SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 August 2003. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

This was a full application to obtain a single European Marketing Authorisation via the centralised procedure for interferon alfa-2b. National Marketing Authorisations exist in all Member States for the use of interferon alfa–2b (IntronA). IntronA is indicated in the treatment of Chronic Hepatitis B, Chronic Hepatitis C, Hairy Cell Leukemia, Chronic Myelogenous Leukemia, Multiple Myeloma, Follicular Lymphoma, Carcinoid tumor, Malignant Melanoma and AIDS-related Kaposi's Sarcoma.

The harmonization of the SPC for the listed indications was achieved in June 1997 through a referral under Article 11 of Council directive 75/319/EEC as amended.

The new data filed with the centralised application concerned an extension of Chronic Hepatitis B approval in adults to children (1 to 17 years of age), the combination of interferon alfa-2b with ribavirin as first line treatment for patients with Chronic Hepatitis C and an update of the other indications including acknowledgement that cytarabine is commonly used with interferon alfa-2b in Chronic Myelogenous Leukemia. The indication AIDS-related Kaposi's Sarcoma was deleted.

The CPMP focused the evaluation on the new information provided in support of the centralised application.

2. Chemical, pharmaceutical and biologicals aspects

The qualitative and quantitative composition of the medicinal product centrally authorised IntronA and of the nationally licensed IntronA, are strictly identical. The manufacturers and the manufacturing process are those already approved for the manufacture of the nationally authorized Intron-A.
This centralised application relates to three formulations: a lyophilised powder (containing human serum albumin as stabiliser) and two solutions for injection (vials and pens) which are Human Serum Albumin (HSA) free.

The main goal of the development of the HSA-free formulation was to identify a stable interferon alfa-2b solution free of human serum albumin and remains essentially free from visible particles. An additional goal was to have a product meeting both European Pharmacopeia and USP antimicrobial preservative effectiveness criteria so that it would be suitable for worldwide marketing.

The application consisted of the full information contained in the original approved applications as well as the information submitted in the subsequent variations evaluated in the Mutual Recognition procedure. The assessment report focused in particular on the few additional changes that have been introduced in the centralised marketing authorisation application.

Composition and product development

The optimum pH for the formulation was determined based on a pH/stability profile of interferon alfa-2b.

Excipient screening studies were conducted to determine the compatibility of interferon alfa-2b with a variety of tonicity adjusting agents, antimicrobial preservatives, and protein stabilizers.

During the course of the formulation development program, the European Pharmacopeia adopted new criteria for antimicrobial preservative effectiveness. The solution was reformulated by changing its antimicrobial preservative system in order to meet both USP and Ph. Eur. acceptance criteria.

An ongoing stability study was performed with the m-cresol formulation filled into Type I flint glass carpoules. The package showed good compatibility with interferon alfa-2b in the formulation.

Appropriate formulation validation studies were conducted. The pH validation studies demonstrated that the product is stable in the proposed pH range.

The formulation in a vial was found not to be adversely affected by light, and it was shown to be able to withstand exposure to temperatures up to 35° for as long as seven days.

Active substance

Recombinant interferon alfa-2b is a sterile, stable formulation of highly purified interferon alfa–2b produced by recombinant DNA techniques. Interferon alfa–2b is a water soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of *E.coli* which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa–2b gene from human leukocytes. The activity of interferon is expressed in terms of IU, with 1 mg of recombinant interferon alfa–2b protein corresponding to 2.6×10^8 International Units (IU).

Other ingredients

HSA is utilised only in the lyophilised powder formulation. It complies with the current guidelines.

Finished product

The specifications and routine tests have been upgraded as compared to those previously submitted by the Company for interferon alfa-2b lyophilized powder for injection and the interferon alfa-2b injectable solution. The absence of Human Serum Albumin (HSA) in some formulations has allowed new purity test methods to be introduced.

In addition, identification and assay of the m-cresol preservative is described and the proposed efficacy of antimicrobial preservation complies with the Ph. Eur. requirements.

The other routine tests (determination of the colour and clarity of the solution, pH, bacterial endotoxins (LAL) and sterility) are performed in compliance with the Ph. Eur., and the proposed limits are acceptable for this type of product.

Stability

Stability studies were conducted on different batches of interferon alfa-2b drug substance manufactured.

The available stability data justify 24 months storage at -80°C.

The following shelf lives have been accepted for the finished products:
- IntronA powder and solvent for solution for injection: 3 years at 2-8°C;
- IntronA solution for injection, single dose vials: 18 months at 2-8°C;
- IntronA solution for injection multiple dose vials: 2 years at 2-8°C;
- IntronA solution for injection multidose pen: 15 months at 2-8°C.

3. Toxico-pharmacological aspects

Recombinant human interferon alfa-2b is a potent cytokine that possesses antiviral, immunomodulating and antiproliferative activities (Haworth, et al, 1994). It is a non-glycosolated protein. Interferon alfa-2b is produced by most cells in response to viral infection and a variety of other stimuli, including double-stranded RNA and certain cytokines (e.g. interleukin 1, interleukin 2, and tumor necrosis factor) (Hayden, 1996; DeMaeyer-Guignard, 1994). It is generally believed that interferons ameliorate viral infections by exerting direct antiviral effects and/or by modifying the immune response to infection (Hayden, 1996).

In addition to controlling infection, interferons may mediate some of the systemic symptoms associated with viral infections and contribute to immunologically mediated tissue damage in certain viral diseases. Interferons bind to specific cell surface receptor molecules signaling the cell to produce antiviral proteins (DeMaeyer-Guignard, 1994; Sen & Raanshoff, 1993). The antiviral proteins inhibit viral replication primarily through inhibition of transcription, protein processing, and virus maturation (Hayden, 1996). In addition interferons suppress cell proliferation and have immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells.

The specificity of biologic activity (Balkwill, *et al.,* 1982; Gresser & Morel-Maroger, 1976; Herberman, 1982) and the development of neutralising activity to interferon affect the testing of interferon alfa-2b, a human interferon, in laboratory animal species. Consequently, the value of studies conducted in rodents is limited. Although interferon alfa-2b does have biologic activity in monkeys, the development of neutralising antibodies may also have effected the outcome of these studies. However, there is considerable toxicologic experience with interferon alfa-2b in monkeys and most findings can be related to those observed in humans. Thus the monkey is considered to be an adequate species for characterisation of the toxicity of interferon alfa-2b.

Pharmacodynamics

Interferon alfa-2b has pleotrophic biologic activity. It binds to cell surface receptors and, through activation of a protein kinase signal transduction system, mediates the transcription of a set of genes called interferon-stimulated genes. Interferon alfa is immunomodulatory (increases NK cell, macrophage, neutrophil and T cell activity), antiproliferative (prolongs the cell cycle, modulates oncogene expression) and antiviral. It protects a variety of cell types, derived from a variety of species, against many RNA and DNA viruses.

Pharmacokinetics

Information on the absorption of interferon alfa-2b from the intramuscular route is limited to single blood samples being taken 1 hr following dose administration to rats and monkeys. Throughout the development of interferon alfa-2b, activity in serum has been measured using an antiviral cytopathic effect (CPE) inhibition assay. The CPE bioassay measures the ability of serum samples to protect a human fibroblast cell line sensitive to interferon alfa-2b from the cytopathic effects of encephalomyocarditis (EMC) virus. For more recent evaluations, a sandwich immunoassay (ELISA) has also been employed to determine concentrations of interferon alfa 2-b in serum. Pharmacokinetic parameters calculated from the data generated by the two assays were usually in good agreement leading to the same scientific interpretation. Therefore, although both sets of data were documented in the reports for the individual studies, the results from the ELISA are given in this overview. Serum neutralising antibodies to interferon alfa-2b were detected using an enzyme immunoassay (EIA) method that employed immobilised interferon alfa-2b on polystyrene beads. The CPE assay was also utilised to measure the neutralisation of the antiviral activity of interferon alfa-2b toward the EMC virus/fibroblast cell system.

