold higher risk for the development of non-melanoma cancer as patients treated with interferon alfa.

Natural history of the indicated condition in the untreated population:

PV characteristically displays trilineage (erythroid, megakaryocytic and granulocytic) proliferation in the bone marrow with predominantly erythrocytosis in the peripheral blood and commonly suppressed endogenous erythropoietin production. (Amerikanou et al., 2022)

Clinical features in PV include mild-to moderate degree of splenomegaly, mild-to-moderate degree of constitutional symptoms, including fatigue and pruritus, weight loss, night sweats, early satiety, bone pain, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia), thrombotic and bleeding complications, and risk of leukaemic transformation or fibrotic progression. (Gerds et al., 2022, Tefferi et al., 2018b)

About one-third (36 %) of PV patients present with palpable splenomegaly, 14 % with significant constitutional symptoms, and 25 % with a history of thrombosis (15 %-16 % arterial and 8 %-13 %

venous) or major haemorrhage (4 %). Pruritus is common in PV (48 %) and may be provoked by warm water ("aquagenic"). (Tefferi, Barbui, 2023)

In a retrospective study of 1545 adult patients (median age 61 years) with WHO-defined PV, conducted by the International Working Group for myeloproliferative neoplasms (MPN) Research and Treatment, thrombosis history at diagnosis was documented in 23 % of the patients (16 % arterial and 7.4 % venous events). The rate of post-diagnosis vascular events, after a median follow-up of 6.9 years, was 21 % (12 % arterial and 9 % venous events). Leukaemic transformation incidence ranges from 5.5–18.7 % over the course of 15 years. (Tefferi et al., 2018b)

Overall survival in PV exceeds 13 years and maybe as high as 37 years in younger patients (age <40 years). Variables associated with reduced survival in PV include advanced age, leukocytosis, abnormal karyotype, SRSF2 mutation, and treatment with pipobroman, chlorambucil or radioactive phosphorous. (Thiele et al., 2022)

The analysis of JAK2 mutations plays a pivotal role in the diagnosis of PV. After the seminal discovery of the JAK2 gain-of-function mutation in 2005, additional JAK2 mutations in exon 12 were described in JAK2-V617F-negative patients with PV in 2007 (Scott et al., 2007). JAK2 mutational frequencies in PV are estimated at 97 % for JAK2-V617F (exon 14) and 3 % for other JAK2 mutations, including JAK2 exon 12. JAK2 exon 12 mutation-positive patients usually present with predominantly erythroid myelopoiesis, subnormal serum erythropoietin level and younger age at diagnosis, but were prognostically similar to their counterparts with JAK2-V617F. In PV, a higher JAK2-V617F mutant allele burden has been associated with pruritus, fibrotic transformation, and venous thrombosis. (Tefferi, Barbui, 2023)

Survival in patients with any one of the 3 JAK2 mutation-enriched MPN is significantly shorter than that of the sex- and age-adjusted control population. The major life-threatening complications in PV are leukaemic transformation, fibrotic progression and thrombosis, with incidence ranges of 5.5–18.7 %, 6–14 %, and 6–17 %, respectively, over the course of 15, 15, and 3 years. (Tefferi et al., 2018b)

SI.7 Essential thrombocythaemia (ET)

Incidence:

ET is a rare disease with a annual incidence rate of 0.38–1.7 per 100,000 in the EU. (Stockklausner et al., 2021, Titmarsh et al., 2014)

Prevalence:

In 2022, the overall prevalence of ET in the EU was approximately 3.4 in 10,000 people (EMA, 2022b).

Demographics and risk factors:

The median age at ET diagnosis ranges from 54 to 73 years (Shallis et al., 2021).

The main existing treatment options:

The main goal of current treatments in ET, similar to that of PV, are directed at reducing the risk of thrombosis and haemorrhage, and transformation to acute myeloid leukaemia and MF, as well as at the palliation of symptoms (How, Hobbs, 2022).

A risk-adapted therapy in ET patients is based on the likelihood of patients developing thrombotic complications. These complications are the leading cause of morbidity and mortality in ET patients. (Vannucchi et al., 2015)

Very low risk ET (age ≤60 years, no thrombosis history) might not require treatment while low-dose aspirin (81-100 mg) therapy is advised for low-risk disease, in the absence of contraindications. (Gerds et al., 2021, Thiele et al., 2022)

Cytoreductive therapy is dictated by individual risk for thrombosis, which considers 2 major risk factors: age >60 years and history of thrombosis. The presence of either one of these 2 risk factors defines high-risk for thrombosis and their absence low-risk. (Thiele et al., 2022)

First-line drug of choice for cytoreductive therapy is HU (Thiele et al., 2022). As described before, the exact mechanism of action is unknown for HU, while its most important effect appears to be in blocking the ribonucleotide reductase system resulting in the inhibition of DNA synthesis. Dosing depends on the clinical response and the effect on the FBC, the recommended dose of HU is initially 15–20 mg/kg, adjusted according to response on HCT and platelet count; a usual daily dose is 500–1000 mg given orally. ET patients treated with HU may develop resistance or intolerance. Symptoms of intolerance may include gastrointestinal symptoms, pneumonitis, and fever at any dose of HU. (Nurgat, Lawrence, 2022) Additionally, skin ulcers, a reduction in blood cells, gastrointestinal problems, oral ulcers, stomatitis, hyperkeratosis, or actinic keratosis have been reported as symptoms of HU intolerance (Griesshammer et al., 2015). HU treatment has a potential genotoxic risk that contraindicates conception during treatment for both men and women. In addition, patients who have received or are receiving HU for long periods have developed secondary leukaemia, with no established link to HU treatment or the primary disease itself, or skin cancer. (Bristol-Myers Squibb, 2021, Cheplapharm, 2023) Consequently, younger patients, who may have had longer exposure to HU, potentially have an increased carcinogenic risk (Tremblay, Mascarenhas, 2020). Of note, although supposed in multiple publications, neither prospective nor well-designed retrospective studies in ET patients implicate HU as amplifying the intrinsic vulnerability of ET patients for leukaemic transformation (Tefferi, Barbui, 2023).

Alternatively, anagrelide is authorised in the EU for the reduction of elevated platelet counts in at risk ET patients (60 years of age or older or a platelet count >1000×109/L or a history of thrombo-haemorrhagic events) who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. The recommended starting dose of anagrelide is initially 0.5 mg given orally twice daily with dose adjustments at weekly intervals (max 0.5 mg/day in any one week) according to the response; the usual dose is 1-3 mg daily in divided doses, the recommended maximum single dose should not exceed 2.5 mg. (Nurgat, Lawrence, 2022)

Natural history of the indicated condition in the untreated population:

ET belongs to the chronic MPNs characterised by the expansion of mature haematopoietic cells. Although this disease has an increased risk of transformation to acute leukaemia and progression to MF, the major causes of morbidity and mortality in ET are cardiovascular complications. (How, Hobbs, 2022)

The hallmarks of ET are megakaryocyte hyperplasia with resultant thrombocytosis and abnormally high platelet production (Amerikanou et al., 2022, Bose, Verstovsek, 2019).

Clinical symptoms in ET include mild splenomegaly, leukocytosis, microvascular symptoms, thrombotic and bleeding complications, increased occurrence of first trimester miscarriage, and time-dependent risk of leukaemic transformation or fibrotic progression (Tefferi et al., 2018a).

Thrombotic complications occur in 10–20 % of ET patients with a predominance of arterial thrombotic events. For example, 109 (12 %) of 891 adult ET patients experienced arterial (n=79) or venous (n=37) thrombosis after a median follow-up of 6.2 years. (Tefferi et al., 2018a, Tefferi, Barbui, 2020)

Leukaemic transformation incidence ranges from ~2.1–5.3 % over the course of 15 years for adult ET patients. (Tefferi et al., 2018a)

Median survival in ET has been reported to range from approximately 15-22 years. Age is by far the most important risk factor for survival in ET, with median survival of 35 years for patients age ≤40 years, 22 years for ages 41-60 years, and 11 years for ages >60 years. Beside age, the absolute neutrophil count, and the absolute lymphocyte count, abnormal karyotype and mutations in SF3B1, SRSF2, and TP53 might also be relevant risk factors. (Thiele et al., 2022)

The disease has been associated with genetic mutations in the genes encoding JAK2, CALR and thrombopoietin receptor (MPL), although some patients are 'triple negative'. (Bose, Verstovsek, 2019) The driver mutation distributions in ET are 50-65 % of the patients being JAK2-V617F mutated, 15-30 % being CALR mutated, and 4-8 % being MPL mutated, while 10-20 % of the patients might not express any one of the 3 mutations (i.e., are triple-negative). (Tefferi et al., 2018a)

Survival in patients with any one of the 3 JAK2 mutation-enriched MPN is significantly shorter than that of the sex- and age-adjusted control population, with median estimates of 20 years for ET. Causes of death include leukaemic transformation, with 15-year estimates of ~2.1–5.3 % for ET. (Tefferi et al., 2018a)

Part II: Module SII - Non-clinical part of the safety specification

Toxicity studies

Findings observed in PEG-IFN alfa-2a dosed animals were similar in nature to those produced by IFN alfa-2a. The most important effects, at PEG-IFN alfa-2a doses 400-fold greater than the clinical dose, were transient decreases in platelet and white blood cell (WBC) counts, protein, and calcium, elevated ALT and/or aspartate aminotransferase (AST) activity, and inflammation at the injection site.

