

1. Summary statement of the proposal for inclusion, change or deletion

Inclusion of the injectable formulation of peginterferon alfa-2a and -2b is proposed for the treatment of hepatitis C among adults.

The principal reasons for requesting this inclusion are as follows:

1. There is significant burden of hepatitis C disease among adults living in resource-limited settings.
2. The combination of interferon alfa 2a or 2b and ribavirin is the current first line and only commercially available treatment for hepatitis C disease.
3. Treatment of hepatitis C will be improved with wider availability of this injectable treatment.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Stefan Wiktor, Team Leader, Global Hepatitis Programme, Pandemic and Epidemic Diseases Department, WHO

3. Name of the organization(s) consulted and/or supporting the application

MSF/Médecins Sans Frontières - Access Campaign

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4. International Nonproprietary Name (INN, generic name) of the medicine

peginterferon alfa-2a

peginterferon alfa-2b

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Peginterferon alfa-2a (Pegasys, Hoffmann-la Roche) 180 mcg as vial or prefilled syringe

PEGASYS, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alpha moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

Peginterferon alfa-2b (PEG-Intron, Merck) 80 mcg, 100 mcg as vial or prefilled syringe

PEG-Intron, peginterferon alfa-2b is a covalent conjugate of recombinant alfa interferon with monomethoxy polyethylene glycol (PEG). The molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the PEG-Intron molecule is approximately 31,000 daltons. The specific activity of pegylated interferon alpha-2b is approximately 0.7×10^8 IU/mg protein. Interferon alpha-2b, the starting material used to manufacture PEG-Intron, is a water soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon gene from human leukocytes.

6. International availability - sources, if possible manufacturers and trade names

Peginterferon alfa-2a (Trade name: Pegasys, Manufacturer: Hoffmann-la Roche)

Peginterferon alfa-2b (Trade name: PEG-Intron (US), Manufacturer: Merck). Other trade names exist in countries other than the United States of America for PEG-Intron. The product was formerly produced and marketed by Schering. Following the merging of Schering with Merck, the product has been subsequently marketed by Merck.

Biosimilar versions exist and are marketed in developing countries. Nevertheless, there is not a WHO prequalification system for biologics that could support Member States to access safe and effective biosimilar versions. The International Centre for Genetic Engineering and Biotechnology (ICGEB), an organization of the United Nations, has a technology transfer programme for biologics which include also Peginterferon alfa-2a which has been used by companies in developing countries.ⁱ

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

The request for inclusion is for the single medicines peginterferon alfa-2a and peginterferon alfa-2b.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Epidemiological information

Globally, approximately 150 million people are infected with hepatitis C (HCV) and it is estimated that 350,000 people die each year from HCV-related liver disease.ⁱⁱ While there are incomplete seroprevalence studies of HCV in low- and middle-income countries, initial seroprevalence studies have revealed significant burden of disease. Many countries in Central Africa and Central Asia have seroprevalence of 5-10%.ⁱⁱⁱ Egypt has among the highest rates of HCV in the world at 22%.^{iv} In Médecins Sans Frontières' own seroprevalence studies have revealed HCV seroprevalence of 17% and 18% in HIV populations in Central African Republic and Nigeria, respectively.

Infection with chronic hepatitis C will lead to cirrhosis in 15-35% of patients within 25-30 years of infection^v, but fibrosis and cirrhosis occurs more commonly and more rapidly in certain populations, notably those co-infected with HIV.^{vi} Patients with HCV are thus at risk for end-stage liver disease and are also have a 15-20 fold increased risk to develop hepatocellular carcinoma (HCC) as compared with their HCV negative peers.^{vii} Approximately 80% of HCCs are associated with hepatitis B or C and globally, over 80% of HCC cases occur in sub-Saharan Africa and Eastern Asia, suggesting that viral hepatitis is a major driver of significant morbidity in low- and middle-income countries.^{viii}

Peginterferon alfa-2a or -2b in combination with ribavirin is indicated for treatment of chronic hepatitis C and is the current standard of care.^{ix} The target population is all patients infected with chronic hepatitis C, regardless of genotype or stage of fibrosis, although patients with unfavorable prognostic factors (e.g. genotype 1) and little evidence of liver damage may elect to defer therapy while awaiting newer therapies.^x

Hepatitis C is a potentially curable disease and the goal of therapy is to obtain a sustainable virological response (SVR). Treatment can result in reversal of liver injury and prevention of serious consequences such as cirrhosis, end stage liver disease, HCC and death. Treatment with peginterferon alfa-2a or -2b and ribavirin for 48 weeks has resulted in SVR rates of 45% for genotypes 1 and 4 and for genotypes 2 and 3, 24 weeks of therapy has resulted in 80% SVR rates.^{xi} Further, a recent meta-analysis revealed that treatment success rates in low- and middle-income countries were similar to those obtained in high-income countries.^{xii}