Interferon alfa-2b is rapidly cleared from the circulation of animals and humans via renal metabolism. Whereas interferon alfa-2b readily induces the formation of neutralising antibodies in animals upon repeated dosing because of species specificity, this appears to occur infrequently in humans.

Toxicology

The absence of signs of toxicity in rhesus monkeys given high single intramuscular or intravenous doses of interferon alfa-2b indicate that interferon alfa-2b has no apparent potential for causing acute toxic effects. The highest dose tested by both routes was approximately 7 times the maximum therapeutic dose and 130 times the minimum therapeutic dose of interferon alfa-2b. Although interferon alfa-2b has apparently little biologic activity in rodents, the results of single dose toxicity studies in mice and rats and the absence of effects on cardiovascular, renal and CNS function in the safety pharmacology studies support the conclusion that interferon alfa-2b has no apparent potential for causing acute toxixity.

Irritation at the injection site in repeated dose toxicity studies occurred in both rats and monkeys. The potential for irritation appeared to be mild to moderate and, at least in part, dependent on tonicity of the formulation.

Multiple dose studies for up to three months have shown no evidence of toxicity in mice, rats, or rabbits. Daily dosing of cynomolgus monkeys with 20 x 10^6 IU/kg/day for three months caused no remarkable toxicity. However, toxicity was shown in monkeys administered the highest dose of 100 x 10^6 IU/kg/day for three months.

Mutagenicity studies with interferon alfa-2b revealed no adverse effects.

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

4. Clinical aspects

The harmonisation of the SPC was achieved in June 1997 through a referral under Article 11 of Council directive 75/319/EEC as amended for the following indications: treatment of Chronic Hepatitis B, Chronic Hepatitis C, Hairy Cell Leukemia, Chronic Myelogenous Leukemia, Multiple Myeloma, Follicular Lymphoma, Carcinoid tumor, Malignant Melanoma and AIDS-related Kaposi's Sarcoma.

During the centralised application, the assessment focused on the new data submitted and/or changes in the Summary of Product Characteristics (SPC) as compared to the IntronA dossier reviewed by CPMP and the SmPC approved during Article 11 referral:

1. efficacy and safety of interferon alfa-2b in paediatric patients suffering from chronic hepatitis B;
2. modifications of SmPC's wording relative to hepatitis C indication in order to introduce the concomitant use of ribavirin and interferon alfa-2b;
3. clinical data submitted on the concomitant use of interferon alfa-2b and cytosine arabinoside for the treatment of chronic myelogenous leukaemia.

In addition, the indication AIDS-related Kaposi's Sarcoma was not submitted in the centralised application.

Follicular lymphoma

Follicular non-Hodgkin's lymphomas (NHL) consist of the follicular centroblastic centrocytic lymphomas and of the follicular small cleaved, follicular mixed and follicular large cells. Treatment of follicular NHL can induce frequent and durable responses, leading in some patients to extended survival (40% to 60% at 10 years).

The efficacy of interferon alfa-2b given concurrently in patients with follicular lymphoma has been demonstrated by the results of the GELF study, on the basis of which Intron A has been approved for this indication in 1992 under the Concertation Procedure No 18. The GELF study was a randomised study (CHVP versus CHVP + Intron A), including 242 patients with follicular lymphoma with high tumour burden, who received 5 million IU three times a week for 18 months. Although the optimal dosage and duration of treatment for Intron A was not yet established, the dosing regimen and schedule of the GELF study showed a benefit/risk ratio in favour of this combination therapy. Intron A was relatively well tolerated at the proposed dose, which should be therefore recommended. The best results, i.e. a significantly longer overall survival, were described in the GELF study that gave 18 months of treatment compared to 8 to 12 months in others trials. Treatment longer than 18-month has not yet been tested.

As a result of the evaluation, the CPMP agreed on the treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as CHOP-like regimens.

Hairy cell leukaemia

Hairy Cell Leukaemia (HCL) or leukemic reticuloendotheliosis, is a rare malignant lymphoproliferative disorder. The disease is characterised by circulating B lymphocytes that display prominent cytoplasmic projections and that have a characteristic pattern of infiltration in bone marrow and spleen. Patients often present with splenomegaly and rare lymphoadenopathy, and examination of the peripheral blood usually reveals pancytopenia. Therapy can induce remissions in HCL which modify the prognosis for patients with this disease.

Several clinical trials with Intron A in the treatment of HCL were carried out. A total of 752 patients were evaluated in 16 different studies. An overview of the results obtained in these studies showed that Intron A therapy is associated with high overall responses rates. Intron A induced a normalisation of peripheral blood count in more than 80% of treated patients. Partial response was achieved in 60.5% of patients; complete response was achieved in 11.5% while the remaining patients showed only a minor response or a progression of the disease.

A flu-like syndrome consisting of fever, myalgia, and fatigue is the most common adverse effect observed. Other adverse effects include skin rash, nausea and vomiting, headache, back pain and taste changes.

As a result of the evaluation, the CPMP agreed to maintain the treatment of patients with hairy cell leukemia.

Carcinoid tumours

Carcinoid tumours are rare neoplasms developing in lung or in the gastrointestinal tract. Almost all gastrointestinal carcinoid tumours are found in three locations: appendix, small bowel and rectum. They arise from enterochromaffin cells, which produce serotonin as well as histamine and vasoactive peptides. The carcinoid syndrome is a manifestation of an advanced disease. In most patients manifesting the carcinoid syndrome an abdominal mass is palpable or a hepatomegaly clinically detectable. The clinical hallmarks of the carcinoid syndrome are flushing of the upper body and watery diarrhea confirmed by the findings of increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.

The documentation supporting the use of Intron A in the treatment of carcinoid tumours covers published and unpublished studies including 264 patients with carcinoid tumours predominantly of mid-gut origin, and with metastases. It was considered that a response occured in 101 patients, although response criteria differ between studies. Response rate (remission of diarrhea and of flushing) in patients with carcinoid syndrome was 70%. Objective tumour regression occurs only in a small percentage of patients. The Norwegian Carcinoid Study, in which patients treated for more than one year survived longer than those treated for only one year, suggests that life is extended. However, this is the only publication to suggest prolongation of life. The documentation contains only one case of a complete response to Intron A and the duration of that response is unknown.

The adverse events encountered during treatment were in general those commonly experienced with interferon treatment, maily the presence of "flu-like" symptoms. Persistent fatigue (up to 60% of patients), augmentation of hepatic enzymes (in about 20% of patients), depression (in about 10% of patients) was also observed in the course of treatment.

The company proposed also to include treatment of patients with or without carcinoid syndrome. The evidence from the original dossier was that approximately 70% of patients with hormonally induced symptoms had some degree of relief. But those with non-hormonally induced symptoms, such as pain, had little benefit. Since the company provided no new data to support the claim, the CPMP recommended treatment only for patients with carcinoid syndrome.

As a result of the evaluation the CPMP agreed to the treatment of carcinoid tumours with lymph node or liver metastases and with carcinoid syndrome.

Malignant melanoma

Melanomas are malignant neoplasms arising from melanin-producing cells of the basal layer of the epidermis. The exact cause of melanoma is unknown although risk factors have been intensively studied. Melanomas tend to occur at sites of intermittent, intensive sun exposure rather than at body sites receiving the greatest UV irradiation. Major risk factors for melanoma include changing nevus, increased age, large number of moles, and history of multiple atypical moles.

Surgery is the primary mode of treatment for localised cutaneous melanoma, i.e. stages II, using the American Joint Committeee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) staging system for malignant melanoma and I. The risk of local recurrence (as well as metastatic disease) increases with tumour depth (4 mm or more), anatomic location of the primary tumour, and histologic evidence of ulceration in the primary melanoma.

