NIHS Notification No. 3490

18th September 2001

To: Director-General of Pharmaceutical and Medical Safety Bureau,
Ministry of Health, Labour and Welfare

From: Director of the National Institute of Health Sciences

Evaluation Report

This is to report the outcome of the evaluation of the approval application of the said medicinal products in the Pharmaceutical and Medical Devices Evaluation Centre.

[Product Name] Rebetol Capsules 200mg

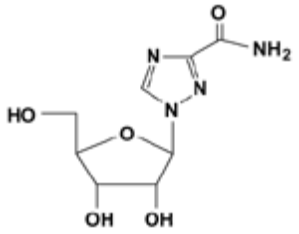
[Non-propriety Name] Ribavirin

[Applicant] Schering-Plough KK

[Submission Date] 27th April 2001

[Application Category] 1-(1) A medicine containing a new active ingredient

[Chemical Structure]



Molecular Weight: 244.40

Structural Formula: $C_8H_{12}N_4O_5$

Chemical Name: 1-β-D-Ribofuranosyl 1H-1,2,4-triazole-3-carboxamide

[Product Name] Intron A Injections 300, 600 and 1,000

[Non-propriety Name] Interferon alpha-2b, recombinant

[Applicant] Schering-Plough KK

[Submission Date] 27th April 2001

[Application Category] 1-(4) A medicines with new indications

[Chemical Structure]

Molecular Weight: 19,268.91

Structural Formula: $C_{860}H_{1353}N_{229}O_{255}S_9$

Chemical Name: see the attachment.

[Remarks] Priority evaluation item

[Evaluated by] Evaluation Division I

(Attachment)

cysteinyl-aspartyl-leucyl-prolyl-glutaminyl-threonyl-histidyl-seryl-leucyl-glycyl-seryl-arginyl-arginyl-threonyl-leucyl-methionyl-leucyl-leucyl-alanyl-glutaminyl-methionyl-arginyl-arginyl-isoleucyl-seryl-leucyl-phenylalanyl-seryl-cysteinyl-leucyl-lysyl-asparatyl-arginyl-histidyl-aspartyl-phenylalanyl-glycyl-phenylalanyl-prolyl-glutaminyl-glutamyl-glutamyl-phenylalanyl-glycyl-asparaginyl-glutaminyl-phenylalanyl-glutaminyl-lysyl-alanyl-glutamyl-threonyl-isoleucyl-prolyl-valyl-leucyl-histidyl-glutamyl-methioyl-isoleucyl-glutaminyl-glutaminyl-isoleucyl-phenylalanyl-asparaginyl-leucyl-phenylalanyl-seryl-threonyl-lysyl-aspartyl-seryl-seryl-alanyl-alanyl-tryptophyl-asparatyl-glutamyl-threonyl-leucyl-leucyl-aspartyl-lysyl-phenylalanyl-tyrosyl-threonyl-glutamyl-leucyl-tyrosyl-glutaminyl-glutaminyl-leucyl-asparaginyl-aspartyl-leucyl-glutamyl-alanyl-cysteinyl-valyl-isoleucyl-glutaminyl-glycyl-valyl-glycyl-valyl-threonyl-glutamyl-threonyl-prolyl-leucyl-methionyl-lysyl-glutamyl-aspartyl-seryl-isoleucyl-leucyl-alanyl-valyl-arginyl-lysyl-tyrosyl-phenylalanyl-glutaminyl-arginyl-isoleucyl-threonyl-leucyl-tyrosyl-leucyl-lysyl-glutamyl-lysyl-lysyl-tyrosyl-seryl-prolyl-cysteinyl-alanyl-tryptophyl-glutamyl-valyl-valyl-arginyl-alanyl-glutamyl-isoleucyl-methionyl-arginyl-seryl-phenylalanyl-seryl-leucyl-seryl-threonyl-asparaginyl-leucyl-glutaminyl-glutamyl-seryl-leucyl-arginyl-seryl-lysyl-glutamic acid