8.2 Assessment of current use

Statistics on the number of patients on peginterferon alfa-2a or 2b are not collected. Information on cumulative use and sales are presented in section 11. The World Hepatitis Alliance performed a recent survey which demonstrated that in all WHO regions except Afro, the majority of countries provided domestic funds to partially or completely fund HCV care and treatment programs.^{xiii}

8.3 Target population

The target population is all patients, adults and children, infected with chronic hepatitis C, regardless of genotype or stage of fibrosis, although patients with unfavorable prognostic factors (e.g. genotype 1) and little evidence of liver damage may elect to defer therapy while awaiting newer therapies.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

9.1 Reference to existing WHO and other clinical guidelines

The WHO does not currently have guidance on the treatment of HCV, although guidelines are currently under development. However, a number of other expert bodies have evidence-based guidelines using GRADE methodology including the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD).^{xiv}

Both guidelines have relatively consistent indications for therapy initiation. The EASL guidelines recommend:

- (1) All treatment-naïve patients with compensated disease due to HCV should be considered for therapy (A2).
- (2) Treatment should be initiated promptly in patients with advanced fibrosis (METAVIR score F3–F4), and strongly considered in patients with moderate fibrosis (METAVIR score F2) (B2).
- (3) In patients with less severe disease, indication for therapy is individual (C2).

Both guidelines recommend use of peginterferon alfa-2a or -2b and ribavirin. The EASL guidelines state their recommendations for first-line therapy of HCV:

- (1) The combination of pegylated IFN- α and ribavirin is the approved SoC for chronic hepatitis C (A1).
- (2) Two pegylated IFN- α molecules, pegylated IFN- α 2a (180 μ g once per week) and pegylated IFN- α 2b (1.5 μ g/kg once per week), can be used in combination with ribavirin.
- (3) Ribavirin should be given at a weight-based dose of 15 mg/kg per day for genotypes 1 and 4–6 (A2) and at a flat dose of 800 mg/day for genotypes 2 and 3 (A2).
- (4) Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15 mg/kg per day (C2).

9.2 Dosage regimen

Peginterferon alfa-2a

Peginterferon alfa-2a is recommended for treatment of HCV in combination with ribavirin for adults and children >5 years.

For genotypes 1 and 4, weekly subcutaneous injections of 180 micrograms of peginterferon alfa-2a for 48 weeks are recommended in combination with oral ribavirin. For genotypes 2 and 3, weekly subcutaneous injections of 180 micrograms of peginterferon alfa-2a for 24 weeks are recommended in combination with oral ribavirin.

Hepatic impairment ALT progressively rising above baseline: Decrease dose to 135 mcg weekly and monitor LFTs more frequently. If ALT continues to rise despite dose reduction or ALT increase is accompanied by increased bilirubin or hepatic decompensation, discontinue therapy immediately. Therapy may resume after ALT flare subsides.

Renal impairment

Cl_{cr} \geq 30 mL/minute: No adjustment required.

Cl_{cr} <30 mL/minute: 135 mcg weekly; monitor for toxicity

End-stage renal disease (ESRD) requiring hemodialysis: 135 mcg weekly; monitor for toxicity

Pediatric dosing

Children ≥ 5 years and Adolescents: SubQ: 180 mcg/1.73 m² x body surface area (BSA) once weekly (maximum dose: 180 mcg) with ribavirin

Pediatric Hepatic Impairment

ALT ≥ 5 but < 10 x ULN: Decrease interferon dose to 135 mcg/1.73 m² x BSA once weekly. Monitor weekly; further modify dose if needed until ALT stabilizes or decreases.

ALT ≥ 10 x ULN (persistent): Discontinue interferon.

Pediatric Renal Impairment

Not sufficient evidence to recommend dose adjustments

Peginterferon alfa-2b

Peginterferon alfa-2b is recommended for treatment of HCV in combination with ribavirin for adults and children > 3 years.

For genotypes 1 and 4, weekly subcutaneous injections of weight-based peginterferon alfa-2b for 48 weeks are recommended in combination with oral ribavirin. For genotypes 2 and 3, weekly subcutaneous injections of weight-based peginterferon alfa-2b for 24 weeks are recommended in combination with oral ribavirin.