Metastases from melanoma may occur locally, regionally and distally. The most common initial sites of disease relapse are the skin, subcutaneous tissue and lymph nodes. Visceral metastases are most often seen in the lungs, followed by the brain, liver, gastrointestinal tract, and bone. Stage III melanoma (AJCC) is defined as regional lymph node metastasis and occurs in patients with primary cutaneous melanomas with a mean thickness of 3-4 mm. The number and percentage of positive lymph nodes (i.e. tumour burden) affect prognosis in stage III disease. Distant skin, nodal, visceral, skeletal or central nervous system metastases are classified as stage IV disease.

The company applied for the following indication: "Malignant Melanoma: Adjuvant therapy following surgery in patients who are at high risk of relapse" with detailed posology recommendations.

A newly performed assessment of the efficacy and toxicity data of the ECOG study provides a positive efficacy/toxicity profile. A quality adjusted retrospective survival analysis was also carried out for the ECOG study data.

A randomised, controlled study involving 287 patients with either a deep primary (T4, Breslow index more than 4 mm) or a regionally metastatic (N1) melanoma was performed between 1984 and 1990. Analysis of the results shows a significant impact of adjuvant treatment with Intron A on relapse-free and overall median survival times of patients.

Adverse events observed with high doses of Intron A in the regimen recommended for melanoma therapy are similar in nature and in incidence to those seen with other indications. These adverse events include fatigue, depression, leukopenia, or hepatic toxicity.

The company indicated that they maintain their commitment to provide the CPMP with the results of two ongoing clinical trials (ECOG 1690 and ECOG 18952), which test lower dose regimens. Revision of the posology section of the SPC would be made if a lower regimen were proved to be the minimum (optimum) effective dosage.

Further to the evaluation of supportive data, the CPMP agreed on the treatment as adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g. patients with primary or recurrent (clinical or pathological) lymph node involvement.

Multiple myeloma

Multiple myeloma is characterised by the proliferation of a single clone of plasma cells producing a monoclonal protein (immunoglobulin) refered to as the M-protein. The plasma cell proliferation usually results in extensive skeletal destruction with osteolytic lesions, hypercalcaemia, anemia, and, occasionally, plasma cell infiltration in different organs and tissues. The excessive production of M-protein can lead to renal failure, recurrent bacterial infections, or hyperviscosity syndrome.

The clinical manifestations of patients with multiple myeloma consist of bone pain, weakness and fatigue, which are often associated with anemia. Major symptoms may result from an acute infection, renal failure, hypercalcaemia or amyloidosis. Diagnosis is confirmed by the presence of the M-protein in the serum or urine and an increased number of bone marrow plasma cells.

The CPMP considered the claimed indication: "Multiple Myeloma: as part of induction therapy, as maintenance therapy in patients who achieved objective remission on induction therapy, and in patients who have relapsed".

The CPMP performed a critical assessment of the benefit/risk ratio of Intron A on the basis of submitted data, the existing conclusions of the Concertation Procedure No 18 of 10 July 1991 and the present state of scientific knowledge on treatment of multiple myeloma.

The CPMP agreed to consider maintenance therapy as a potential indication if the company would provide appropriate answers to the CPMP list of questions.

In particular, the company was asked to submit the final report of the Westin J trial, as requested with CPMP opinion on Concertation Procedure No 18 var 2 of 10 July 1991 and further data of randomised controlled clinical trials which can better characterise the exact role of interferon alfa-2b in maintenance therapy in multiple myeloma.

As a result of the evaluation, the CPMP agreed on the treatment as maintenance therapy in patients who achieved objective remission (more than 50% reduction in myeloma protein) following initial induction chemotherapy. Current clinical experience indicates that maintenance therapy with Intron A prolongs the plateau phase; however effects on overall survival have not been conclusively demonstrated.

Chronic Myelogenous Leukemia

The Chronic Myelogenous Leukemia (CML) is a disease characterized by three well defined stages: an initial (chronic) phase, of variable duration ranging from a few months to a few years, an accelerated phase of variable duration and a terminal (blast) phase, which has a median duration of 2 to 4 months. The disease progresses in most cases from the chronic phase to accelerated and blast phases. In some patients, blast crisis develops without an antecedent of accelerated phase.

The accelerated phase is accompanied by acquisition of cytogenic abnormalities in addition to the Philadelphia chromosome (translocation between chromosomes 9 and 22) and by an increased resistance to therapy, including severe thrombocytopenia, basophilia, and increased blasts. The blast crisis is a highly malignant, secondary acute leukemia, defined by the presence of 30% or more blasts in the peripheral blood or bone marrow, or extramedullary blasts. The blasts affect the normal elements of the marrow, leading to bleeding or hemorrhage, infection and thrombosis in the central nervous system, which result in the death of the patient.

Symptoms and signs usually develop slowly in the chronic phase and are related to leukocytosis, splenomegaly or thrombocytosis.

The documentation supporting the use of Intron A in the treatment of CML consisteds of four controlled studies, including two phase III clinical trials, and four uncontrolled phase II studies. Interferon alfa-2b has been administered in monotherapy in 591 patients and in combination therapy in 221 patients (hydroxyurea, low-dose cytosine arabinoside). Most patients were in early chronic phase CML. The median duration of treatment ranged from 5 to 21 months (frequency of administration ranged from once daily to three times weekly).

Therapy with interferon alfa-2b is associated with side effects observed early in the course of treatment. Initially patients might experience flu-like symptoms, including fever, fatigue, headache, myalgia, arthralgia.

Research initiatives for the treatment of CML have been historically aimed at achieving a durable or long-lasting cytogenetic response. A cytogenetic response has been associated with a decrease in tumour burden and prolonged survival in several studies.

The only treatment modalities that have consistently demonstrated significant prolongation of survival are alpha-interferons and allogeneic stem cell transplantation. Allogeneic stem cell transplantation is to date the only proven method of cure of the disease. However this treatment modality is only feasible in a minority of patients with the disease, either because of age or lack of a suitable stem cell donor.

Large randomised clinical studies, comparing interferon alfa-2b alone with conventional chemotherapy, have demonstrated a significant improvement in haematological and cytogenetic response and consequently a survival benefit for interferon alfa-2b treated patients. Despite these promising data, the majority of patients treated with interferon alfa-2b alone are still not able to achieve a durable cytogenetic response.

Combination therapy is considered as a rational approach, as laboratory studies have demonstrated synergistic growth inhibition of leukaemic myeloid progenitors with the co-administration of interferon-alfa and cytarabine (Ara-C). Unfortunately, the molecular or functional mechanism whereby interferon-alfa induces clinical haematological and cytogenetic responses in CML is not clearly elucidated.

Clinical efficacy (controlled studies only)

The following submitted studies compared the survival of patients treated with interferon alfa-2b or hydroxyurea as conventional therapy (Table 1):

- study I-87-204 (Broustet, MD), C86-047 (Dosik, MD), I87-306 (Bormanis, MD) ,
- M-87-756A (Benelux CML Study Group - Prof. Kluin-Nelemans, MD),
- German Multicenter Study Group CML I Study (Prof. Hehlmann, MD). This study was assessed in 1995.
- study H96-211 (F. Guilhot and al.) This study was designed as follow up of the former LMC-88 study, assessed in 1995.

Except for the German CML-1 study (Hehlmann), all patients had Ph+CML.