Outcome of Evaluation

18th September 2001

[Product Name]	Rebetol Capsules 200mg
[Non-propriety Name]	Ribavirin
[Applicant]	Schering-Plough KK
[Submission Date]	27th April 2001
[Product Name]	Intron A Injections 300, 600 and 1,000
[Non-propriety Name]	Interferon alpha-2b, recombinant
[Applicant]	Schering-Plough KK
[Submission Date]	27th April 2001

[Outcome]

<Efficacy>

In a study investigating an effect of ribavirin in combination with interferon alpha-2b in chronic hepatitis C patients who had not respond to interferon therapy or who had relapsed after interferon therapy, the combination therapy has shown a significantly higher response rate than interferon alpha-2b monotherapy. In a study investigating dosage and administration of interferon alpha-2b for the combination use, which targeted patients with "genotype 1b and a high viral load" who are said to be intractable, the combination therapy has demonstrated significantly higher response rates compared with the interferon alpha-2b monotherapy, regardless of the dose level of interferon alpha-2b.

<Safety>

In addition to the adverse drug reactions known to the interferon alpha-2b monotherapy, such as fever, reductions of haemoglobin levels (63.1%) and reductions of red blood cell counts (51.3%), which were attributed to the ribavirin toxicity, were observed at high incidences with the combination therapy. Furthermore, higher

incidences of reduced white blood cell counts, respiratory system disorders, pruritus and rashes were observed in the combination therapy compared with the monotherapy. Ribavirin showed teratogenicity and morphological changes of the testis/sperms in non-clinical studies, and it may be excreted in seminal fluids. Necessary measures have been taken to warn about those adverse drug reactions,, for example, they are described in the "Warnings" column of the prescribing information.

<Overall Assessment>

As a result of evaluation at the Pharmaceutical and Medical Device Evaluation Centre, we judge that it is appropriate to grant an approval based on the following Indications and Dosage and Administration, providing the approval conditions below are set.

Rebetol Capsules 200mg

[Indications]

Virological improvement of chronic hepatitis C in combination with interferon alpha-2b, recombinant.

[Dosage and Administration]

Rebetol Capsules should be used in combination with interferon alpha-2b, recombinant.

Usually in adults, 600 to 800mg/day of ribavirin should be administered orally in two divided doses after breakfast and evening meals everyday. If the bodyweight of the patient is 60kg or less, the daily dose should be 600mg, and if the bodyweight is over 60kg, it should be 800mg. When administering 600mg/day, 200mg should be administered orally after breakfast and 400mg after evening meals.

Six to 10 million IU of interferon alpha-2b, recombinant should be administered intramuscularly once daily for six times per week or three times per week.

[Approval Conditions]

As clinical data by cerotype (genotype) and viral load are not sufficiently available, the applicant has to perform post-marketing surveillance, including post-marketing clinical

trials and collect clinical data by cerotype (genotype) and virus load, at once. The applicant has to report the result without delay and reflect it in the prescribing information, etc., as appropriate.

Intron A Injections 300, 600 and 1,000

[Indications]

- Virological improvement of chronic hepatitis C
- Virological improvement of chronic active hepatitis B patients who are both HBe antigen and DNA polymerase positive.
- Kidney cancer, chronic myeloid leukaemia, multiple myeloma

[Dosage and Administration]

- Virological improvement of chronic hepatitis C

  Before starting the treatment, confirm that HCV RNA is positive.

  1) Intron A Monotherapy (excluding when the blood HCV RNA level is high) note1

     Usually in adults, six to ten million IU of interferon alpha-2b, recombinant note 2 should be administered intramuscularly once daily for six times per week or three times per week.

  2) Combination Therapy with Ribavirin note 1

     Usually in adults, six to ten million IU of interferon alpha-2b, recombinant should be administered intramuscularly, once daily for six times per week or three times per week. Six hundred to 800mg/day of ribavirin should be administered orally in two divided doses after breakfast and evening meals, everyday. If the bodyweight of the patient is 60kg or less, the daily dose of ribavirin should be 600mg and if the bodyweight is over 60kg, it should be 800mg. When administering 600mg/day, 200mg should be orally administered after breakfast and 400mg after evening meals note 2.