Relevance to human usage: No

Discussion: No significant clinical risk identified in patients given suggested therapeutic doses.

Carcinogenicity

No study of the carcinogenicity potential of PEG-IFN alfa-2a has been conducted.

Relevance to human usage: N/A

Discussion: N/A

Genotoxicity

PEG-IFN alfa-2a was neither mutagenic nor clastogenic when tested in the Ames bacterial mutagenicity assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Relevance to human usage: No

Discussion: No human risk identified based on in vitro genotoxicity testing.

Reproductive and Developmental Toxicity

IFN alfa-2a has been shown to be an abortifacient in rhesus monkeys, and PEG-IFN alfa-2a can be assumed to also have such an effect. PEG-IFN alfa-2a prolonged the menstrual cycle in female monkeys, with both a decrease and delay in estradiol and progesterone levels.

Relevance to human usage: Yes

Discussion: Potential risk for humans is unknown. Effective contraception should be used during treatment. PEG-IFN alfa-2a should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Part II: Module SIII - Clinical trial exposure

SIII.1 Exposure / demographics – Clinical trials in Adults

Clinical and demographic exposure data are presented in the following sections by disease indication. Exposure and demographic data are presented by dose, duration of treatment, age group and gender, and ethnicity in clinical trials conducted in adults in the following indications:

- Pegasys® monotherapy for CHC
- Pegasys®/Ribavirin combination therapy for CHC
- Pegasys®/Ribavirin combination therapy in HIV/HCV coinfection
- Pegasys®/Ribavirin combination therapy for treatment-experienced patients (i.e., prior treatment non-responders)
- Pegasys® monotherapy for CHB

SIII.1.1 Chronic Hepatitis C Pegasys Monotherapy Trials

Monotherapy clinical trials in adults included registration studies NV15489, NV15495, NV15496 and NV15497. Across the monotherapy trials, a total of 995 patients received treatment with PEG-IFN alfa-2a; the majority (604 patients) received treatment with 180 µg of PEG-IFN alfa-2a, the recommended therapeutic dose for the general CHC population. NV15489 was a dose-finding study in which once-weekly doses of 45, 90, 180, and 270 µg of PEG-IFN alfa-2a were evaluated. Subsequent studies evaluated the 180 µg dose of PEG-IFN alfa-2a administered once weekly for 48 weeks. In NV15495, a study in cirrhotic patients, a 90 µg dose was also evaluated and in NV15496, a dose of 135 µg of PEG-IFN alfa-2a was evaluated in parallel with the 180 µg dose. These studies consistently indicated that PEG-IFN alfa-2a 180 µg was the appropriate dose to initiate therapy in CHC patients, including those with compensated cirrhosis. Duration of PEG-IFN alfa-2a exposure in these studies for the safety population is shown in Table 5.

Table 5 - Pegasys Monotherapy Treatment: Cumulative Number of Weeks Exposure by Dose

	48 Weeks PEG-IFN 45 µg (N=20)	48 Weeks PEG-IFN 90 µg (N=116)	48 Weeks PEG-IFN 135 µg (N=215)	48 Weeks PEG-IFN 180 µg (N=1113)	48 Weeks PEG-IFN 270 µg (N=40)	Total (N=1504)
Cumulative up to 4 weeks	20 (100.0%)	116 (100.0%)	215 (100.0%)	1113 (100.0%)	40 (100.0%)	1504 (100.0%)
5 - 8 weeks	20 (100.0%)	116 (100.0%)	211 (98.1%)	1091 (98.0%)	39 (97.5%)	1477 (98.2%)
9 - 12 weeks	20 (100.0%)	115 (99.1%)	208 (96.7%)	1075 (96.6%)	39 (97.5%)	1457 (96.9%)
13 - 16 weeks	20 (100.0%)	112 (96.6%)	206 (95.8%)	1059 (95.1%)	37 (92.5%)	1434 (95.3%)
17 - 20 weeks	19 (95.0%)	111 (95.7%)	205 (95.3%)	1033 (92.8%)	36 (90.0%)	1404 (93.4%)
21 - 24 weeks	19 (95.0%)	110 (94.8%)	205 (95.3%)	1021 (91.7%)	35 (87.5%)	1390 (92.4%)
25 - 28 weeks	19 (95.0%)	109 (94.0%)	202 (94.0%)	994 (89.3%)	34 (85.0%)	1358 (90.3%)
29 - 32 weeks	19 (95.0%)	104 (89.7%)	193 (89.8%)	931 (83.6%)	32 (80.0%)	1279 (85.0%)
33 - 36 weeks	19 (95.0%)	103 (88.8%)	190 (88.4%)	915 (82.2%)	32 (80.0%)	1259 (83.7%)
37 - 40 weeks	18 (90.0%)	103 (88.8%)	187 (87.0%)	896 (80.5%)	31 (77.5%)	1235 (82.1%)
41 - 44 weeks	18 (90.0%)	102 (87.9%)	182 (84.7%)	874 (78.5%)	31 (77.5%)	1207 (80.3%)
45 - 48 weeks	17 (85.0%)	97 (83.6%)	177 (82.3%)	850 (76.4%)	31 (77.5%)	1172 (77.9%)
> 48 weeks	0	3 (2.6%)	3 (1.4%)	32 (2.9%)	0	38 (2.5%)

Source: Studies: NR15961, NV15489, NV15495, NV15496, NV15497, and NV15801. Also monotherapy arms from HIV/HCV non-responders and combination therapy were added into the above table.

The mean cumulative dose exposure received during the 48-week treatment period was 94% of the maximum possible cumulative dose received for the PEG-IFN alfa-2a 45 µg group, 90% for each of the PEG-IFN alfa-2a 90 µg and 135 µg groups, 87% for the PEG-IFN alfa-2a 180 µg group, and 75% for the PEG-IFN alfa-2a 270 µg group (Table 6).

Table 6 - Pegasys Monotherapy Treatment: Exposure by Dose

	48 Weeks PEG-IFN 45 µg (N=20)	48 Weeks PEG-IFN 90 µg (N=116)	48 Weeks PEG-IFN 135 µg (N=215)	48 Weeks PEG-IFN 180 µg (N=1113)	48 Weeks PEG-IFN 270 µg (N=40)	Total (N=1504)
Total cumulative dose for PEG-IFN						
Mean	2020	3877	5820	7250	9780	6783
SD	341.5	928.9	1400.1	2213.5	3968.1	2422.2
SEM	76.4	86.2	95.5	66.3	627.4	62.5
Median	2138	4320	6480	8640	12128	7830
Q1-Q3	2048-2160	3957-4320	6062-6480	6480-8640	6785-12960	5040-8640
Min-Max	675-2160	540-4680	270-6885	180-9000	676-12960	180-12960
n	20	116	215	1113	40	1504

Source: Studies: NR15961, NV15489, NV15495, NV15496, NV15497, and NV15801. Also monotherapy arms from HIV/HCV non-responders and combination therapy were added into the above table

Across all doses used in these studies, the majority of patients exposed to PEG-IFN alfa-2a were male, their median age at entry into the studies ranged from 41 to 46 years (Table 7) and their ethnicity was predominately Caucasian (Table 8).

Table 7 - Pegasys Monotherapy Treatment: Age and Gender by Dose Groups

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
48 Weeks PEG-IFN 45 µg	18-40	6	2	4.6	1.8
	41-65	7	5	6.3	4.4
48 Weeks PEG-IFN 90 µg	18-40	19	9	15.6	8.2
	41-65	64	20	54.1	16.3
	>=66	2	2	1.8	1.8
48 Weeks PEG-IFN 135 µg	18-40	69	22	58.1	18.4
	41-65	88	34	72.2	28.8
	>=66	0	2	0.0	1.8
48 Weeks PEG-IFN 180 µg	18-40	384	139	311.8	109.2
	41-65	417	163	334.9	129.6
	>=66	7	3	5.1	2.3
48 Weeks PEG-IFN 270 µg	18-40	13	3	11.2	2.4
	41-65	21	3	15.8	2.0

Source: Studies: NR15961, NV15489, NV15495, NV15496, NV15497, and NV15801. Also monotherapy arms from HIV/HCV non-responders and combination therapy were added into the above table.