Patient population (Controlled Studies in CML; post-1995 submission update)

STUDY CODE	Patients entered	Patients evaluated	Patients treated with interferon alfa-2b alone	Patients treated with comparator
C-86-047/I-87-204/I-87-306	209	202	103	99 HU
CML-1	622	513	43 (90 interferon alfa-2a)	380 (194 HU 186 BU)
M-87-756-A	200	195	100	95 HU
LMC-88	237	206	104	102 (interferon alfa-2b+ARA-C)
H96-211	745	745	373	372 (interferon alfa-2b+ARA-C)
TOTAL	**2013**	**1861**	**723**	**1048 (474 interferon alfa-2b)**

A total of 1197 patients of both sexes have been treated with interferon alfa-2b in the controlled phase 3 clinical trials, including 474 patients were treated with interferon alfa-2b in combination with Ara-C. All these studies restricted the patient population to early stage or newly diagnosed chronic phase CML. Patients with blastic transformation or disease acceleration were excluded.

The 1197 patients were treated with interferon alfa-2b with doses ranging from 3 x 10^6 IU three times a week to 5x10^6 IU/m²/day in the five phases 3 controlled trials. Median treatment duration ranged from 5 months to 20.9 months. The majority of patients was treated more than one year and were adults.

Based on the results of an early pilot study of continuous infusion low-dose cytarabine in patients with stable chronic phase CML, Phase II and III studies of interferon alfa-2b in combination with cytarabine for the treatment of CML were initiated, to determine if this approach improved major cytogenetic response rates and thereby overall survival in CML.

Study H96-211, designed as follow up of the former LMC-88 study and lasting from january 1991 to december 1996, included 745 patients with Ph+ chronic phase CML, who received at random the combined treatment interferon alfa-2b + low dose Ara-C (n=372), or interferon alfa-2b alone (n=373). All subjects also received concurrent hydroxyurea (10-50 mg/kg/day) at study entry to control the white cell blood count.

Patients receiving combination therapy were treated during an average of 364 days with interferon alfa-2b 5x10^6 units/m²/day (maximum 9/10^6 units per day, plus Ara-C 20 mg/M²/day for 10 consecutive days a month (maximum of 40 mg for 15 consecutive days per month, once daily, subcutaneously).

Patients receiving monotherapy with interferon alfa-2b 5x10^6 units/m² once daily subcutaneously (to a maximum dose of 9x10^6 units a day), were treated on an average of 291 days.

In study H96-211 the 3 year survival rate was significantly longer in the interferon alfa-2b plus Ara-C group than in the interferon alfa-2b alone group (86% vs.80%, hazard ratio 0.62, p=0.0057).

Median survival has not yet been reached in either group.

The 6 month haematological response was significantly higher in the associated therapy group compared to the monotherapy group (65% vs.55%, p=0.004).

Major cytogenetic responses at 12 months of treatment were more frequent with combination therapy than with monotherapy (36% vs. 24%, p<0.001).

The combination of Ara-C and interferon alfa-2b prolonged the overall survival at 3 years in the study patients.

This correlated with the higher incidence of major cytogenetic responses observed in the combination therapy group, a finding that confirms at least four previous studies, showing that improved cytogenetic response is associated with improved survival.

Clinical safety

(In studies C-86-047/I-87-204/I-87 - CML 1 306 - M-87-756-A - LMC-88 - H 96-211)

A majority of patients (≥ 80%) receiving interferon alfa-2b experienced at least one adverse event. The only adverse events reported with a greater than 50% frequency were associated with the flu-like syndrome seen commonly with inferferon use, e.g. fever, fatigue, myalgia, arthralgia, and headache. Additional adverse experiences wihch were reported by more than 10% of the patients in either treatment arm included : anorexia, vomiting, back pain, dizziness, bone pain, myalgia, depression, insomnia, viral infection, alopecia, pruritus, rash and increased sweating.

In the Guilhot study, the incidence and severity of adverse events were similar to previous interferon monotherapy study i.e. 79% of the patients treated with interferon alfa-2b and 75% of patients treated with the association of interferon alfa + ARA-C.

Of note, a greater incidence of Grade 3 and 4 neutropenia and asthenia was observed with the association of interferon alfa + ARA-C.

A higher haematological toxicity was noticed in the combination therapy arm, but this was not associated with significant clinical sequelae.

In summary, the trials presented in this file have demonstrated that:

- Interferon alfa-2b (used alone or in association with Ara-C), for the treatment of CML, is able to induce durable and lasting haematological, cytogenetic and clinical remissions and represents a significant prolongation of survival. Overall, interferon alfa-2b treatment is associated with remission of disease (both cytogenetically and haematological) in a minority of patients.
- Moreover, these results can be significantly improved when interferon-alfa 2b is associated with chemotherapy i.e. Ara-C : survival is numerically prolonged in interferon treated patients in comparison to patients treated with conventional chemotherapy (hydroxyurea or busulfan). In all randomised trials to date, interferon treated patients have a median survival of alfa 60 months.

As a result of the evaluation, the CPMP concluded that the benefit/risk ratio for interferon alfa-2b in combination with cytarabine in the treatment of CML was as favourable.

Hepatitis B

Viral hepatitis ranks as a major public health concern in industrialised countries. Hepatitis B and Hepatitis C are both serious diseases whose complications are life-threatening.

Chronic hepatitis B (CHB) is one of the leading causes of death in adults worldwide. Approximately 5% of the world population, more than 300 million people, are chronic carriers of hepatitis B surface antigen (HBsAg). An appreciable number of these people have chronic liver disease and are therefore at risk of progression to cirrhosis or hepatocellular carcinoma.

Nearly 80% of all HBV carriers are found in the Asian subcontinent, where the prevalence of HBsAg positivity ranges from 8% to 10%.

Countries in Southern Europe, the Middle East and Japan have intermediate prevalence rates (1%-3%), while the lowest rates are found in central and Northern Europe and in the United States (<0.5%) Hepatitis B virus can be found in the blood and, to a lesser extent, in saliva, semen and other body fluids of an infected person. The symptoms of hepatitis B include fatigue, poor appetite, fever,

vomiting and occasionally joint pain, hives or rash. Symptoms may appear 2 to 6 months after exposure, but usually within 3 months. Asymptomatic carriers are known. Hepatitis B may either heal slowly or leads to chronic liver disease and cirrhosis.

The majority of patients who are infected with the hepatitis B virus do not develop chronic disease.

High serum levels of HBsAg and the presence of HBeAg appear early in the infection course. When acute HBV infection heals without chronicity, these antigens are replaced with the respective antibodies anti-HBs and anti-HBe. Persistent serum levels of HBsAg indicate chronic HBV infection.

However, since serum HBsAg is frequently part of incomplete viral forms rather than the complete HBV virion, some HBsAg carriers do not exhibit detectable HBV DNA in serum nor in the liver.

Generally, undetectable serum HBeAg and HBV-DNA in chronic HBsAg carriers are neither associated with abnormal liver histology nor with chronic liver disease. By contrast, detectable serum HBeAg or HBV-DNA are highly correlated with the presence of HBV virions in serum (electron microscopy), with infectivity of serum and with actively replicating HBV in liver cells.

Longitudinal studies of the natural history of chronic HBV infection indicate an annual rate of spontaneous loss of HBeAg of about 7 to 20%.

Interferon therapy is to date the only anti-viral treatment whose long-lasting efficacy has been established as a treatment of chronic hepatitis B in adults.

During harmonisation of IntronA SmPC in the frame of the Article 11 referral, consensus was reached regarding the target population to be treated among chronic carriers of HBV. Treatment was recommended in patients with chronic hepatitis (persistently elevated serum ALT, HBsAg) showing signs of viral replication (HBeAg, HBV-DNA or DNA polymerase), and at high risk of progression towards cirrhosis (histologically proven chronic active hepatitis as assessed by the Knodell inflammatory and fibrosis score on biopsy samples).

The aim of treatment is to interrupt viral replication and reach the non-replicative phase quicker than allowed by the natural history of the disease, in order to avoid progression towards cirrhosis.

Those efficacy criteria are only surrogate markers of efficacy, and it is not known whether the risk of hepatocellular carcinoma is significantly reduced, all the more as HBsAg is rarely totally eliminated. In adults, about 30% of patients are responders, and low pre-treatment serum HBV-DNA levels are a positive predictor of treatment success.