- Virological improvement of chronic active hepatitis B patients who are both HBe antigen and DNA polymerase positive.

  Usually in adults, six to ten million IU of interferon alpha-2b, recombinant [note 2] should be administered intramuscularly once daily for the first week and then six million IU should be administered once daily from the second week. On the initial day of the treatment, the dose should be three or six million IU once daily.

- Kidney cancer, chronic myeloid leukaemia, multiple myeloma

  Usually in adults, three to ten million IU of interferon alpha-2b, recombinant [note 2] should be administered intramuscularly once daily.

  Adjust the dose according to the age and conditions of the patient.

When administering interferon alpha-2b, recombinant [note 2], it should be dissolved in 1mL per vial of the provided JP "Water-for-Injection".

Note 1: Additions to the existing Dosage and Administration following the addition of the new indications.

Note 2: Maintenance of the existing indications.

[Approval Conditions]

- Virological improvement of chronic hepatitis C in combination with ribavirin

As clinical data by cerotype (genotype) and viral load are not sufficiently available, the applicant has to perform post-marketing surveillance, including post-marketing clinical trials, and collect clinical data by cerotype (genotype) and virus load, at once. The applicant has to report the result without delay and reflect it in the prescribing information, etc., as appropriate.

10th August 2001

Evaluation Report (1)

1. Application

[Product Name] Rebetol Capsules 200mg

[Non-propriety Name]

Ribavirin

[Applicant] Schering-Plough KK

[Submission Date] 27th April 2001

[Dosage Form and Content]

An oral formulation containing 200mg of ribavirin per capsule

[Filed Indications] Virological improvement of chronic hepatitis C in combination with an interferon alpha-2b, recombinant formulation.

[Filed Dosage and Administration]

Rebetol Capsules should be used in combination with an interferon alpha-2b, recombinant formulation.

Usually in adults, 600 to 800 mg/day of ribavirin should be administered orally in two divided doses after breakfast and evening meals everyday.

If the bodyweight of the patient is over 60 kg, the daily dose should be 800 mg and if the bodyweight is 60 kg or less, it should be 600 mg.

Six to 10 million IU of an interferon alpha-2b, recombinant formulation should be administered intramuscularly once daily for six times per week or three times per week.

[Product Name] Intron A Injections 300, 600 and 1,000

[Non-propriety Name]

Interferon alpha-2b, recombinant

[Applicant] Schering-Plough KK

[Submission Date] 27th April 2001

[Dosage Form and Contents]

An intramuscular injection formulation containing 3, 6 or 10 million IU of interferon alpha-2b, recombinant per vial.

[Filed Indications] Kidney cancer, chronic myeloid leukaemia, multiple myeloma, virological improvement in chronic active hepatitis B patients who are both HBe antigen and DNA polymerase positive, virological improvement of chronic hepatitis C <u>in combination with ribavirin or as Intron A alone</u>. (The underlined part is added)

[Filed Dosage and Administration]

Virological improvement of chronic hepatitis C in combination with ribavirin or as Intron A alone.

Before starting the treatment, confirm that HCV RNA is positive.

Usually in adults, six to ten million IU of interferon alpha-2b, recombinant should be administered intramuscularly once daily for six times per week or three times per week.

Virological improvement in chronic active hepatitis B patients who are both HBe antigen and DNA polymerase positive

Usually in adults, six to ten million IU should be administered intramuscularly once daily for the first week and then six million IU should be administered once daily from the second week. On the initial day of

the treatment, the dose should be three or six million IU once a day.

Kidney cancer, chronic myeloid leukaemia, multiple myeloma

Usually in adults, three to ten million IU of interferon alpha-2b, recombinant [note 2] should be administered intramuscularly once daily.

Adjust the dose according to the age and conditions of the patient.

When administering, it should be dissolved in 1 mL per vial of provided JP "Water-for-Injection".