Weight based dosing:

< 40 kg: 50 mcg once weekly (with ribavirin 800 mg/day)

40-50 kg: 64 mcg once weekly (with ribavirin 800 mg/day)

51-60 kg: 80 mcg once weekly (with ribavirin 800 mg/day)

61-65 kg: 96 mcg once weekly (with ribavirin 800 mg/day)

66-75 kg: 96 mcg once weekly (with ribavirin 1000 mg/day)

76-80 kg: 120 mcg once weekly (with ribavirin 1000 mg/day)

81-85 kg: 120 mcg once weekly (with ribavirin 1200 mg/day)

86-105 kg: 150 mcg once weekly (with ribavirin 1200 mg/day)

> 105 kg: 1.5 mcg/kg once weekly (with ribavirin 1400 mg/day)

Hepatic impairment

Decompensated liver disease or autoimmune hepatitis: Use is contraindicated.

Hepatic decompensation or severe hepatic injury during treatment (Child-Pugh score > 6 [class B or C]): Discontinue immediately.

Renal Impairment

Peginterferon alfa-2b combination with ribavirin: Clcr < 50 mL/minute: Combination therapy with ribavirin is not recommended.

Pediatric dosing

60 mcg/m² once weekly in combination with ribavirin

Pediatric renal impairment

Serum creatinine > 2 mg/dL: Discontinue treatment.

10. Summary of comparative effectiveness in a variety of clinical settings:

As compared to standard interferon-alfa alone, interferon-alfa in combination with ribavirin has increased SVR from 10-20% to 40-60%^{xv} The long-acting pegylated

formulation in combination with ribavirin has further increased SVR rates to 50-60% for genotype 1 and 80% for genotype 2 and 3.^{xvi xvii}

Treatment naïve patients

Peginterferon alfa-2a and 2b have also been compared. Data in obtaining rapid virological response (RVR) and early virological response (EVR) with studies show either equivalence of 2a and 2b or superiority of 2a (see table 1).^{xviii}

Table 1 (from Foster 2010)

Table III. Comparative clinical efficacy of pegylated interferons (peginterferons): rapid (week 4) or early (week 12) virological response to peginterferon- α -2a (PEG-IFN-2a) or peginterferon- α -2b (PEG-IFN-2b)

Study	Details	Treatment regimen (weekly)	Ribavirin dosage ^a (mg/day)	No. of evaluable patients	RVR ^b (%)	EVR ^b (%)
Treatment-naïve patients						
McHutchison et al. ^[49] (2009)	IDEAL study RCT genotype 1	PEG-IFN-2a 180 μ g	1000–1200	1035	11.9	45.0
		PEG-IFN-2b 1.0 μ g/kg	800–1400	1016	7.8 [†]	36.0
		PEG-IFN-2b 1.5 μ g/kg	800–1400	1019	11.4	39.9 [‡]
Mangia et al. ^[50] (2008)	RCT genotype 1	PEG-IFN-2a 180 μ g	1000–1200	334	24	
		PEG-IFN-2b 1.5 μ g/kg	1000–1200	362	29	
Di Bisceglie et al. ^[36] (2007)	RCT genotype 1	PEG-IFN-2a 180 μ g	1000–1200	189	41.8 ^c	66.1
		PEG-IFN-2b 1.5 μ g/kg	1000–1200	191	49.2	63.3
Silva et al. ^[34] (2006)	RCT	PEG-IFN-2a 180 μ g	13 mg/kg/day (from week 5)	18	28 ^d	
		PEG-IFN-2b 1.5 μ g/kg	13 mg/kg/day (from week 5)	18	50	
Bruno et al. ^[35] (2004)	RCT	PEG-IFN-2a 180 μ g	1000–1200	10	70	90
		PEG-IFN-2b 1.0 μ g/kg	1000–1200	12	58	50
Sporea et al. ^[51] (2006)	RCT ^e	PEG-IFN-2a 180 μ g	nd	58		82.8 ^d
		PEG-IFN-2b 1.5 μ g/kg	nd	58		67.2
Escudero et al. ^[52] (2008)	Non-randomized	PEG-IFN-2a 180 μ g	800–1200	91	46.2	70.3
		PEG-IFN-2b 1.5 μ g/kg	800–1200	92	39.1	65.2
Non-responders to previous treatment with interferon-α plus ribavirin						
Scotto et al. ^[53,54] (2008)	RCT	PEG-IFN-2a 180 μ g	15 mg/kg/day	54		27.8
		PEG-IFN-2b 1.5 μ g/kg	15 mg/kg/day	54		31.5
HIV/HCV co-infected patients						
Laguno et al. ^[55] (2009)	RCT	PEG-IFN-2a 180 μ g	800–1200	96	35.1	80.5 ^c
		PEG-IFN-2b 1.5 μ g/kg	800–1200	86	34.7	69.0
Vispo et al. ^[56] (2008)	Retrospective analysis	PEG-IFN-2a 180 μ g	1000–1200	138	45	65
		PEG-IFN-2b 1.5 μ g/kg	1000–1200	80	27 [*]	45 [*]

a Ribavirin dose was based on bodyweight.