The data supporting the use of IntronA in chronic hepatitis B consist of results from several randomised controlled clinical trials. Intron A was shown to inhibit replication of the HBV. Loss of markers of viral replication occurs in 30 % to 40% of treated patients and this rate is significantly higher than the spontaneous response rate observed in untreated control patients.

The results of a single randomised placebo-controlled clinical trial in children aged 1- 17 years with chronic hepatitis B were assessed during the Centralised procedure. Patients were treated for 6 months 6 MIU/m^2, followed by a 24-week observation period post-treatment. Due to a methodological flaw in the analysis of the results, CPMP determined that an assessment of efficacy could not be made. Although the safety analysis from this study shows that the overall safety profile of interferon alfa-2b in children is essentially similar to that in adults, a safety concern was raised by CPMP due to a lower mean height gain in the 2-12 years treated subgroup compared to the untreated/control group. Therefore, the indication for treatment of hepatitis B in children was not granted, but information on the trial and safety in children is to be provided in Section 5.1 of the SPC.

Hepatitis C

Viral hepatitis ranks as a major public health concern in industrialised countries. Hepatitis B and Hepatitis C are both serious diseases whose complications are life threatening.

Hepatitis C is spread by exposure to blood from an infected person, such as through a blood transfusion or sharing needles. Patients with hepatitis C may experience appetite loss, fatigue, nausea and vomiting, vague stomach pain and jaundice. Symptoms may occur from 2 weeks to 6 months after exposure but usually after 2 months. Some people carry the virus in their bloodstream and may remain contagious for years. The disease may occur in the acute form and be followed by recovery or it may become chronic and cause symptoms for years. Chronic hepatitis C accounts for a large number of cirrhosis and liver failure.

Moreover Hepatitis C Virus (HCV) infection has been identified as risk factors for the development of hepatocellular carcinoma.

Once an individual is infected with HCV, use of antiviral therapy to prevent or reverse the chronic carrier state is the main therapeutic option.

In chronic hepatitis C Intron A treatment produces normalisation of alanine aminotransferase (ALT) levels in 40% to 50% of treated patients. Sustained normalisation after discontinuation of treatment is seen in 15% to 20% of patients.

The optimal duration of interferon alfa-2b monotherapy in chronic hepatitis C has not been established. However, the prolongation of treatment up to 18 months might be useful in some cases of chronic hepatitis C and this has been taken into consideration in the recommendation in section 4.2 of the SPC.

Combination therapy with ribavirin in the treatment of chronic Hepatitis C.

An application for a centralised Marketing authorisation for the use of ribavirin in association with interferon alfa-2b in the treatment of chronic hepatitis C was submitted by SP Europe in June 1998.

During the February 1999 CPMP meeting, it was recommended that a Marketing Authorisation be granted for ribavirin as associated with interferon alfa-2b in the treatment of chronic hepatitis C.

The European Commission granted a Marketing Authorisation for ribavirin (Rebetol/Cotronak) on 7 May 1999.

The data on the co-administration of interferon alfa-2b with ribavirin reviewed in the Rebetol assessment were included with the centralised application to support an extension of the interferon alfa-2b indication for hepatitis C to include combination with ribavirin as first line treatment.

IntronA contains the active ingredient interferon alfa-2b. In Europe there are other interferons available for the treatment of chronic hepatitis C (HCV) infection, but interferon alfa-2b is the only interferon for which the efficacy of the combination with ribavirin has been shown and approved.

Clinical efficacy

Since the assessment of the clinical data made during the Article 11 referral, new technology has become available which changes the standard by which efficacy is judged for hepatitis C therapy. Previously, efficacy was based on the sustained normalisation of ALT. However, now that testing for HCV RNA has become available, the potential for discrepancies between serum HCV RNA and ALT responses has become apparent. Therefore, efficacy is now based on the sustained virologic response defined as the loss of HCV RNA at least 6 months after the end of treatment.

The efficacy of the combination therapy was evaluated in:

- one phase II study (H095-058, Reichard *et al*., Lancet 1998) in naïve patients (n=100),
- two phase III studies (C95-144, I95-145) in patients who relapsed after interferon treatment (n=153 and n=192).
- two phase III studies (C95-132, I95-143) in patients with chronic HCV not previously treated with interferon (n=912 and n=832),

All were double blind, placebo-controlled trials, comparing interferon alfa-2b (3 MIU t.i.w.) monotherapy with interferon alfa-2b (3 MIU t.i.w.) plus ribavirin 1,000 (for weight <75 kg) or 1,200 (for weight >75 kg) mg/day.

Dose reductions were allowed in patients with abnormal laboratory findings, who could continue on treatment if the abnormality was within the cut-off value requiring discontinuation. Ribavirin dose was reduced for abnormalities in haemoglobin (<10 g/dl) and bilirubin (>5 mg/dl); interferon dose was reduced in case of decrease of white blood cells (<1.5 10^9/l), neutrophil (<0.75 10^9/l) and platelet (<50 10^9/l) counts.

Studies in relapse patients

The standard treatment period was 24 weeks, followed by 24 weeks of untreated follow-up. Final assessment was performed at week 48.

Response was defined as a composite endpoint combining virological response at week 48 (loss of detectable HCV-RNA /qPCR <100 copies/ml) with improvement in the HAI score in the 48 week liver biopsy (Knodell score for sum of categories I+II+III $\geq$2).

Overall responders showed improvement in both parameters. Patients with missing data (missing HCV-RNA, biopsy or both) were classified as non-responders. Relapsers were HCV-RNA negative at week 24 but positive at week 48.

The following secondary endpoints were also examined:

- response rate at week 24 (HCV-RNA qPCR)
- proportion of patients with normalisation of ALT at week 24 and 48
- proportion of patients with improvement in biopsy (categories I+II+III combined scores)
- change from pre-treatment in biopsy scores (categories I+II+III combined scores)

The primary endpoint (overall response) was evaluated at week 48, end of follow-up period, together with the histologic parameters. End of follow-up virological response rate after combined therapy was 48.6% (p<0.0001), compared with the significantly inferior rate of 4.7% for patients who received interferon alfa-2b monotherapy. Sustained improvement in Knodell score occurred in 63% of combination patients, compared to 41% of monotherapy. The overall response was 37.0% in the combination arms, 3.5 % in the monotherapy (p <0.001).

Some secondary endpoints were evaluated at end of therapy (week 24). The ALT response was evaluated as well at week 48. End of therapy virological response rates were significantly superior with combined therapy: rates were 81% for combined and 46% for monotherapy. ALT response was 89% for combined and 57% for monotherapy at week 24; 52% for combined and 15% for monotherapy at week 48.

Each of the two studies independently demonstrated that the addition of ribavirin to interferon alfa-2b resulted in an approximately 10-fold enhancement in efficacy compared to retreatment with interferon alfa-2b alone.

Also, response induced by the combined treatment seems to be more stable: of those patients who had a virologic response at the end of treatment, 58% (83/141) in the interferon alfa-2b+ribavirin group

compared to 9% (7/80) in the interferon alfa-2b+placebo group maintained the response at the end of follow-up.

In the clinical trials, patients who failed to show virological response at week 24, failed to show sustained response at week 48 (one interferon alfa-2b + ribavirin relapse patient had PCR = 200 copies/ml and became sustained responder).