Table 8 - Pegasys Monotherapy Treatment: Exposure by Ethnic Origin

		Persons		Person Years	
	Ethnic Origin	Male	Female	Male	Female
48 Weeks PEG-IFN 45 µg	Caucasian	12	6	10.0	5.3
	Black	1	1	0.9	0.9
48 Weeks PEG-IFN 90 µg	Caucasian	79	27	67.5	22.7
	Black	1	0	0.3	0.0
	Oriental/Asian	2	1	1.4	0.9
	Hispanic	2	1	1.7	0.9
	Other	1	2	0.5	1.8
48 Weeks PEG-IFN 135 µg	Caucasian	139	50	116.5	41.7
	Black	8	1	6.4	0.9
	Oriental/Asian	6	3	4.7	2.8
	Hispanic	3	1	1.9	0.9
	Other	1	3	0.9	2.7
48 Weeks PEG-IFN 180 µg	Caucasian	673	254	546.0	202.1
	Black	46	22	33.4	15.5
	Oriental/Asian	35	15	30.2	12.8
	Hispanic	44	10	33.5	7.1
	Other	10	4	8.7	3.6
48 Weeks PEG-IFN 270 µg	Caucasian	30	5	23.4	3.5
	Black	3	1	2.7	0.9
	Hispanic	1	0	0.9	0.0

Source: Studies: NR15961, NV15489, NV15495, NV15496, NV15497, and NV15801. Also monotherapy arms from HIV/HCV non-responders and combination therapy were added into the above table.

Patients with cirrhosis and transition to cirrhosis were included in all studies, with the exception of the initial dose finding study of PEG-IFN alfa-2a, NV15489 (Table 9).

Table 9 - Pegasys Monotherapy Treatment: Exposure by Special Population

		Persons	Years
48 Weeks PEG-IFN 45 µg	Transition of Cirrhosis	3	2.7
	No Cirrhosis	17	14.4
48 Weeks PEG-IFN 90 µg	Cirrhosis	76	62.0
	Transition of Cirrhosis	20	18.1
	No Cirrhosis	20	17.8
48 Weeks PEG-IFN 135 µg	Cirrhosis	19	14.1
	Transition of Cirrhosis	23	19.3
	No Cirrhosis	173	146.0
48 Weeks PEG-IFN 180 µg	Cirrhosis	170	133.3
	Transition of Cirrhosis	68	58.2
	No Cirrhosis	875	701.4
48 Weeks PEG-IFN 270 µg	Transition of Cirrhosis	1	0.0
	No Cirrhosis	39	31.3

Source: Studies: NR15961, NV15489, NV15495, NV15496, NV15497, and NV15801. Also monotherapy arms from HIV/HCV non-responders and combination therapy were added into the above table.

SIII.1.2 Chronic Hepatitis C Pegasys/Ribavirin Combination Therapy Trials

The combined treatment of Pegasys with Ribavirin was evaluated in registration studies NV15942, NV15801 and NV17317. A total of 451 CHC patients in study NV15801 and 1284 CHC patients in study NV15942 were treated with 180 µg PEG-IFN alfa-2a plus 800 or 1000/1200 mg ribavirin for 24 or 48 weeks; HCV genotypes 1, 2 and 3 were enrolled in these studies. In NV17317, CHC patients with HCV genotype 2 or 3 were treated for 16 weeks (731 patients) or 24 weeks (728 patients) with 180 µg PEG- IFN alfa-2a plus 800 mg ribavirin. Duration of exposure in these studies for the safety population is shown in Table 10 by weeks of treatment for the three patient group assigned to 48, 24 or 16 weeks of combination treatment with 180 µg PEG-IFN alfa-2a plus ribavirin (any dose) and Table 11 summarizes the overall exposure. In study NV15942 the mean cumulative dose of PEG-IFN alfa-2a in the two 48-week arms of the study were similar and represented approximately 80% of the cumulative dose achieved if all patients completed the full course of treatment. In study NV15801 the median cumulative doses of PEG-IFN alfa-2 in the monotherapy and combination arm were similar. A higher proportion of patients received treatment up to a duration of at least 45 weeks in the combination treatment arm than in the monotherapy treatment arm. Study NV17317 and the two arms of study NV15942 exposed patients to drug for a planned duration of 24 weeks. Exposure by age group and gender is summarized in Table 12 and by ethnicity in Table 13. Patients with cirrhosis and transition to cirrhosis were included in all three of these studies as can be seen in Table 14.

Table 10 - Pegasys/Ribavirin Combination Treatment: Cumulative Number of Weeks Exposure

	48 Weeks PEG-IFN 180 µg Ribavirin (N=1248)	48 Weeks PEG-IFN 180 µg Ribavirin (N=1215)	24 Weeks PEG-IFN 180 µg Ribavirin (N=731)	16 Weeks Total (N=3194)
Cumulative up to 4 weeks	1248 (100.0%)	1215 (100.0%)	731 (100.0%)	3194 (100.0%)
5 - 8 weeks	1236 (99.0%)	1199 (98.7%)	718 (98.2%)	3153 (98.7%)
9 - 12 weeks	1220 (97.8%)	1184 (97.4%)	710 (97.1%)	3114 (97.5%)
13 - 16 weeks	1202 (96.3%)	1160 (95.5%)	698 (95.5%)	3060 (95.8%)
17 - 20 weeks	1183 (94.8%)	1120 (92.2%)	31 (4.2%)	2334 (73.1%)
21 - 24 weeks	1163 (93.2%)	1097 (90.3%)	2 (0.3%)	2262 (70.8%)
25 - 28 weeks	1098 (88.0%)	40 (3.3%)	0	1138 (35.6%)
29 - 32 weeks	1016 (81.4%)	2 (0.2%)	0	1018 (31.9%)
33 - 36 weeks	973 (78.0%)	1 (<0.1%)	0	974 (30.5%)
37 - 40 weeks	947 (75.9%)	1 (<0.1%)	0	948 (29.7%)
41 - 44 weeks	932 (74.7%)	1 (<0.1%)	0	933 (29.2%)
45 - 48 weeks	921 (73.8%)	1 (<0.1%)	0	922 (28.9%)
> 48 weeks	32 (2.6%)	0	0	32 (1.0%)

Source: Studies: NV15801 (only Pegasys/Ribavirin combination therapy), NV15942, NV17317

Table 11 - Pegasys/Ribavirin Combination Treatment: Summary of Exposure

	48 Weeks PEG-IFN 180 µg Ribavirin (N=1248)	24 Weeks PEG-IFN 180 µg Ribavirin (N=1215)	16 Weeks PEG-IFN 180 µg Ribavirin (N=731)	Total (N=3194)
Total cumulative dose for PEG-IFN				
Mean	7086	3990	2780	4923
SD	2195.5	779.1	421.3	2316.1
SEM	62.1	22.4	15.6	41.0
Median	8460	4320	2880	4320
Q1-Q3	5580-8640	4140-4320	2880-2880	2880-7290
Min-Max	180-9540	180-8640	180-4320	180-9540
n	1248	1215	731	3194
Total cumulative dose for Ribavirin				
Mean	272536	133512	85048	176711
SD	100480.3	33798.3	13934.3	103158.5
SEM	2845.4	969.6	515.4	1825.6
Median	268800	133600	89200	134400
Q1-Q3	210400-337800	129000-135200	86800-89600	90400-253600
Min-Max	600-435600	800-205800	400-135600	400-435600
n	1247	1215	731	3193

Source: Studies: NV15801 (only Pegasys/Ribavirin combination therapy), NV15942, NV17317

Table 12 - Pegasys/Ribavirin Combination Treatment: Exposure by Age Group and Gender

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Ribavirin	18-40	348	172	281.2	137.5
	41-65	473	230	376.1	183.0
	>=66	14	11	10.9	9.3
24 Weeks PEG-IFN 180 µg + Ribavirin	18-40	274	144	120.1	63.9
	41-65	500	278	219.2	120.5
	>=66	9	10	4.3	4.1
16 Weeks PEG-IFN 180 µg + Ribavirin	18-40	106	76	31.7	22.8
	41-65	328	200	98.1	59.8
	>=66	13	8	4.0	2.3

Source: Studies: NV15801 (only Pegasys/Ribavirin combination therapy), NV15942, NV17317

Table 13 - Pegasys/Ribavirin Combination Treatment: Exposure by Ethnic Origin

		Persons		Person Years	
	Ethnic Origin	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Ribavirin	Caucasian	730	351	584.2	282.7
	Black	27	21	19.9	15.2
	Oriental/Asian	55	29	45.7	23.2
	Hispanic	16	9	13.1	7.4
	Other	7	3	5.1	1.3
24 Weeks PEG-IFN 180 µg + Ribavirin	Caucasian	684	389	300.4	169.5
	Black	22	15	9.9	6.4
	Oriental/Asian	34	14	14.9	6.1
	Hispanic	41	10	17.5	4.6
	Other	2	4	0.9	1.8
16 Weeks PEG-IFN 180 µg + Ribavirin	Caucasian	382	252	114.5	75.0
	Black	13	9	3.7	2.7
	Oriental/Asian	15	7	4.3	2.1
	Hispanic	34	14	10.3	4.3
	Other	3	2	0.9	0.6