[Remarks] Priority Evaluation

2. Summary of Application Data and Evaluation

A Origin, Details of Discovery, Use in Foreign Countries, etc.

It is estimated that, in Japan, between one to two million people have continuous infection (carriers) of hepatitis C viruses (HCV). Many HCV carriers present symptoms of chronic hepatitis and some of them develop cirrhosis and hepatic cancer. Currently, about 45,000 people dies annually from cirrhosis or hepatic cancer in Japan and about 70% of them are thought to be caused by continuous infection with HCV. In Japan, various interferons (IFN), including interferon alpha-2b, were approved for chronic active hepatitis C in 1992, and IFN are now widely used for treatment of chronic hepatitis C. However, it has been found that genotypes of virus and pre-treatment viral loads are the major factors that affect the therapeutic effects of IFN and IFN show very poor therapeutic effects in patients with genotype 1b virus (over 70% of chronic hepatitis C patients in Japan are reported to have genotype 1b virus) or a high viral load.

Ribavirin is a nucleoside analogue synthesised by Witkowski, et al., in 1972. In overseas country, it has been developed as an agent for treating various viral infections, as it demonstrated a wide range of antiviral activity, and it has been

approved with indications including RSV lower respiratory tract infection and influenza infection in the West. In the USA and Europe, monotherapy of chronic hepatitis C was investigated, but failed to demonstrate viral eradication and histological improvement in hepatic tissues. Then, Schvarcz, et al., investigated IFN α-2b in combination with ribavirin in chronic hepatitis C patients who failed to respond to previous IFN α treatment or relapsed after successful treatment. They reported that the combination therapy showed a superior viral eradication and sustained ALT improvement (J.Med.Virol., 46,43,1995: J. Hepatol., 23 (suppll.2), 17, 1995). Based on those findings, Schering-Plough in the US proceeded with development of ribavirin in combination with IFN α-2b. In the US, the use of ribavirin in combination with IFN α-2b was approved in 1998, it was approved in 1999 in Europe and it is currently approved in 50 countries.

Clinical trials of the combination therapy were also carried out in Japan and similar results to the results abroad were obtained. Therefore, the applicant submitted the approval application of ribavirin in combination with IFN α-2b for virological improvement of chronic hepatitis C.

This application is treated as a priority evaluation item.

B. Data on Physical and Chemical Characteristics and Specifications and Test Methods

Only data on ribavirin were submitted in this application.

Ribavirin is a purine nucleoside analogue, which consists of D-ribose bonding with 1,2,4-triazole-3-carboxamide. The structure was determined by elementary analysis, ultraviolet spectroscopy, infrared spectroscopy (IR), ^{1}H- and ^{13}C-nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry. It occurs as crystalline powder and two crystal forms with different melting points are available depending on a choice of solvents used for re-crystallisation. It is freely soluble in water and buffers (pH 2 to 12) and, it was mostly dissolved in the water phase of 1-octanol / water partition (Log P= -2.42 ~ -3.77). It is an optically active substance and laevorotatory. Forced degradation products under the acid solution condition (1 mol/L hydrochloric

acid, 28 days) are RTCOOH, which is formed by hydrolysis of amide at the 3rd position of the triazole ring, $TCONH_2$, which is formed by breakage of the bond of the ribose and the triazole ring, and TCOOH, which is formed by further hydrolysation of amide of $TCONH_2$. Under the alkaline solution condition (0.01 mol/L sodium hydroxide, 4 days), RTCOOH was produced. However, it was stable as an aqueous solution, in light and when the solid was heated.

As the specifications and test methods of the drug substance, the descriptions (appearance, solubility), the identification (IR), the melting point, the optical rotation, the purity tests (heavy metals, related substances [TCOOH, $TCONH_2$, RTCOOH, xxxxxxxx, etc.,] residual solvents), the loss on drying, the residue on ignition and the assay (high performance liquid chromatography [HPLC]) have been established. The specification of xxxxxxxx was established in the related substances section. This compound may contaminate the drug substance during the synthesis process.