An analysis of the correlation among endpoints has been made:

- Virological response and ALT level: a sustained ALT normal level is highly correlated with the eradication of detectable HCV-RNA at the end of follow-up: the number of patients with normal ALT / number of sustained virologic responders (%) is 80/83 (96%) for interferon alfa-2b + ribavirin; 8/8 (100%) for interferon alfa-2b + placebo.
- Virological response and HAI Knodell score: the decrease in hepatic inflammation is highly correlated with the eradication of HCV-RNA whatever the treatment.
- Early relapses and genotype:
  - in HCV genotype1, sustained virologic response was obtained in 29% of interferon alfa-2b + ribavirin treated patients versus 3% interferon alfa-2b + placebo treated. In other HCV genotypes, a sustained virologic response was obtained in 74% interferon alfa-2b + ribavirin treated patients versus 6% interferon alfa-2b + placebo treated.
  - in the interferon alfa-2b+ribavirin group, relapse between the end of the treatment and the end of the follow-up occurred more frequently in patients infected with HCV genotype 1.
  - logistic regression analysis of sustained virologic response demonstrated that, in addition to treatment group, HCV genotype other than 1 was a significant predictor ($p<0.001$).
- Sustained virological response and high viral load: the combined treatment is associated with sustained virological responses (40-44% for interferon alfa-2b + ribavirin against 0-3% for interferon alfa-2b + placebo) also in patients with a high HCV-RNA level at baseline:

Predictors of sustained response

Logistic regression analysis of the pooled data using virological response as the endpoint, showed that combined treatment (interferon alfa-2b + ribavirin), HCV genotype other than 1 and baseline high viral load were significant predictors of sustained virological response at 6 months after the end of treatment.

Sustained Virological Response by Baseline HCV Genotype and Virus Level/Combined results for relapse patients:

	Interferon alfa-2b + Ribavirin	**Interferon alfa-2b + Placebo**
Other Genotypes/< 2 million copies/ml	95% (19/20)	18% (3/17)
Other Genotypes/ > 2 million copies/ml	67% (36/54)	3% (2/60)
Genotype 1/< 2 million copies/ml	44% (11/25)	13% (3/24)
Genotype 1/ > 2 million copies/ml	24% (18/74)	0 (0/71)

The patients before therapy completed a QOL questionnaire, during therapy and six months following the end of therapy. All sustained responders had improvement of QOL, whatever their treatment.

Updated information on the durability of sustained virological response from a six month follow up of clinical trial patients is provided in section 6 of this EPAR.

A virologic response at 1 and 3 months is partly predictive of sustained response but does not allow to stop the treatment if it is not reached.

Studies in naïve patients

Phase II trial

The treatment period was 24 weeks, followed by 24 weeks of untreated follow-up. Final assessment was performed at week 48.

In the evaluable population, sustained response was seen in 49% of combination and 20% of interferon alfa-2b mono-therapy patients. At 24 weeks, 68% of combination and 54% of mono therapy had normal ALT, dropping to 46 % and 28 % respectively at 48 weeks.

Phase III trials

The trials (C95-132 and I95-143) evaluated the safety and efficacy of ribavirin plus interferon alfa-2b in patients with chronic HCV infection who had not previously been treated with interferon. Both trials were multicentre, double blind and placebo-controlled.

Patients were selected according to criteria similar to those employed in the interferon-experienced patient trials except that they had no past exposure to interferon or ribavirin. Adults had to have detectable HCV-RNA by the National Genetics Institute (NGI) PCR assay, had a liver biopsy within one year which showed changes consistent with chronic hepatitis, and had elevated ALT for the past six months. Patients with decompensated cirrhosis were excluded.

Treatment regimens and dose adjustments in patients who developed laboratory abnormalities outside of the prescribed limits were as for the previous studies. The major difference was that these trials allowed for some patients to be treated for up to 48 weeks.

Patients in C95-132 were randomised to one of four treatment groups, which were balanced according to presence/absence of cirrhosis, pre-treatment HCV-RNA level and HCV genotype; 912 patients received treatment as follows:

- interferon alfa-2b plus ribavirin for 24 weeks [I/R(24)] 228 patients
- interferon alfa-2b plus ribavirin for 48 weeks [I/R(48)] 228 patients
- interferon alfa-2b plus placebo for 24 weeks [I/P(24)] 231 patients
- interferon alfa-2b plus placebo for 48 weeks [I/P(48)] 225 patients

In this study, fibrosis was graded with Knodell HAI score and METAVIR SCORE.

Patients in I95-143 were similarly randomised with balancing for the same factors as in C95-132. The difference was that the interferon alfa-2b/placebo 24-weeks group was omitted in this study since current recommendations were to give 48 weeks interferon alfa-2b in naive patients: 832 patients received treatment as follows:

- interferon alfa-2b plus ribavirin for 24 weeks [I/R(24)] 277 patients
- interferon alfa-2b plus ribavirin for 48 weeks [I/R(48)] 277 patients
- interferon alfa-2b plus placebo for 48 weeks [I/P(48)] 278 patients

In this study, fibrosis was graded with Knodell HAI score and METAVIR score.

Groups were well balanced with regard to age, sex, ALT and source and duration of infection. There were 58-70% of patients in each group who had more than 2 million copies/ml of HCV-RNA at baseline. Overall, 64-72% had HCV genotype 1 infection, while 11-17% had genotype 2, 10-20% had type 3? From biopsies 4-5% had cirrhotic changes, 15-19% showed bridging fibrosis. (These figures do not take into account the interferon alfa-2b +placebo 24 weeks group, which is not considered in the assessment of efficacy).

A 24-week post-therapy follow-up phase then ensued in all treatment groups in both trials.

The primary efficacy variable in individual study analysis was sustained virological response (undetectable HCV-RNA as measured by the NGI PCR assay, which has a cut-off limit of <100 copies/ml) at 24 weeks post-therapy.

Secondary efficacy endpoints were: improvement in liver biopsy scores at the end of follow-up, biochemical response (ALT normalisation at the end of follow-up), combined biochemical/virological response.

For the combined results, the primary efficacy endpoint was overall response, a composite endpoint defined as the association of virological and histological responses.

In both trials, there were fewer patients who completed 48 weeks therapy compared with 24 weeks therapy; however, the losses were similar for both combined and monotherapy groups and about 70% of patients assigned to 48 weeks actually completed therapy. Almost all the patients who reached the end of treatment were available for the post-therapy follow-up.

Combined results of the studies were as follows:

- End of follow-up virological response rates after combination therapy were 33% for the 24-week treatment group and 41% for the 48-week group, compared with significantly inferior rates of 6% and 16% for patients who received monotherapy for these respective treatment periods. This shows borderline superiority for 48 *vs.* 24 weeks in each individual study (p=0.053 and 0.055), and the low percentage of sustained responders in interferon monotherapy has to be noted. The treatment difference between combination 24-week and 48-week is found to be statistically significant (p=0.008) in the meta-analysis of both individual studies.
- End of therapy virological response rates were also significantly superior with combined therapy. In the 24-week treatment groups, rates were 55%; after 48 weeks of treatment, rates were 51% Monotherapy rates were 29% (24 weeks and 48 weeks).
- Combination therapy with I/R decreased relapse rates compared to I/P. Extending duration with I/R(48) further decreased the relapse rate, making I/R(48) significantly more effective than I/R(24) (p=0.008). This was true for all HCV genotypes, particularly type 1 in which relapse rates were reduced to 26% with I/R(48). Consistently higher relapse rates were noted with type 1 than with types 2 or 3.

Relapse Rate by HCV Genotype (C95-132, I95-143)				
	I/R(24)	**I/P(24)**	**I/R(48)**	**I/P(48)**
All Genotypes	**42% (118/278)[a]**	**80% (53/66)**	**21% (55/260)**	**46% (67/147)**
1	62% (84/136)	89% (25/28)	26% (33/127)	56% (37/66)
2/3	21% (27/230)	76% (28/37)	15% (18/120)	37% (29/79)
4/5/6	58% (7/12)	0/1	31% (4/13)	50% (1/2)
a: Patients who had positive or missing HCV-RNA at End of FU÷patients who were HCV-RNA negative at the end of treatment.				