Source: Studies: NV15801 (only Pegasys/Ribavirin combination therapy), NV15942, NV17317

Table 14 - Pegasys/Ribavirin Combination Treatment: Exposure by Special Populations

		Persons	Person Years
48 Weeks PEG-IFN 180 µg + Ribavirin	Cirrhosis [a]	116	92.3
	Transition of Cirrhosis [b]	146	115.7
	No Cirrhosis	986	790.0
24 Weeks PEG-IFN 180 µg + Ribavirin	Cirrhosis	195	84.5
	Transition of Cirrhosis	85	38.7
	No Cirrhosis	935	408.8
16 Weeks PEG-IFN 180 µg + Ribavirin	Cirrhosis	185	55.6
	No Cirrhosis	546	163.1

a Cirrhosis includes mild, moderate, or marked necroinflammatory changes with cirrhosis.
b Transition to cirrhosis includes mild, moderate, or marked necroinflammatory changes with incomplete septa.Source: Studies: NV15801 (only Pegasys/Ribavirin combination therapy), NV15942, NV17317

SIII.1.3 Pegasys/Ribavirin Combination Therapy Trials in HIV/HCV Co- infected Patients

Clinical trials with Pegasys/Ribavirin studying HIV/HCV co-infected adult patients include registration studies NR15961 and NV18209. The mean cumulative doses of PEG-IFN alfa-2a were similar in the two groups in NR15961 and represented 81% to 82% of the mean cumulative dose achieved if all patients had completed the full treatment as planned. In NV18209, the mean cumulative doses of PEG-IFN alfa-2a were similar in both groups and represented 66% to 69% of the mean cumulative dose achieved if all patients had completed the full treatment as planned. Table 15 gives the cumulative number of weeks of exposure and Table 16 summarizes the overall exposure.

Table 15 - Pegasys/Ribavirin Combination Treatment in HIV/HCV Coinfection Trials: Cumulative Number of Weeks of Exposure

	48 Weeks PEG-IFN 180 µg Ribavirin (N=697)
Cumulative up to 4 weeks	697 (100.0%)
5 - 8 weeks	664 (95.3%)
9 - 12 weeks	640 (91.8%)
13 - 16 weeks	624 (89.5%)
17 - 20 weeks	588 (84.4%)
21 - 24 weeks	560 (80.3%)
25 - 28 weeks	532 (76.3%)
29 - 32 weeks	493 (70.7%)
33 - 36 weeks	459 (65.9%)
37 - 40 weeks	437 (62.7%)
41 - 44 weeks	423 (60.7%)
45 - 48 weeks	411 (59.0%)
> 48 weeks	22 (3.2%)

Source: Studies: NR15961(only Pegasys®/Ribavirin combination therapy), NV18209.

Table 16 - Pegasys/Ribavirin Combination Treatment in HIV/HCV Coinfection Trials: Summary of Exposure

	48 Weeks PEG-IFN 180 µg Ribavirin (N=697)
Total cumulative dose for PEG-IFN	
Mean	6382
SD	2710.5
SEM	102.7
Median	7920
Q1-Q3	4455-8640
Min-Max	180-9180
n	697
Total cumulative dose for Ribavirin	
Mean	222273
SD	105255.7
SEM	3986.8
Median	258400
Q1-Q3	144800-269200
Min-Max	800-438000
n	697

Source: Studies: NR15961(only Pegasys®/Ribavirin combination therapy), NV18209.

Table 17 shows a breakdown of treated patients by age and gender and Table 18 by patient ethnicity in HIV/HCV coinfection trials. Table 19 presents patients with cirrhosis in the HIV/HCV coinfection trials.

Table 17 - Pegasys/Ribavirin Combination Treatment in HIV/HCV Coinfection Trials: Exposure by Age Group and Gender

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Ribavirin	18-40	204	69	153.7	51.6
	41-65	354	67	241.6	43.0
	>=66	2	1	1.1	0.5

Figures for age represent values from the Safety Populations for all studies shown.
Source: Studies: NR15961 (only Pegasys®/Ribavirin combination therapy), NV18209

Table 18 - Pegasys/Ribavirin Combination Treatment in HIV/HCV Coinfection Trials: Exposure by Ethnic Origin

		Persons		Person Years	
	Ethnic Origin	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Ribavirin	Caucasian	404	87	294.9	62.4
	Black	128	41	80.0	25.3
	Oriental/Asian	5	1	4.4	0.7
	Hispanic	18	4	14.5	3.2
	Other	5	4	2.5	3.3

Source: Studies: NR15961(only Pegasys®/Ribavirin combination therapy),NV18209)

Table 19 - Pegasys/Ribavirin Combination Treatment in HIV/HCV Coinfection Trials: Exposure by Special Populations

		Persons	Person Years
48 Weeks PEG-IFN 180 µg + Ribavirin	Cirrhosis	90	61.8
	No Cirrhosis	607	429.6

Cirrhosis judged by the investigator or local pathologist based on pretreatment liver biopsy.
Source: Studies: NR15961(only Pegasys®/Ribavirin combination therapy), NV18209.)

SIII.1.4 Pegasys/Ribavirin Combination Therapy: Chronic Hepatitis C Prior Treatment Non-Responder Patients

The registration clinical trial MV17150 with Pegasys and Ribavirin was conducted in previously treated patients who did not respond to treatment. In this study, in the two 48- week treatment groups, 72% of patients received the full treatment course of PEG-IFN alfa-2a (Table 20). In the 72-week treatment groups, 55% and 54% of patients received the full course of PEG-IFN alfa-2a. Table 21 summarizes the overall exposure in this study.

Table 20 - Pegasys/Ribavirin Treatment in CHC trials in Prior Non-Responder Patients: Cumulative Number of Weeks of Exposure

	48 Weeks PEG-IFN 180 µg Ribavirin (N=313)	72 Weeks PEG-IFN 180 µg Ribavirin (N=156)	48 Weeks PEG-IFN 360/180 µg Ribavirin (N=156)	72 Weeks PEG-IFN 360/180 µg Ribavirin (N=317)	Total (N=942)
Cumulative up to 4 weeks	313 (100.0%)	156 (100.0%)	156 (100.0%)	317 (100.0%)	942 (100.0%)
5 - 8 weeks	309 (98.7%)	153 (98.1%)	150 (96.2%)	310 (97.8%)	922 (97.9%)
9 - 12 weeks	304 (97.1%)	150 (96.2%)	148 (94.9%)	301 (95.0%)	903 (95.9%)
13 - 16 weeks	302 (96.5%)	148 (94.9%)	148 (94.9%)	296 (93.4%)	894 (94.9%)
17 - 20 weeks	295 (94.2%)	143 (91.7%)	147 (94.2%)	286 (90.2%)	871 (92.5%)
21 - 24 weeks	293 (93.6%)	141 (90.4%)	143 (91.7%)	280 (88.3%)	857 (91.0%)
25 - 28 weeks	285 (91.1%)	139 (89.1%)	140 (89.7%)	277 (87.4%)	841 (89.3%)
29 - 32 weeks	266 (85.0%)	130 (83.3%)	132 (84.6%)	252 (79.5%)	780 (82.8%)
33 - 36 weeks	248 (79.2%)	117 (75.0%)	124 (79.5%)	229 (72.2%)	718 (76.2%)
37 - 40 weeks	243 (77.6%)	115 (73.7%)	121 (77.6%)	222 (70.0%)	701 (74.4%)
41 - 44 weeks	238 (76.0%)	114 (73.1%)	115 (73.7%)	218 (68.8%)	685 (72.7%)
45 - 48 weeks	232 (74.1%)	111 (71.2%)	115 (73.7%)	214 (67.5%)	672 (71.3%)
49 - 52 weeks	39 (12.5%)	106 (67.9%)	14 (9.0%)	207 (65.3%)	366 (38.9%)
53 - 56 weeks	0	102 (65.4%)	0	201 (63.4%)	303 (32.2%)
57 - 60 weeks	0	99 (63.5%)	0	194 (61.2%)	293 (31.1%)
61 - 64 weeks	0	97 (62.2%)	0	191 (60.3%)	288 (30.6%)
65 - 68 weeks	0	93 (59.6%)	0	189 (59.6%)	282 (29.9%)
69 - 72 weeks	0	93 (59.6%)	0	186 (58.7%)	279 (29.6%)
> 72 weeks	0	4 (2.6%)	0	21 (6.6%)	25 (2.7%)

Source: Study MV17150

Table 21 - Pegasys/Ribavirin Treatment in CHC trials in Prior Non-Responder Patients: Summary of Exposure

	48 Weeks PEG-IFN 180 µg Ribavirin (N=313)	72 Weeks PEG-IFN 180 µg Ribavirin (N=156)	48 Weeks PEG-IFN 360/180 µg Ribavirin (N=156)	72 Weeks PEG-IFN 360/180 µg Ribavirin (N=317)	Total (N=942)
Total cumulative dose for PEG-IFN					
Mean	7418	9652	9338	11566	9502
SD	2090.4	3900.9	2555.3	4348.0	3777.3
SEM	118.2	312.3	204.6	244.2	123.1
Median	8640	11678	10620	14400	8820
Q1-Q3	6300-8640	5850-12960	8753-10800	7740-15120	7200-12870
Min-Max	180-9360	180-13320	360-13140	360-16560	180-16560
n	313	156	156	317	942
Total cumulative dose for Ribavirin					
Mean	316926	413015	303260	395358	356969
SD	97878.6	173360.9	103769.6	180740.4	151325.5
SEM	5532.4	13880.0	8308.2	10151.4	4930.5
Median	336000	466300	334000	471800	363700
Q1-Q3	267600-400800	264000-596400	250000-397200	236000-526600	252000-471600
Min-Max	7200-439200	3600-614400	2400-415200	3000-627600	2400-627600
n	313	156	156	317	942

Source: Studies: Study MV17150.