b RVR and EVR defined as no detectable virus after 4 or 12 weeks of treatment, respectively, unless otherwise specified.

c Endpoint defined as no detectable virus or $\geq 2 \log_{10}$ reduction from baseline in viral titre.

d Endpoint defined as $\geq 2 \log_{10}$ reduction from baseline in viral titre.

e Study included 35 patients (30%) who were relapsers or non-responders to previous treatment.

EVR = early virological response; **HCV** = hepatitis C virus; **nd** = not defined; **RCT** = randomized controlled trial; **RVR** = rapid virological response; * $p < 0.05$; † $p < 0.01$ for PEG-IFN-2b 1.5 μ g/kg vs PEG-IFN-2b 1.0 μ g/kg; ‡ $p < 0.05$ for PEG-IFN-2b 1.5 μ g/kg vs PEG-IFN-2a 180 μ g.

The largest trial to assess differences in SVR between peginterferon alfa-2a and peginterferon alfa-2b was the IDEAL trial, a randomized clinical trial with over 3000 patients who were treatment naïve and had genotype 1 HCV. This study demonstrated that there were not significant differences in SVR between. A number of other studies which include non-genotype 1 HCV have also supported this finding (see Table 2).

Table 2 (from Foster 2010)

Table IV. Comparative clinical efficacy of pegylated interferons (peginterferons): sustained virological response (24 weeks after end of treatment) to peginterferon- α -2a (PEG-IFN-2a) or peginterferon- α -2b (PEG-IFN-2b)

Study	Details	Treatment regimen (weekly)	Ribavirin* (mg/day)	No. of evaluable patients	SVR (%)	Parameter
Treatment-naïve patients						
McHutchison et al. ^[69] (2009)	IDEAL study	PEG-IFN-2a 180 μ g	1000–1200	1035	40.9	
	RCT	PEG-IFN-2b 1.0 μ g/kg	800–1400	1016	38.0	
	Genotype 1	PEG-IFN-2b 1.5 μ g/kg	800–1400	1019	39.8	
Mangia et al. ^[50] (2008)	RCT	PEG-IFN-2a 180 μ g	1000–1200	334	49.1	
	Genotype 1	PEG-IFN-2b 1.5 μ g/kg	1000–1200	362	45.6	
Rumi et al. ^[61] (2008) [abstract]	MIST study	PEG-IFN-2a 180 μ g	800–1200 ^b	212	66	48 genotype 1 or 4
	RCT	PEG-IFN-2b 1.5 μ g/kg	800–1400	219	54 [†]	32 [†] genotype 1 or 4
Ascione et al. ^[62] (2008) [abstract]	RCT	PEG-IFN-2a 180 μ g	1000–1200	160	68.7	54.8 genotype 1 or 4
		PEG-IFN-2b 1.5 μ g/kg	1000–1200	160	54.4 ^{**}	39.8 [†] genotype 1 or 4
Berak et al. ^[63] (2007) [abstract]	RCT	PEG-IFN-2a 180 μ g	nd	92	54.3	
		PEG-IFN-2b 1.5 μ g/kg	nd	103	47.6	
Yenice et al. ^[64] (2006)	RCT	PEG-IFN-2a 180 μ g	800–1200	37	48.6	
		Genotype 1	PEG-IFN-2b 1.5 μ g/kg	800–1200	37	35.1
Escudero et al. ^[52] (2008)	Non-randomized	PEG-IFN-2a 180 μ g	800–1200	91	65.9	
		PEG-IFN-2b 1.5 μ g/kg	800–1200	92	62.0	
Craxi et al. ^[65] (2008) [abstract]	PROBE study Prospective, observational Genotype 1	PEG-IFN-2a 180 μ g	nd	663	36	
		PEG-IFN-2b 1.5 μ g/kg	nd	354	29 [†]	
Backus et al. ^[66] (2007)	Retrospective cohort	PEG-IFN-2a 180 μ g	nd	2091	31	25 genotype 1
		PEG-IFN-2b 1.5 μ g/kg	nd	3853	24 ^{***}	18 ^{***} genotype 1
Witthoef et al. ^[67] (2008) [abstract]	PRACTICE study Retrospective, matched-pair	PEG-IFN-2a 180 μ g	nd	1784	53.1	
		PEG-IFN-2b 1.5 μ g/kg	nd	1686	50.7	
Thuy and Dat ^[68] (2007) [abstract]	Matched-pair	PEG-IFN-2a 180 μ g	15 mg/kg/day	107	60.7	28.6 weight >75 kg
		PEG-IFN-2b 1.5 μ g/kg	15 mg/kg/day	131	62.6	61.9 ^{***} weight >75 kg
Mauss et al. ^[69] (2004) [abstract]	Matched-pair	PEG-IFN-2a 180 μ g	800–1200	56	45	
		PEG-IFN-2b 1.5 μ g/kg	800–1200	56	48	
Non-responders to previous treatment with interferon-α plus ribavirin						
Scotto et al. ^[53,54] (2008)	RCT	PEG-IFN-2a 180 μ g	15 mg/kg/day	71	19.7	
		PEG-IFN-2b 1.5 μ g/kg	15 mg/kg/day	72	18.0	
HIV/HCV co-infected patients						
Vispo et al. ^[70] (2009)	Retrospective analysis	PEG-IFN-2a 180 μ g	1000–1200	138	53	
		PEG-IFN-2b 1.5 μ g/kg	1000–1200	81	43	
Laguno et al. ^[55] (2009)	RCT	PEG-IFN-2a 180 μ g	800–1200	96	46	
		PEG-IFN-2b 1.5 μ g/kg	800–1200	86	42	