Sustained virological response rates were markedly lower for genotype 1 HCV infections compared with all non-genotype 1, whatever the treatment or duration. However, combination therapy was still superior to interferon alfa-2b alone against genotype 1.

- A virological response to therapy at 4 weeks strongly predicted a sustained response; the likelihood of a sustained response decreased with increased duration of therapy before a finding of undetectable HCV RNA. None of the patients who first became negative after Week 24 became sustained responders.

Sustained Virologic Response by Time to First Negative HCV–RNA/RT–PCR				
Time to First HCV–RNA Negative	**I/R(24)**	**I/P(24)**	**I/R(48)**	**I/P(48)**
4 wks	83% (92/111)[a]	48% (10/21)	82% (94/115)	71% (47/66)
12 wks	44% (66/149)	9% (3/32)	66% (91/137)	35% (29/84)
24 wks	19% (8/42)	0% (0/22)	44% (20/45)	15% (6/39)
36 wks	–	–	0 (0/6)	0 (0/11)
48 wks	–	–	0 (0/2)	0 (0/2)
a: Number of sustained responders÷number of patients HCV–RNA negative for the first time in the interval				

Nevertheless in study C95-132, of the 87 patients in the 48-week combination therapy group who had a sustained virological response, 40 first became negative for HCV-RNA at week 12, and 11 others at week 24 on therapy. Also, 15/29 responders in the 48-week monotherapy group first became negative for HCV RNA after the 4-week visit (11 at 12 weeks and 4 at 24 weeks).

Delayed viral clearance was also documented in 35/70 who received 24 weeks of combination therapy and had a sustained virological response at follow-up, including 30 first negative at 12 weeks and 5 at 24 weeks.

These findings indicate that treatment should not be interrupted in non-responders at week 12, contrarily to what is currently done under interferon monotherapy. In such late responders (first negative PCR at week 24), treatment should on the contrary be continued until week 48. On the other hand, the data suggest that it is not worth continuing treatment in patients with still detectable HCV-RNA at week 24.

- Baseline viral loads and HCV genotype influenced the sustained virologic response as follows:

Sustained Virologic Response to Treatment by HCV Genotype and Virus Levels (Naïve patients 24 weeks after the end of treatment)				
	Interferon alfa-2b + ribavirin 24 weeks	**Interferon alfa-2b + placebo 24 weeks**	**Interferon alfa-2b + ribavirin 48 weeks**	**Interferon alfa-2b + placebo 48 weeks**
HCV Genotype 1 and ≤ 2 million copies/ml	32 %	4 %	33 %	25 %
HCV Genotype 1 and > 2 million copies/ml	10 %	0.9 %	27 %	3 %
HCV Genotype other than 1 and ≤ 2 million copies/ml	61 %	25 %	64 %	36 %
HCV Genotype other than 1 and > 2 million copies/ml	62 %	11 %	63 %	26 %

- Overall sustained histologic response showed for the 48 weeks therapy group a mean change in Knodell score of –2.6 in the combination groups against –1.0 in monotherapy, improvement in both groups being higher compared with 24 weeks (-1.9 and -0.6 respectively).
- The majority of the patients had disease for more than 5 years. For those patients, in study C95-132, combined therapy was clearly superior to monotherapy, but 48 weeks was not better than 24 weeks of combined treatment. In trial I95-143 response rates were markedly higher than those achieved with 24 weeks or monotherapy (61% *vs* 39% and 24%).

The majority of patients included were mildly injured, with fibrosis score corresponding to the F1 METAVIR quotation.. Nevertheless, due to the high number of patients included, the 5% cirrhosis (F4 stage) and the 15% bridging fibrosis (F3 stage) correspond to approximately 400 patients (100 patients per arm), which seems enough to enable efficacy evaluation in this subgroup as a whole. For naive

patients, it is proposed that only patients with liver fibrosis or high inflammatory activity be treated with the combination (see Section 4.1 of the SPC).

Clinical safety

Overall, the reporting of adverse events was similar with interferon alfa-2b + ribavirin compared with interferon alfa-2b alone. The patterns of adverse events reported by both relapse and naïve populations were similar, and the combination therapy reflects the safety profiles of interferon alfa-2b and ribavirin administered alone.

The safety profile of interferon alfa-2b is well known. The side effects are generally dose related. Anaemia and decreases in haemoglobin are known to be associated with ribavirin and occurred more frequently in patients treated with the combination compared with those treated with interferon alfa-2b alone. Some cardio-vascular events were correlated with large haemoglobin drops, and severe and life-threatening cardiovascular complications occurred slightly more frequently in patients treated with the combination. Dosage modification guidelines have been defined for all patients, with additional restrictions for patients at risk for cardiovascular complications.

Conclusions

The results of these trials independently demonstrated that the addition of ribavirin to interferon alfa-2b results in a significant increase in efficacy in both naïve and relapse patients compared to treatment with interferon alfa-2b alone. These studies also confirm that interferon alfa-2b as monotherapy offers clinical benefit following one year of therapy in naïve patients. However, only 5 % of relapse patients respond to additional course of interferon alfa-2b monotherapy. Therefore, the benefit of monotherapy in relapse patients is questionable and a recommendation for combination therapy for these patients is to be included in the SPC.

As a result of the evaluation, the CPMP concluded that the benefit/risk profile for interferon alfa-2b is favourable in the treatment of chronic hepatitis C. An enhancement of efficacy is seen when interferon alfa-2b is co-administered with ribavirin and is the optimal therapy for most patients. Interferon alfa-2b as monotherapy provides potential benefit only for a subgroup of patients intolerant or contraindicated for ribavirin. Therefore, the recommended posology in the SPC is modified to show that:

- In relapse patients, interferon alfa-2b must be used in combination with ribavirin.
- In naïve patients, the optimal therapy is the combination of interferon alfa-2b + ribavirin, but interferon alfa-2b may still have a useful therapeutic role in some patients, mainly those intolerant to or contraindicated for ribavirin.

5. Overall initial conclusions and benefit/risk assessment

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral Safety and batch-to-batch consistency has been documented and the relevant tests are performed according to the agreed specifications.

Taking into account both the preclinical data and the extensive human clinical exposure to interferon alfa-2b, it is concluded that the benefit/risk for the use in humans is positive. The adverse effects to patients given the therapeutic dosing regimen can be monitored and are reversible. It is the overall conclusion that patients can be safely treated for prolonged periods with interferon alfa-2b.

As far as the indication treatment of **hepatitis B** in children is concerned, the CPMP considered that the study presented major methodological concerns, and given the ADRs profile of interferon alfa-2b

is not satisfactory, this indication shall not be granted. Information on the trial conducted in children is provided in Section 5.1 of the SPC.

The update of the indication "treatment of Chronic **Hepatitis C**" is acceptable, as it puts in line the prescribing information of IntronA with the authorised indication for ribavirin.

According to the most recent international Consensus, the target population with hepatitis C should exhibit histologically proven signs of activity of the disease as demonstrated on a pre-treatment biopsy graded with the Knodell HAI score. Only histologically proven chronic hepatitis should be treated, therefore the need for biopsy is maintained in the SPC and Package Leaflet.

With reference to the treatment of **CML,** it has been demonstrated that the association of Ara-C and interferon alfa produced significantly more major cytogenetic responses after 12 months of treatment and significantly prolonged the overall survival at 3 years, compared to interferon alfa alone.

Although haematological toxicity was higher for the combination of Ara-C+ interferon alfa-2b, compared to interferon alfa-2b alone, this was not associated with significant clinical sequelae.

Therefore, the CPMP is of the opinion that the risk/benefit ratio for the association of Ara-C + interferon alfa-2b therapy, is favourable.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, (partly already assessed in the Article 11 harmonisation procedure), the CPMP considered by consensus that the benefit/risk profile of IntronA was favourable in the treatment of:

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated ALT and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C: Treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g., those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.
The efficacy of interferon alfa-2b in the treatment of hepatitis C is enhanced when combined with ribavirin.