Table 22 shows a breakdown of treated prior non-responder patients by age and gender and Table 23 by patient ethnicity. Table 24 provides the number of non-responder HCV patients with cirrhosis that enrolled into each arm of this study; this ranged from 25% - 30% of the total number of patients enrolled in each arm.

Table 22 - Pegasys/Ribavirin Treatment in CHC trials in Prior Non-Responder Patients: Exposure by Age Group and Gender

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Ribavirin	18-40	39	11	34.1	10.0
	41-65	169	88	133.1	70.9
	>=66	4	2	3.6	1.8
72 Weeks PEG-IFN 180 µg + Ribavirin	18-40	12	4	13.4	3.3
	41-65	92	43	100.3	45.0
	>=66	3	2	2.5	2.7
48 Weeks PEG-IFN 360/180 µg + Ribavirin	18-40	14	12	11.4	9.0
	41-65	76	45	61.3	36.3
	>=66	4	5	2.8	3.8
72 Weeks PEG-IFN 360/180 µg + Ribavirin	18-40	42	17	44.8	20.5
	41-65	158	92	165.5	94.3
	>=66	3	5	3.6	3.1

Figures for age represent values from the Safety Populations for all studies shown.
Source: Study MV17150.

Table 23 - Pegasys/Ribavirin Treatment in CHC trials in Prior Non-Responder Patients: Exposure by Ethnic Origin

		Persons		Person Years	
	Ethnic Origin	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Ribavirin	Caucasian	188	94	150.9	76.8
	Black	20	5	16.5	4.1
	Oriental/Asian	3	2	2.8	1.9
	Other	1	0	0.6	0.0
72 Weeks PEG-IFN 180 µg + Ribavirin	Caucasian	94	43	101.8	45.4
	Black	12	5	13.0	5.1
	Oriental/Asian	1	0	1.4	0.0
	Other	0	1	0.0	0.6
48 Weeks PEG-IFN 360/180 µg + Ribavirin	Caucasian	87	54	69.1	43.8
	Black	3	7	2.7	4.3
	Oriental/Asian	4	1	3.7	0.9
72 Weeks PEG-IFN 360/180 µg + Ribavirin	Caucasian	182	97	192.0	103.7
	Black	14	15	13.9	12.8
	Oriental/Asian	7	0	7.9	0.0
	Other	0	2	0.0	1.4

Source: Study MV17150.

Table 24 - Pegasys/Ribavirin Treatment in CHC trials in Prior Non-Responder Patients: Exposure by Special Populations

		Persons	Person Years
48 Weeks PEG-IFN 180 µg + Ribavirin	Cirrhosis	88	69.1
	No Cirrhosis	223	183.0
	Unknown	2	1.6
72 Weeks PEG-IFN 180 µg + Ribavirin	Cirrhosis	46	49.2
	No Cirrhosis	109	117.3
	Unknown	1	0.8
48 Weeks PEG-IFN 360/180 µg + Ribavirin	Cirrhosis	45	36.1
	No Cirrhosis	110	87.6
	Unknown	1	0.9
72 Weeks PEG-IFN 360/180 µg + Ribavirin	Cirrhosis	79	73.2
	No Cirrhosis	237	258.0

Source: Study MV17150

SIII.1.5 Pegasys Monotherapy in Chronic Hepatitis B Trials

Registration clinical trials with Pegasys monotherapy in CHB patients include studies WV16240 and WV16214. Mean cumulative PEG-IFN alfa-2a doses that patients were exposed to in WV16240 accounted for ≥91% of the total planned PEG-IFN dose over the 48-week study (Table 25). The mean cumulative dose patients were exposed to equaled 91% of the planned cumulative doses in both groups in study WV16214. A summary of overall exposure shown in Table 26, by age and gender in Table 27, and by ethnicity in Table 28. Table 29 provides the number of CHB patients with cirrhosis enrolled into these studies.

Table 25 - Pegasys Monotherapy and Pegasys/Lamivudine Treatment in CHB Trials: Cumulative Number of Weeks Exposure

	48 Weeks PEG-IFN 180 µg Placebo (N=448)	48 Weeks PEG-IFN 180 µg Lamivudine 100 mg (N=450)	Total (N=898)
Cumulative up to 4 weeks	448 (100.0%)	450 (100.0%)	898 (100.0%)
5 - 8 weeks	443 (98.9%)	449 (99.8%)	892 (99.3%)
9 - 12 weeks	441 (98.4%)	447 (99.3%)	888 (98.9%)
13 - 16 weeks	441 (98.4%)	445 (98.9%)	886 (98.7%)
17 - 20 weeks	440 (98.2%)	444 (98.7%)	884 (98.4%)
21 - 24 weeks	438 (97.8%)	442 (98.2%)	880 (98.0%)
25 - 28 weeks	437 (97.5%)	438 (97.3%)	875 (97.4%)
29 - 32 weeks	435 (97.1%)	436 (96.9%)	871 (97.0%)
33 - 36 weeks	432 (96.4%)	432 (96.0%)	864 (96.2%)
37 - 40 weeks	429 (95.8%)	428 (95.1%)	857 (95.4%)
41 - 44 weeks	426 (95.1%)	427 (94.9%)	853 (95.0%)
45 - 48 weeks	419 (93.5%)	426 (94.7%)	845 (94.1%)
> 48 weeks	1 (0.2%)	29 (6.4%)	30 (3.3%)

Source: Study WV16240; Study WV16241.

Table 26 - Pegasys Monotherapy and Pegasys/Lamivudine Treatment in CHB Trials: Summary of Exposure

	48 Weeks PEG-IFN 180 µg Placebo (N=448)	48 Weeks PEG-IFN 180 µg Lamivudine 100 mg (N=450)	Total (N=898)
Total cumulative dose for PEG-IFN			
Mean	7866	7921	7893
SD	1562.9	1504.0	1533.1
SEM	73.8	70.9	51.2
Median	8640	8640	8640
Q1-Q3	7920-8640	8145-8640	8010-8640
Min-Max	180-9540	540-9000	180-9540
n	448	450	898

Source: Study WV16240; Study WV16241.

Table 27 - Pegasys Monotherapy and Pegasys/Lamivudine Treatment in CHB Trials: Exposure Age Group and Gender

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Placebo	>=18	365	83	320.0	74.3
48 Weeks PEG-IFN 180 µg + Lamivudine 100 mg	>=18	355	95	319.0	84.2

Source: Study WV16240; Study WV16241.

Table 28 - Pegasys Monotherapy and Pegasys/Lamivudine Treatment in CHB Trials: Exposure by Ethnic Origin

		Persons		Person Years	
	Ethnic Origin	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg + Placebo	Caucasian	75	15	64.1	13.5
	Black	7	0	6.4	0.0
	Oriental/Asian	279	67	246.0	59.8
	Other	4	1	3.6	0.9
48 Weeks PEG-IFN 180 µg + Lamivudine 100 mg	Caucasian	70	18	63.5	15.2
	Black	6	0	5.5	0.0
	Oriental/Asian	274	76	246.3	68.1
	Other	5	1	3.8	0.9

Source: Study WV16240; Study WV16241.

Table 29 - Pegasys Monotherapy and Pegasys/Lamivudine Treatment in CHB Patients: Exposure by Special Population

	Person		
		Persons	Years
48 Weeks PEG-IFN 180 µg + Placebo	Cirrhosis	103	90.1
	No Cirrhosis	345	304.2
48 Weeks PEG-IFN 180 µg + Lamivudine 100 mg	Cirrhosis	80	72.4
	No Cirrhosis	369	330.0

Source: Study WV16240; Study WV16241.