a Ribavirin dose was based on bodyweight.

b Patients with genotype 2 or 3 received a fixed dose of 800 mg/day. Patients with genotype 1 or 4 received ribavirin dose based on weight.

HCV = hepatitis C virus; nd = not defined; RCT = randomized controlled trial; SVR = sustained virological response; * p < 0.05; ** p < 0.01; *** p < 0.001.

Several studies have shown improved RVR with peginterferon alfa-2a as compared with peginterferon alfa-2b. Two RCTs, the MIST study and a study by Ascione et al (2008) included patients with HCV genotypes 1, 2, 3 and 4 and demonstrated significantly higher SVR with use of peginterferon alfa-2a in combination with ribavirin as compared to peginterferon alfa-2b in combination with ribavirin.^{xix}

^{xx}Two observational studies, the PROBE study in Italy and a study by Backus (2007) also demonstrate higher rates of SVR for peginterferon alfa-2a in combination with ribavirin as compared to peginterferon alfa-2b in combination with ribavirin.^{xxi xxii}

Non-responders and Relapsers: Treatment experienced patients

Patients previously treated with standard interferon-alfa who either did not experience virologic response or relapsed after end of treatment may achieve SVR with peginterferon alfa 2a or 2b plus ribavirin. When considering such patients who were also treated with or without ribavirin, subsequent treatment with peginterferon alfa-2a or -2b will result in SVR of 20–40% or 8–10%, respectively.^{xxiii} With limited numbers of studies, there appears to be no difference in retreatment with peginterferon alfa-2a or 2b in combination with ribavirin for this group of patients.^{xxiv}

Unfortunately, rates of SVR upon retreatment with peginterferon alfa-2a after unsuccessful treatment with pegylated alfa-2b are not robust, with only 7–16% achieving SVR after extended treatment of 72 weeks.^{xxv}

HIV co-infected patients

Overall, patients co-infected with HIV have lower rates of SVR after treatment with peginterferon alfa-2a or -2b as compared to their non-HIV infected peers. In patients

with co-infection, cure rates are 30-50%. However, cure rates can be as low as 15% in patients with low CD4 and genotype 1 HCV.^{xxvi} However, at this point, the combination of peginterferon alfa-2a or 2b with ribavirin remains the treatment of choice for HIV-HCV coinfecting patients.^{xxvii}

Combination therapy with new oral regimens

In 2011, the introduction of two oral HCV protease inhibitors, telaprevir and boceprevir, offers the potential to improve SVR and shorten treatment times. Both protease inhibitors are for treatment of genotype 1 and to be used with the combination of peginterferon alfa-2a or 2b and ribavirin. Large RCTs, PROVE1 and PROVE2 demonstrated statistically significant improved rates of SVR when using the combination of one oral protease inhibitor with peginterferon alfa-2a or 2b and ribavirin for either 24 or 48 weeks as compared with standard 48 weeks of therapy with peginterferon alfa-2a or 2b and ribavirin.^{xxviii}

Although new all-oral therapies that do not use interferon and ribavirin are in development, these products are not yet available and will likely not be available to those living in low- and middle-income countries for years to come.