Hairy Cell Leukaemia: Treatment of patients with hairy cell leukaemia.

Chronic Myelogenous Leukaemia: Monotherapy: Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematologic and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy: The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple Myeloma: As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular Lymphoma: Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, fever > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serious effusion, or leukaemia.

Carcinoid Tumour: Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant Melanoma: As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

On these grounds the CPMP, during the meeting of 21 October 1999, recommended the granting of a Marketing Authorisation for IntronA for the above mentioned indications.

6. Clinical efficacy data in the indication of chronic hepatitis C submitted post authorisation

Additional efficacy information was gathered in the indication of chronic hepatitis C from clinical trials which were still ongoing at the time of the authorisation. In this update the number of patients with chronic hepatitis C treated in clinical trials with interferon alfa-2b, alone or in combination with ribavirin, had increased to 2,522.

In trial C/198-580, the sustained response rate increased to 56% for patients receiving combination interferon alfa-2b with ribavirin who were compliant with the treatment regimen (≥80% of their treatment) compared with 32% in patients who received <80%.

Additional information for the treatment of naïve patients was provided on the sustained virological response by genotype and viral load as shown in the table below.

Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	***I N=503 C95-132/I95-143***	***I/R N=505 C95-132/I95-143***	***I/R N=505 C/I98-580***
All Genotypes	***16 %***	***41 %***	***47 %***
Genotype 1	*9 %*	*29 %*	*33 %*
Genotype 1 ≤2 million copies/ml	*25 %*	*33 %*	*45 %*
Genotype 1 > 2 million copies/ml	*3 %*	*27 %*	*29 %*
Genotype 2/3	*31 %*	*65 %*	*79 %*

I IntronA (3 MIU TIW)
I/R IntronA (3 MIU TIW) + ribavirin (1,000/1,200 mg/day)

Increased efficacy of Intron A when used in combination with ribavirin was noted.

Furthermore, the CPMP decided that not all patients with chronic hepatitis C need to have a liver biopsy before treatment commences. In the Consensus statement from the French Consensus Conference on Hepatitis C, it is stated that biopsy may not be necessary if a decision to treat already has been made on other grounds and the primary objective is viral eradication. This is basically in line with the NIH Consensus Guideline and some other National Guidelines. The viral eradication rate is so high for patients with genotype 2/3, for example, that treatment is indicated in many cases even if the histology turns out to be benign. Therefore histology is not always needed.

The CPMP recommended that although the term "histologically treated" should be deleted from section 4.1 of the SPC, the following warning should be added to section 4.4: *"All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment."*

The additional information led to changes to the efficacy information in the SPC. Section 5.1 of the SPC was updated to reflect that the number of patients with chronic hepatitis C treated in clinical trials with interferon alfa-2b, alone or in combination with ribavirin, had increased to 2,522. In trial C/198-580, the response rate increased with compliance with 56% of patients who had received ≥80% of their treatment having a sustained response 6 months after completion of treatment compared with 32% of patients who received <80%. Information on the increased efficacy of interferon alfa-2b when used in combination with ribavirin was also included.

7. Clinical safety data submitted post authorisation

Although warnings about central nervous system (CNS) effects were included the SPC at the time of authorisation, these warnings, in section 4.4, were strengthened. The adverse events of suicide and suicidal ideation were added to section 4.8 to highlight the safety concerns regarding CNS reactions. Following issues raised during the initial assessment of the product and in the first Public Safety Update Report (PSUR), the MAH also proposed addition of the adverse events: peripheral ischaemia, seizure, hypertriglyceridaemia and aplastic anaemia to section 4.8 of the SPC.

Cases of patients developing cutaneous or pulmonary sarcoidosis have been reported in the literature and 11 cases were reported in the 2nd PSUR. There is also a plausible explanation as to why this may occur with the use of interferons. The CPMP agreed with the proposal of the MAH to include statements on sarcoidosis in sections 4.4 and 4.8 of the SPC.

Following a review of 82 cases of hypertriglyceridaemia, it was concluded that elevations in triglycerides occur in patients with and without other risk factors or history of dyslipidaemia. Elevations are often significant, may have clinical sequelae and may require treatment. Although hypertriglyceridaemia was already mentioned in the current SPC, the CPMP agreed that the addition of a sentence in section 4.4, recommending the monitoring of lipid levels, appeared necessary given the data.

The SPC already contained a warning in section 4.4 that patients experiencing ophthalmic symptoms during treatment with Intron A should have an eye examination and that a baseline examination was desirable in patients with hypertension or diabetes mellitus. Following the submission of the 4th PSUR (9 Sept 2001- 8 March 2002) and a change in the US labelling for all marketed alpha interferon products, the MAH decided to strengthen the EU SPC warning with regard to ocular disorders and to suggest that all patients should have baseline eye examinations. The MAH suggested that patients with other disorders associated with retinopathy be advised to have periodic eye examinations during therapy and discontinuation of Intron A therapy should be considered in patients who develop new or worsening ophthalmological disorders.

The adverse reactions: retinopathies (including macular oedema), loss of visual acuity or visual field, optic neuritis and papilloedema were added to section 4.8.

Section 4.8 was also updated to include a statement that the common adverse reactions reported in patients receiving IntronA in combination with ribavirin were also reported during Intron A monotherapy

Section 4.4 already contained a warning regarding the development of autoantibodies and autoimmune disease. This warning was strengthened with regard to the risk of developing autoimmune disorders along with a recommendation that there should be a careful evaluation of the benefit risk of continued interferon therapy in patients developing signs or symptoms compatible with autoimmune disorders.

Following discussions at the CPMP and PhVWP, a class labelling was adopted to warn of the increased risk of adverse reactions when alfa interferons and ribavirin are used in conjunction with Highly Active Anti-Retroviral Therapy in patients co-infected with HCV/HIV. This warning was incorporated into section 4.4.

The MAH reviewed all cases of erythema multiforme (EM), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which had occurred in patients treated with either Intron A/Viraferon or Pegintron/ViraferonPeg up until 30 August 2002. Almost half of the cases involved use in combination with ribavirin. IntronA has been marketed for over 10 years (initially authorised nationally then as a centrally authorised product since March 2000) but ribavirin only for 4 years so it may be indicative that combination therapy carries a higher risk of EM, SJS or TEN. As a result of the review, section 4.8 was updated to add the adverse events: Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme.

Information on autoimmune and immune mediated disorders was also added. The MAH took the opportunity to bring section 4.8 into line with current guidelines with the consequential change of section 4.8 to a tabular format with the addition of adverse reactions occurring at the 1% level. As a consequence the following adverse reactions occurring at a frequency of 1% were added: tremor, dehydration, gingivitis, stomatitis ulcerative, hypocalcaemia, thirst, arthritis, sleep disorder, breast pain, dysmenorrhoea, vaginal disorder, bronchitis, rhinorrhoea, eczema, psoriasis (new or aggravated), skin disorder, micturation frequency, lymphadenopathy and lymphopenia.
A warning regarding the teratogenicity and embryocidicity of ribavirin was added to section 4.6 since the recommended use of Intron A in the treatment of hepatitis C is in combination with ribavirin.

8. Overall Conclusions

IntronA treatment has been demonstrated to have a positive risk/benefit ratio in the following patient populations when used as indicated:

Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated ALT and histologically proven active liver inflammation and/or fibrosis.

Chronic Hepatitis C: Treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The best way to use IntronA in this indication is in combination with ribavirin.

Hairy Cell Leukaemia: Treatment of patients with hairy cell leukaemia.

Chronic Myelogenous Leukaemia:
Monotherapy: Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematologic and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy: The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple Myeloma: As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular Lymphoma: Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, fever > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serious effusion, or leukaemia.

Carcinoid Tumour: Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant Melanoma: As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.