SIII.2 Exposure / demographics – Clinical trials in Pediatrics

SIII.2.1 Paediatric Studies in Chronic Hepatitis C

Clinical exposure and demographic data are presented in the following section for clinical studies of Pegasys, alone or in combination with ribavirin, in the treatment of HCV in paediatrics. Following are brief descriptions of each paediatric study.

Study NR16141 was a phase II, multicenter, open-label study of the safety and viral kinetic and pharmacokinetic characteristics of PEG-IFN alfa-2a monotherapy. Fourteen children between 2 and 8 years old (8 male, 6 female) with CHC infection who had not received previous IFN or ribavirin therapy were enrolled to receive weekly doses of PEG-IFN alfa-2a 180 µg x BSA (m2)/1.73 m2 for 48 weeks. Nine of the 14 patients completed 48 weeks of treatment plus 24 weeks of treatment free follow-up.

Study NV17424 (PEDS-C) was a phase III, multicenter, randomized, blinded (through at least week 24 of treatment), placebo-controlled study that compared the efficacy and safety of PEG-IFN alfa-2a (180 µg x BSA (m2)/1.73 m2) alone and in combination with ribavirin in treatment-naive children 5 to <18 years of age with chronic HCV infection and compensated liver disease. Patients who were responders at week 24 continued on treatment for a total of 48 weeks. Paediatric patients who received Pegasys monotherapy and did not respond at week 24 went on to receive compassionate use of combination therapy for up to an additional 48 weeks. More than two thirds of the patients (≥65%) were still receiving PEG-IFN alfa-2a therapy at week 47. Patients were followed for 24 weeks after the end of treatment and they had two annual visits at one year and two years after the end of treatment during the long-term follow-up period.

The cumulative number of weeks of exposure in studies NR16141 and NV17424 is shown in Table 30, and the cumulative dose of study drug in studies NR16141 and NV17424 is presented in Table 31. In study NV17424, the cumulative dose of PEG-IFN alfa-2a was similar for the PEG-IFN alfa-2a monotherapy and PEG-IFN alfa-2a plus ribavirin combination therapy groups (mean 5168 µg and 5135 µg, respectively) and was, as expected, higher in the PEG-IFN alfa-2a monotherapy non-responder/ compassionate combination therapy group (mean 8086 µg) due to the longer treatment duration (approximately 72 weeks). Table 32 displays a summary of exposure by gender and age and Table 33 shows a summary of exposure by ethnicity for NR16141 and NV17424.

Study ML17718 (CHIPS) was a non-randomized, multicenter study of Pegasys and ribavirin in the treatment of HCV in children. In this study, 65 children, 6 to 18 years of age, were divided into two treatment groups according to genotype: patients with genotype 1, 4, 5, or 6 infection (47 patients) received once-weekly sc injections of PEG- IFN alfa-2a 100 µg/m2 x BSA (maximum 180 µg) and ribavirin, 15 mg/kg/day, for 48 weeks of treatment and patients with genotype 2 or 3 infection (18 patients) received 24 weeks of the same treatment. Patients were then followed for 24 weeks after the end of treatment. There were an equal number of boys and girls in the 24-week group and their mean age was 11.9 years (range= 6.1 to 16 years). In the 48-week group, there were 21 boys and 26 girls and their mean age was 13.2 years (range = 5.8 to 17.9 years). The majority of children in both groups were white (17/18 in the 24-week group and 40/47 in the 48- week group).

The marketing authorization holder (MAH) does not have access to the CHIPS (ML17718) study dataset. The principal investigator for this investigator initiated study provided the final study report which was submitted to the Committee for Medicinal Products for Human Use (CHMP) as a follow-up measure in 2008. The publication describing this study (Sokal et al. 2010) has been used by the MAH as a reference for some of the results displayed in the pediatric application and RMP. Given that these are the only data sources available to the applicant, it is not possible to integrate safety data from this study with the other pediatric studies presented in the EU RMP.

Table 30 - Cumulative Number of Weeks Exposure in Study NR16141 and Study NV17424

	48 Weeks PEG-IFN 180 µg xBSA/1.73 m² (N=45)	52/76 Weeks PEG-IFN 180 µg xBSA/1.73 m² Plac./Ribavirin 15 mg/kg (N=28)	24/48 Weeks PEG-IFN 180 µg xBSA/1.73 m² Ribavirin 15 mg/kg (N=55)	Total (N=128)
Cumulative up to 4 weeks	45 (100.0%)	28 (100.0%)	55 (100.0%)	128 (100.0%)
5 - 8 weeks	45 (100.0%)	28 (100.0%)	55 (100.0%)	128 (100.0%)
9 - 12 weeks	45 (100.0%)	28 (100.0%)	55 (100.0%)	128 (100.0%)
13 - 16 weeks	43 (95.6%)	28 (100.0%)	55 (100.0%)	126 (98.4%)
17 - 20 weeks	43 (95.6%)	28 (100.0%)	54 (98.2%)	125 (97.7%)
21 - 24 weeks	42 (93.3%)	28 (100.0%)	54 (98.2%)	124 (96.9%)
25 - 28 weeks	39 (86.7%)	28 (100.0%)	53 (96.4%)	120 (93.8%)
29 - 32 weeks	37 (82.2%)	28 (100.0%)	40 (72.7%)	105 (82.0%)
33 - 36 weeks	36 (80.0%)	28 (100.0%)	39 (70.9%)	103 (80.5%)
37 - 40 weeks	35 (77.8%)	28 (100.0%)	38 (69.1%)	101 (78.9%)
41 - 44 weeks	35 (77.8%)	28 (100.0%)	38 (69.1%)	101 (78.9%)
45 - 48 weeks	33 (73.3%)	28 (100.0%)	38 (69.1%)	99 (77.3%)
49 - 52 weeks	5 (11.1%)	28 (100.0%)	15 (27.3%)	48 (37.5%)
53 - 56 weeks	0	26 (92.9%)	0	26 (20.3%)
57 - 60 weeks	0	14 (50.0%)	0	14 (10.9%)

Source: Studies Study 16141, NV17424

Table 31 - Cumulative Dose of Study Drug in Study NR16141 and Study NV17424 by Actual Treatment Group

	48 Weeks PEG-IFN 180 µg xBSA/1.73 m² (N=45)	52/76 Weeks PEG-IFN 180 µg xBSA/1.73 m² Plac./Ribavirin 15 mg/kg (N=28)	24/48 Weeks PEG-IFN 180 µg xBSA/1.73 m² Ribavirin 15 mg/kg (N=55)	Total (N=128)
Total cumulative dose for PEG-IFN				
Mean	4504	8086	5135	5559
SD	2275.8	2597.0	2177.6	2669.3
SEM	339.3	490.8	293.6	235.9
Median	4086	8186	4770	4968
Q1-Q3	2928-5652	6732-9819	3276-7056	3456-7749
Min-Max	990-9400	1989-13680	954-9000	954-13680
n	45	28	55	128
Total cumulative dose for Ribavirin				
Mean	.	177086	181920	180289
SD	.	67658.7	86330.3	80128.7
SEM	.	12786.3	11640.8	8795.3
Median	.	167200	170500	169500
Q1-Q3	.-.	135350-204600	103300-257200	111100-228600
Min-Max	.-.	58800-394200	70000-403200	58800-403200
n	0	28	55	83

Source: studies 16141, NV17424

Table 32 - Summary of Exposure by Gender and Age Group in Study NR16141 and Study NV17424

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg xBSA/1.73 m²	<=5	6	6	5.4	4.7
	6-11	10	9	8.4	7.9
	12-<18	10	4	6.9	3.1
52/76 Weeks PEG-IFN 180 µg xBSA/1.73 m² + Plac./Ribavirin 15 mg/kg	<=5	3	0	4.0	0.0
	6-11	6	4	7.7	5.5
	12-<18	9	6	11.0	6.4
24/48 Weeks PEG-IFN 180 µg xBSA/1.73 m² + Ribavirin 15 mg/kg	<=5	1	4	0.9	3.3
	6-11	12	13	9.5	9.7
	12-<18	14	11	11.9	8.7

Source: Studies 16141, NV17424.

Table 33 - Summary of Exposure by Ethnicity in Study NR16141 and Study NV17424

		Persons		Person Years	
	Ethnic Origin	Male	Female	Male	Female
48 Weeks PEG-IFN 180 µg xBSA/1.73 m²	Caucasian	19	17	15.8	13.8
	Black	0	1	0.0	0.9
	Oriental/Asian	2	0	1.9	0.0
	Other	5	1	3.0	0.9
52/76 Weeks PEG-IFN 180 µg xBSA/1.73 m² + Plac./Ribavirin 15 mg/kg	Caucasian	15	8	19.1	9.7
	Black	2	2	2.1	2.2
	Other	1	0	1.5	0.0
24/48 Weeks PEG-IFN 180 µg xBSA/1.73 m² + Ribavirin 15 mg/kg	Caucasian	20	25	16.2	19.0
	Black	1	0	0.9	0.0
	Oriental/Asian	2	1	1.9	0.9
	Other	4	2	3.3	1.8

aOther = American Indian or Alaskan Native or Multiracial
Source: Studies 16141, NV17424.