11. Summary of comparative evidence on safety:

We could not find clear data about total patient exposure to date. Information is available about current access to HCV testing globally, access to medicines globally and global sales:

Access to testing:

Globally, 59% of the world's population has no access to hepatitis C diagnosis. This findings correlate wealth of the country: 93% in high income countries, 77% of upper middle income, 53% of lower middle income, and 11% of low income countries report that testing is available to more than half of the population. 84% of the population in lower middle income countries and 96% of the population in low income countries live in areas where testing is not widely accessible.^{xxix}

Access to treatment.

Therapy for hepatitis C is extremely expensive, making it largely unaffordable. The availability of full or part government funding for treatment of hepatitis C depends heavily on the income status of a country: such funding is available in 83% of high income, 77% of middle income, and 33% of low income countries respectively, according to WHA Report 2010.

Global sales:

Peg IFN alpha 2 a:

1.655 Billion CHF in 2009, an increase of 5% from 2008.^{xxx}

441 millions CHF in first quarter 2010, a 15% increase from first quarter 2009^{xxxi}.

Pegasys (peginterferon alfa-2a), for hepatitis B and C, fell 11% to 695 million francs for the first six months of 2011.^{xxxii}

Peg IFN alpha 2b:

918 million USD in 2007^{xxxiii}

3rd quarter 2009: 198 million USD^{xxxiv}

4th quarter 2009 (post-merger with Merck): 149 million USD^{xxxv}

Worldwide sales Pegintron (peginterferon alfa-2b) in 2010 were 274 million USD. Worldwide sales of PegIntron for treating chronic hepatitis C were \$319 million for the first six months of 2011, a decrease of 14% compared with the same period in 2010. The Company believes these declines were attributable in part to patient treatment being delayed by health care providers in anticipation of new therapeutic options becoming available.^{xxxvi}

11.2 Description of adverse effects/reactions

The use of interferon- α with or without ribavirin is frequently associated with a range of adverse effects, including influenza-like symptoms, haematological changes and neuropsychiatric disturbances, and this is true also of the peginterferons, with similar levels of adverse events, dose reduction and discontinuation from treatment.

Treatment of chronic hepatitis C with interferon containing regimen has an absolute contra-indication in patients without an option for liver transplantation in the following groups: uncontrolled depression, psychosis, or epilepsy, uncontrolled autoimmune diseases; (Child-Pugh B 7 or more); pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease.

Relative contraindications to treatment are abnormal hematological indices (hemoglobin < 13 g/dl for men and <12 g/dl for women, neutrophil count < 1500/mm³, platelet count <90,000/mm³); serum creatinine level > 1.5mg/dl; significant coronary heart disease; and untreated thyroid diseases.

Although decompensated patients should usually not be treated, treatment of patients with advanced liver disease (Child B cirrhosis) whose parameters may lie below label recommendations may be feasible in experienced centers under careful monitoring. (EASL 2012 guidelines)

Peg IFN alpha 2a: adverse events

- **Common:**

- **Dermatologic:** Alopecia (18 to 28%), Dermatitis (8 to 16%), Dry skin (4% to 10%), Injection site inflammation (10% to 31%), Injection site reaction (22% to 23%), Pruritus (12% to 19%), Rash (5% to 8%)
- **Endocrine metabolic:** Weight Decreased (4 to 16%)
- **Gastrointestinal:** Abdominal pain (8% to 26%), Diarrhea (11% to 31%), Loss of appetite (16% to 24%), Nausea and vomiting (5% to 25%)
- **Hematologic:** Lymphocyte count abnormal (3% to 14%), Thrombocytopenia (5% to 8%)
- **Musculoskeletal:** Arthralgia (22% to 28%), Myalgia (26% to 51%)
- **Neurologic:** Dizziness (13% to 23%), Headache (27% to 54%), Insomnia (19% to 30%), Reduced concentration (8% to 10%)
- **Psychiatric:** Anxiety (19% to 33%), Feeling nervous (19% to 33%), Irritability (19% to 33%)
- **Respiratory:** Cough (4% to 10%), Dyspnea (4% to 13%)
- **Other:** Fatigue (24% to 67%), Fever (24% to 54%), Influenza-like illness, Rigor (25% to 47%)