SIII.2.2 Paediatric Studies in Chronic Hepatitis B

Clinical exposure and demographic data are presented in the following section for clinical study YV25718 of PEG-IFN alfa-2a in the treatment of pediatric patients with CHB. Study YV25718 was included in the PV plan of Pegasys as an additional PV activity as safety results for extended long-term analysis are associated with previously identified safety concerns. Please refer to Part II Module SVII.2, as well as the final CSR submitted with this RMP update, for more information.

This was a 2:1 randomized, controlled, parallel-group, open-label, multicenter study of pegylated interferon alpha-2a (PEG-IFN) treatment compared to an untreated control. Patients without advanced fibrosis were randomized 2:1 to PEG-IFN treatment (Group A) or untreated control (Group B), respectively. Patients with advanced fibrosis were assigned to PEG-IFN treatment (Group C). Patients in Groups A and C received PEG-IFN for 48 weeks.

The first 48 weeks from randomization (or after first dose of study drug in the case of Group C) is referred to as the treatment period for Group A and Group C and as the principal observation period for Group B. The primary endpoint was assessed 24 weeks after the end of treatment/principal observation period. After completing the principal observation period (48 weeks after randomization), PEG-IFN was offered to patients in the untreated control group (Group B) who had not experienced hepatitis B e antigen (HBeAg) seroconversion. This offer remained open for up to 1 year following the Week 48 visit. The eligible patients were allowed to enter the Switch Group and to receive PEG-IFN for 48 weeks.

The cumulative number of weeks of exposure and cumulative dose of study drug in study YV25718 for Group A and Group C patients is presented in Table 34. Table 35 displays a summary of exposure by gender and age, and Table 36 presents a summary of exposure by ethnicity.

The screening period was up to 35 days (under exceptional circumstances, the screen period could be extended by 7 days). For Group A, Group B non-switch, and Group C patients, the study length was approximately 6 years (1-year treatment/ principal observation period and 5 years of follow-up). For Group B switch patients, the study length was up to approximately 8 years (1-year principal observation period, up to 1-year follow-up whilst deciding whether to switch, 1-year switch treatment period, and long-term follow-up period).

Liver elasticity using liver ultrasound elastography, a non-invasive procedure used in some countries to assess liver fibrosis, was also assessed as a substudy at specific sites in both treated and untreated patients.

A pharmacokinetic (PK) substudy was also planned in consenting/assenting patients who received PEG-IFN (those assigned to Group C, randomized to Group A or switching from Group B) with sparse PK sampling.

The results of primary analysis with clinical cut-off 9 January 2016 have already been reported in the Primary CSR.

Table 34 - Cumulative Number of Weeks Study Drug Exposure & Cumulative Dose of Study Drug in Study YV25718

	PEG-IFN Group A (N=101)	PEG-IFN Group C (N=10)	Total (N=111)
Duration of Treatment			
Cumulative up to 4 weeks	101 (100.0%)	10 (100.0%)	111 (100.0%)
5 - 8 weeks	101 (100.0%)	10 (100.0%)	111 (100.0%)
9 - 12 weeks	101 (100.0%)	10 (100.0%)	111 (100.0%)
13 - 16 weeks	100 (99.0%)	10 (100.0%)	110 (99.1%)
17 - 20 weeks	100 (99.0%)	10 (100.0%)	110 (99.1%)
21 - 24 weeks	100 (99.0%)	10 (100.0%)	110 (99.1%)
25 - 28 weeks	100 (99.0%)	10 (100.0%)	110 (99.1%)
29 - 32 weeks	99 (98.0%)	10 (100.0%)	109 (98.2%)
33 - 36 weeks	99 (98.0%)	10 (100.0%)	109 (98.2%)
37 - 40 weeks	99 (98.0%)	10 (100.0%)	109 (98.2%)
41 - 44 weeks	99 (98.0%)	10 (100.0%)	109 (98.2%)
45 - 48 weeks	99 (98.0%)	10 (100.0%)	109 (98.2%)
49 - 52 weeks	3 (3.0%)	1 (10.0%)	4 (3.6%)
Total cumulative dose (ug) for PEG-IFN			
n	101	10	111
Mean	5959.39	4609.62	5837.79
SD	2017.61	1759.43	2026.00
SEM	201	556	192
Median	6390.00	4320.00	6210.00
Q1 - Q3	4320.00 - 8460.00	3412.80 - 4770.00	4320.00 - 8235.00
Min - Max	810.0 - 8640.0	2617.2 - 8595.0	810.0 - 8640.0

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Table 35 - Study Drug Exposure by Gender and Age Group in Study YV25718

		Persons		Person Years	
	Age Group	Male	Female	Male	Female
Group A PEG-IFN	<= 5	15	8	13.5	6.5
	6 - 11	19	11	17.2	9.9
	12 - <18	30	18	27.1	15.8
Group C PEG-IFN	<= 5	5	0	4.5	0
	6 - 11	3	1	2.7	0.9
	12 - <18	0	1	0	0.9
Group A+C PEG-IFN	<= 5	20	8	18.0	6.5
	6 - 11	22	12	19.9	10.8
	12 - <18	30	19	27.1	16.7

Program: /opt/BIOSTAT/prod/cdt3518y/i25718v/t_ext02_rmp.sas / Output:
/opt/BIOSTAT/prod/cdt3518y/i25718v/reports/t_ext02_rmp.out
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Table 36 - Study Drug Exposure by Ethnic Origin in Study YV25718

		Persons			
		Not Hispanic or Latino	Not reported	Unknown	Not Hispanic or Latino
Group A PEG-IFN	Asian	54	1	1	48.3 0.9 0.9
	Black or African American	7	0	0	6.3 0 0
	Multiple	1	0	0	0.9 0 0
	White	32	0	0	28.2 0 0
	Other Race	4	1	0	3.6 0.9 0
Group C PEG-IFN	Asian	7	0	0	6.3 0 0
	Black or African American	1	0	0	0.9 0 0
	White	2	0	0	1.8 0 0
Group A+C PEG-IFN	Asian	61	1	1	54.6 0.9 0.9
	Black or African American	8	0	0	7.3 0 0
	Multiple	1	0	0	0.9 0 0
	White	34	0	0	30.0 0 0
	Other Race	4	1	0	3.6 0.9 0

Program: /opt/BIOSTAT/prod/cdt3518y/i25718v/t_ext02_re_rmp.sas / Output: /opt/BIOSTAT/prod/cdt3518y/i25718v/reports/t_ext02_re_rmp.out
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Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity to Pegasys® or any of the excipients	Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa interferon therapy	No	Patients who are hypersensitive to Pegasys® are contraindicated in the EU SmPC section 4.3 and should not continue treatment
Pregnant and/or breastfeeding women	Studies in animals with interferon alfa-2a have shown reproductive toxicity. The safety and efficacy of Pegasys® have not been established in pregnant or breastfeeding women.	No	Pegasys® is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the potential for adverse reactions in breastfed infants, breastfeeding should be discontinued prior to initiation of treatment. Refer to section 4.6 of the EU SmPC for additional information.
Severe hepatic dysfunction or decompensated cirrhosis of the liver	Use of alfa interferons, including Pegasys® alone or in combination with ribavirin, has been associated with hepatic failure and hepatic dysfunction. Pegasys® has not been evaluated in patients with decompensated cirrhosis (e.g., Child-Pugh B or C or bleeding oesophageal varices).	No	Patients with severe hepatic dysfunction or decompensated cirrhosis of the liver are contraindicated in EU SmPC section 4.3
A history of severe pre-existing cardiac disease,	Use of alfa interferons, especially in combination with ribavirin, has been	No	Patients with severe pre-existing cardiac disease, including unstable or

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
including unstable or uncontrolled cardiac disease in the previous 6 months	associated with the development of anemia that can provoke myocardial ischemia.		uncontrolled cardiac disease in the previous six months are contraindicated in EU SmPC section 4.3
HIV/HCV patients with cirrhosis and a Child-Pugh score ≥ 6	HIV/HCV co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons, including Pegasys.	No	HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6, except if only due to indirect hyperbilirubinemia caused by medicinal products such as atazanavir and indinavir are contraindicated as per EU SmPC section 4.3
Haemoglobinopathies (e.g. thalassemia, sickle-cell anemia)	A decrease in hemoglobin (Hgb) levels to <10g/deciliter (dL) was observed in up to 15% of patients treated for 48 weeks with ribavirin 1000/1200 mg in combination with PEG-IFN alfa-2a. The same was observed in up to 19% of patients in combination with IFN alfa-2a. When ribavirin 800 mg was combined with PEG-IFN alfa-2a for 24 weeks, 3% of patients had a decrease in Hgb levels to <10 g/dL. The risk of developing anemia is higher in the female population. Hemoglobinopathy or/and thalassemia are common causes of anemia, initiation of ribavirin may	No	Adequately described in Section 4.4 of the Pegasys® EU SmPC (Special warnings and precautions) that the occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of CHC patients in clinical trials on the combined treatment of Pegasys® with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin. Haemoglobinopathy (e.g. thalassaemia, sickle-cell anaemia) is a contraindication for Ribavirin as per its EU SmPC section 4.3

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	lead to life-threatening conditions e.g. hemolytic crisis.		
Neutrophil count <1500 cells/cubic meter (mm^3) and/or platelet count <90000 cells/mm^3 at screening.	Patients treated with Ribavirin combination therapy with PEG-IFN alfa-2a or IFN alfa-2a may develop moderate to severe neutropenia In clinical trials, Pegasys® treatment was associated with decreases in total WBC count and absolute neutrophil count (ANC), as well as platelet count, which returned to pre-treatment levels during the post-treatment observation period. Due to the potential for exacerbation, patients with significant neutropenia or thrombocytopenia were not included.	No	Adequately described in Section 4.4 of the EU SmPC (Special warnings and precautions) that ANC ≥ 1500 cells/mm^3 should be considered as baseline value for initiation of treatment.
Serum creatinine concentration >1.5 times the upper limit of normal (ULN) at screening.	The pharmacokinetics of ribavirin is altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Ribavirin, preferably by estimating the patient's creatinine clearance. Substantial increase in	No	Adequately described in Section 4.2 of the EU SmPC that Pegasys® should be initiated at a dose of 135 mcg in patients with severe renal impairment and end stage renal disease. Regardless of the starting dose or degree of renal impairment, monitoring and making appropriate dose reductions of Pegasys® during

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine >2 mg/dL or with creatinine clearance <50 ml/minute. There are insufficient data on the safety, efficacy and pharmacokinetics of ribavirin in patients with serum creatinine >2 mg/dL, whether or not on hemodialysis, to support specific recommendations for dose adjustments		the course of therapy in the event of adverse reactions is recommended.
In adults, a history of severe psychiatric disease, especially depression, characterized by a suicide attempt, hospitalization for psychiatric disease, or a period of disability as a result of psychiatric disease.	Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Pegasys® therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behavior (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons.	No	Adequately described in section 4.4 of the EU SmPC (Special Warnings and precautions) and is also a boxed warning. If treatment with Pegasys® is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	Patients with significant psychiatric illness were therefore not included in clinical trials.		
History of a severe seizure disorder or current anticonvulsant use.	Seizure disorder and convulsions are a rare side effect with the combination of PEG-IFN alfa-2a and ribavirin. A patient with a history of seizures is at risk for developing further seizures. Coma and convulsions have been reported during treatment with Pegasys® and Ribavirin, although rarely. To avoid confounding the effects of treatment, patients with a history of seizure disorder or current anticonvulsant use were excluded from clinical trials.	No	Listed in section 4.8 of the SmPC (Undesirable effects) as it is a rare event.

ANC= absolute neutrophil count ; CNS=Central Nervous System; EU- European Union; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus ; PEG-IFN= Peginterferon; SmPC =Summary of Product Characteristics; ULN=Upper limit normal

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	not included in the clinical development program
Breastfeeding women	not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with severe hepatic impairment	not included in the clinical development program
• Patients with severe renal impairment	not included in the clinical development program
• Patients with cardiac impairment	not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	not included in the clinical development program
Population with relevant different ethnic origin	not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	not included in the clinical development program
Other:	
• Psychiatric conditions	not included in the clinical development program
• Thyroid function	not included in the clinical development program
• Ocular effects	not included in the clinical development program
• Elderly	909
• Children	221

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Post-authorisation exposure data is available until 11 July 2023. Since then, the post-marketing exposure has not changed to a degree where the considerations on the risk evaluation need also to be updated. Data are presented separately due to different presentation of exposure data and methodology.

Note: "Proclick" is also known as the "prefilled pen".

SV.1.1 Method used to calculate exposure

Methodology and Exposure Worldwide

The estimated exposure for PEG-IFN alfa-2a was calculated based on volume of Galenical units sold and weighted length of treatment. The sales records are provided on a monthly basis.

Table 37 - Methodology for Worldwide Marketing Exposure

Indication	Genotype	Distribution	Length of treatment (weeks)	Compliance	Weighted length of treatment
Hepatitis C virus	Genotype 1/4	50%	48	65%	25.8
	Genotype 2/3	50%	24	85%	
Hepatitis B virus	-	100%	48	90%	43.2
Off–label Hematology	-	100%	52	80%	41.6

Note: Not taking into account non-responders who on are therapy longer.

Note: Not taking into account patients who are on therapy more than once.

The age and gender figures are based on the assumption that 65% of patients were male and 35% female and that 5% of patients were between 0 and 25 years old, 60% were between 25 and 50 years old, and 35% were older than 50 years.

Methodology and Exposure

The estimated number of exposure was calculated by using both delivery quantity data (2003-2009) and epidemiology database (2010-2021). The estimated use patterns (sex, age, indication, and dose) were calculated by using the component ratio from epidemiology database.

SV.1.2 Exposure

The estimated cumulative worldwide exposure to PEG-IFN alfa-2a, up to 30 June 2021, is a total of 3,047,614 patients (Table 38).

Table 38 - Cumulative Exposure from Marketing Experience to PEG-IFN alfa-2a Worldwide

	Sex		Age (years)			Dose				Region			
Indication	**Male**	**Female**	**0 to ≤25**	**>26 and ≤50**	**>50**	**180 mcg vials/Pre-filled Syringes/ Proclick**	**135 mcg vials/Pre-filled Syringes/ Proclick**	**90 mcg vials/Pre Filled Syringe**	**45 mcg vials**	**North America**	**Asia**	**RoW**	**Total Exposure**
HBV	232,635	125,265	17,895	214,740	125,265	314,440	35,953	7,504	3	60,016	87,374	210,511	357,900
HIV/HCV Coinfection (incl. Non-Responders) *	136,781	73,651	10,522	126,260	73,651	192,158	17,383	891	0	40,300	45,267	124,865	210,433
HCV Non-Responders (not incl. Co-infected)**	78,161	42,087	6,012	72,148	42,087	109,805	9,933	509	0	23,029	25,867	71,352	120,247
All other HCV infected	1,503,991	809,841	115,692	1,388,299	809,841	2,119,794	187,388	6,648	2	453,071	483,634	1,377,127	2,313,832
Off-label Haematology	29,382	15,821	2,260	27,121	15,821	26,971	10,981	7,247	4	2,551	15,724	26,928	45,202
Total	1,980,949	1,066,665	152,381	1,828,569	1,066,665	2,763,168	261,639	22,799	9	578,966	657,865	1,810,783	3,047,614

HBV - Hepatitis B Virus; HCV - Hepatitis C Virus; HIV - Human Immunodeficiency Virus; RoW - Rest of the World.

The estimated cumulative worldwide exposure to PEG-IFN alfa-2a is presented in Table 40. An estimated total of 3,225,239 patients have received PEG IFN alfa-2a cumulatively (2,809,285 patients with HCV; 370,751 patients with HBV and 45,202 patients with off-label haematology).

Table 40 - Cumulative Exposure from Marketing Experience

Indications	**Worldwide**		**Worldwide Total**
HBV	357,900		370,751
HCV	2,644,511		2,809,285
Off-label Haematology	45,202		45,202
Total	**3,047,614**		**3,225,239**

HBV = hepatitis B Virus; HCV = hepatitis C virus.

Note: Rounding errors may be introduced in the total figure.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Market experience with PEG-IFN alfa-2a and ribavirin has shown no evidence of misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

Changes in the level of scientific evidence for the causal association or risk-benefit impact:

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable as there are no safety concerns for Pegasys.

V.2. Additional Risk Minimisation Measures

Not applicable as there are no safety concerns for Pegasys.

V.3 Summary of risk minimisation measures

Not applicable as there are no safety concerns for Pegasys.

Part VI: Summary of the risk management plan

Summary of risk management plan for Pegasys (peginterferon alfa-2a)

This is a summary of the risk management plan (RMP) for Pegasys. The RMP details important risks of Pegasys, and how more information will be obtained about Pegasys' risks and uncertainties (missing information).

Pegasys' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pegasys should be used.

This summary of the RMP for Pegasys should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pegasys' RMP.

I. The medicine and what it is used for

Pegasys is authorised for chronic hepatitis B (adult and pediatric patients) and chronic hepatitis C (adult and pediatric patients) and polycythaemia vera and essential thrombocythaemia (see SmPC for the full indication). It contains peginterferon alfa-2a as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Pegasys' benefits can be found in Pegasys' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/pegasys.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Pegasys, together with measures to minimise such risks and the proposed studies for learning more about Pegasys' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Pegasys are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pegasys. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Pegasys.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Pegasys.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

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