- **Serious:**
 - **Cardiovascular:** Angina (less than 1%), Cardiac dysrhythmia (less than 1%), Myocardial infarction
 - **Dermatologic:** Erythroderma (rare), Stevens-Johnson syndrome (rare)
 - **Endocrine metabolic:** Diabetes mellitus (less than 1%)
 - **Gastrointestinal:** Colitis (less than 1%), Gastrointestinal hemorrhage (less than 1%), Pancreatitis (less than 1%), Peptic ulcer disease (less than 1%)
 - **Hematologic:** Anemia (2% to 14%), Anemia (Severe), Aplastic anemia (less than 1%), Cytopenia (Severe), Lymphocytopenia (Severe) (5% to 14%), Neutropenia (21% to 40%), Thrombotic thrombocytopenic purpura (less than 1%)
 - **Hepatic:** Abnormal liver function (less than 1%), Cholangitis (less than 1%), Fatty liver (less than 1%), Liver failure
 - **Immunologic:** Autoimmune disease (rare), Hypersensitivity reaction (Severe)
 - **Musculoskeletal:** Myositis (less than 1%)
 - **Neurologic:** Cerebral hemorrhage (less than 1%), Cerebral ischemia, Peripheral neuropathy (less than 1%)
 - **Ophthalmic:** Corneal ulcer (less than 1%), Serous retinal detachment
 - **Psychiatric:** Aggressive behavior (less than 1%), Depression (18% to 20%), Psychotic disorder (less than 1%), Suicide (less than 1%)
 - **Respiratory:** Pulmonary embolism (less than 1%)
 - **Other:** Bacterial infectious disease (3% to 5%), Coma (less than 1%), Drug abuse (less than 1%), Infectious disease.

Peg IFN alpha 2b:

- **Common:**
 - **Dermatologic:** alopecia, diaphoresis, dry skin, erythema at injection site (
 - **Endocrine metabolic:** hyperuricemia
 - **Gastrointestinal:** abdominal pain, decrease in appetite, diarrhea, loss of appetite, nausea, vomiting, weight loss
 - **Musculoskeletal:** arthralgia, musculoskeletal pain, myalgia
 - **Neurologic:** dizziness, headache, insomnia, reduced concentration
 - **Respiratory:** pharyngitis
 - **Other:** fatigue, fever, rigor
- **Serious:**
 - **Gastrointestinal:** colitis, pancreatitis
 - **Hematologic:** autoimmune thrombocytopenia
 - **Hepatic:** Abnormal liver function (less than 1%), Cholangitis (less than 1%), Fatty liver (less than 1%), Liver failure
 - **Ophthalmic:** blindness, thrombosis of retinal vein
 - **Psychiatric:** aggressive behavior, depression, homicidal thoughts, suicidal thoughts, suicide

11.3 Identification of variation in safety due to health systems and patient factors

A systematic review and meta-analysis of studies of HCV treatment programmes in low and middle income countries has been performed. The overall SVR was 52% (95% CI: 48-56). For studies in which patients were predominantly infected with genotype 1 or 4, the pooled SVR rate was 49% (95% CI: 43-55).

Factors associated with successful treatment outcomes included treatment with pegylated interferon and ribavirin, infection with an HCV genotype other than genotype 1 and 4, absence of liver damage or human immunodeficiency virus infection at baseline. Adverse events were reported in 16 studies and experienced by 17% (95% CI: 13-23) of patients in these studies. The drug regimen had no significant effect on these adverse events. Adverse events that resulted in treatment termination were reported in 39 studies and were experienced by 4% of the patients (95% CI: 3-5). These adverse events were significantly more common in patients who were taking weight-adjusted ribavirin dose (4%). (Ford N, 2012).

11.4 Summary of comparative safety against comparators

Peginterferon- α -2a and peginterferon- α -2b appear from comparative studies to be similarly tolerated, with few differences of clinical significance noted. (Forster, Drugs, 2010).

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

12.1 Range of costs of the proposed medicine

From surveys undertaken by MSF and other NGOs, the prices peginterferon alpha-2a and 2b are often listed between US\$200 and \$400 per vial, where no biosimilar exists. The price structures applied by Roche and Merck are aligned in the countries where the two products are registered. Egypt is a notable exception, where the national Hepatitis C programme has reached an agreement to procure Peginterferon alfa-2a (Pegasys) and Peginterferon alfa-2b (PEG-Intron) at \$41 per vial, including a weekly supply of ribavirin.^{xxxvii} In Egypt, competition has reduced the price of both originator products for a 48-week treatment course of pegylated interferon and ribavirin from \$10,000 - \$20,000 to less than \$2000.^{xxxviii}

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

Published data on the cost-effectiveness of peginterferon treatment for HCV is derived from studies conducted in Europe and cost data from the years 2004-2005. However, these may be translatable to low-income settings, as a meta-analysis of studies from low- and middle-income countries found rates of sustained virological load response (SVR, defined as the absence of detectable HCV in the blood 24 weeks after the completion of antiviral therapy) similar to those achieved in resource-rich settings.^{xxxix}

Shepherd et al (2004) conducted a systematic review and economic evaluation of peginterferon alpha-2a and 2b in combination with ribavirin in the treatment of chronic hepatitis C. Two randomized controlled trials compared peginterferon alpha-2a or 2b plus ribavirin with non-pegylated interferon plus ribavirin, while four RCTs compared peginterferon monotherapy with non-pegylated interferon monotherapy. The economic analysis assumed weekly costs of 162 British pounds for pegylated IFN-2b (PegIntron), 53 pounds for non-pegylated interferon alpha-2b (Intron A), and

148 pounds for ribavirin. Given these assumptions the incremental discounted cost per QALY for comparing no active treatment to 48 weeks of dual therapy with peginterferon and ribavirin (PEG + RBV) was 6,045 British pounds. The incremental discounted cost per QALY when moving from no active treatment to 48 weeks of monotherapy with peginterferon was 6,484 pounds. When moving from 48 weeks of monotherapy with IFN to 48 weeks of monotherapy with peginterferon the incremental discounted cost per QALY was 8404 pounds. When moving from 48 weeks of dual therapy with non-pegylated interferon and ribavirin (IFN + RBV) to 48 weeks of dual therapy with PEG + RBV the incremental discounted cost per QALY was 12,123 pounds.^{xi}

Subgroup analyses for dual PEG + RBV therapy demonstrated that the most favorable incremental discounted cost per QALY estimates were for patients infected with genotypes 2 and 3, and with low baseline viral load (3,291 pounds) compared with no active treatment. Results of one-way sensitivity analyses showed that the estimated varied according to differences in SVRs, drug costs, and discount rates.

However, with bulk purchasing, tiered pricing, price negotiations and entry of potential biosimilar versions prices will decrease. Already in Egypt, Merck has agreed to a preferential price for MSF of \$1,971 for the combination of 48 weeks of peginterferon alfa-2b and ribavirin.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Peginterferon alfa-2a (Pegasys, Hoffmann-la Roche) has been registered by Swiss Medic in October 25, 2002. Pegasys has been registered by the US Food and Drug Administration on October 16th, 2002.^{xli}

Peginterferon alfa-2b (PEG-Intron, Merck) has been registered by the US Food and Drug Administration on January 19th, 2001.^{xlii}

The two products are registered in several countries. Biosimilar versions of peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (PEG-Intron) do exist, but there is no international scheme for the evaluation of safety and efficacy of biologics such as the WHO prequalification programme for medicines and vaccines. The availability of affordable quality assured pegylated interferon alpha could be increased if such system was in place.

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Peginterferon alfa-2a (Pegasys and its biosimilars) and Peginterferon alfa-2b (PEG-Intron and its biosimilars) do not have a monography in the British Pharmacopoeia, International Pharmacopoeia and United States Pharmacopoeia. The following assays and monographies have been retrieved:

British Pharmacopoeia 2012:

Volume V, Appendices, Appendix XIV Biological Assays and Tests, Appendix XIV M. Assay of Interferons

Volume I & II, Monographs: Medicinal and Pharmaceutical Substances, Interferon Alfa-2 Concentrated Solution

Volume III, Formulated Preparations: Specific Monographs, Interferon Alfa-2a Injection

15. Proposed (new/adapted) text for the WHO Model Formulary

Treatment of Hepatitis C

Peginterferon alfa-2a 180 mcg as vial or prefilled syringe*

[Covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate molecular weight 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons.]

Peginterferon alfa-2b 80 mcg, 100 mcg as vial or prefilled syringe*

[Covalent conjugate of recombinant alpha interferon (molecular weight of 19,271 daltons) with a linear monomethoxy polyethylene glycol (PEG) chain (molecular weight of 12,000 daltons). The PEG moiety is attached primarily to histidine-34 of interferon-alfa-2b via an unstable urethane bond. The average molecular weight of the Peginterferon alfa-2b molecule is approximately 31,000 daltons.]

* to be used in association with ribavirin capsules.

ⁱ ICGBE Activity report 2010/2011 available at: www.icgeb.org/research-groups.html?file=tl_files/hq/...11.pdf

ⁱⁱ WHO. Hepatitis C. Available at <http://www.who.int/mediacentre/factsheets/fs164/en/index.html>. Accessed on 21 November 2012.

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^{xi} National Institute for Health and Clinical Excellence Technology Appraisal Guidance 75. Hepatitis C – pegylated interferons, ribavirin and alfa interferon. London: NICE, 2004.

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