The formulated product is a hard capsule and contains vehicles, etc. As the specifications and test methods, descriptions (appearance, contents), identification (thin layer chromatography), purity tests (degradation products), water content, a contents uniformity study, a dissolution test and an assay (HPLC) have been established.

The Pharmaceuticals and Medical Devices Evaluation Centre (hereinafter referred to as Evaluation Centre) has asked the applicant if the HPLC procedures used in the tests of related substance and the assay were validated appropriately. The applicant provided the results of studies on the linearity, trueness, accuracy, robustness, specificity, the quantification limits and detection limits. However, the Evaluation Centre believed that further investigations on the intermediate precision were necessary and requested the applicant to submit the data. The applicant replied that they would carry out a study confirming the intermediate precision of the procedures. As a quantitative test rather than a limit test was employed for testing the relative substances, the Evaluation Centre pointed out that system compatibility of HPLC should be established as a procedure for assuring quantification rather than as a procedure for assuring the detection capability near the specification limit. The applicant replied that they would amend the test methods accordingly and the Evaluation Centre accepted these.

As xxxxx xxxxx during the manufacturing process of the drug substance, the Evaluation Centre requested the applicant to set xxxxx as the specification. The applicant replied that they would specify this based on the measured values. The Evaluation Centre accepted the reply.

C. Data on Stability

Only data on ribavirin are submitted in this application.

On the drug substance, a long term storage study (25°C, 60% RH, 36 months), an accelerated study (40°C, 75% RH, 6 months) and stress studies (temperature [60°C, 3 months], humidity [25°C, 90% RH, 3 months], high temperature high humidity [40°C, 90% RH, 3 months], light [25°C, D65 lamp 2000 lux, total illumination 1.2 million lux·hr or over and total near-ultraviolet radiant energy 200 W·h/m^2 or over]) were carried out. Under any study conditions, there was no change in the descriptions, melting points, related substances, loss on drying, contents, etc., and the drug substance was stable.

The formulated products in two types of containers, blister strips and high-density polyethylene bottles, were tested in long-term storage studies (25°C, 60% RH, 36 months [12 months for blister strips]), accelerated studies (40°C, 75% RH, 6 months) and accelerated studies under moderate condition (30°C, 60% RH, 12 months). Also, stressed studies (temperature [in sealed glass bottles, 60°C, 3 months], humidity [open, 40°C, 75% RH, 6 months], light [in glass plates wrapped in polyvinylidene chloride film, 25°C, 60% RH, D65 lamp 2000 lux, total illumination 1.2 million lux·hr or over and total near-ultraviolet radiant energy 200 W·h/m^2 or over]) were carried out. In the accelerated study and stressed studies (temperature, humidity), both blister packed and bottled capsules showed reductions in the dissolution rates and the bottled capsules in the accelerated study were below the specification after 4.5 months. In the long-term storage studies and other test items showed minimum changes and the capsules were stable. Based on those results, the applicant set the storage condition of the formulated product as at room temperature in a sealed container, and the expiration date of the blister packs as 12 months and that of the bottles as 36 months.

As the dissolution test procedure used in stability assessment of the formulated product was different from the procedure established in the specifications of the formulated product, the Evaluation Centre asked the applicant to clarify the appropriateness of the assessment. The applicant submitted data demonstrating that the power of the test procedure used in the stability studies was not inferior to the power of the test method of the specification. The Evaluation Centre accepted the results of the stability studies. Based on this, the Evaluation Centre judged that the expiration date set for the formulated product was appropriate.

D. Data on Toxicity

Data on toxicity of ribavirin alone and ribavirin in combination with IFN α-2b were submitted.

Single dose toxicity studies of ribavirin were carried out in mice, rats, guinea-pigs and dogs. LD_{50} of oral dose is not less than 10g/kg in male mice, 4.1 g/kg in male rats, 5.3 g/kg in female rats and 2.3 g/kg in male guinea-pigs. In male and female dogs, lethality was not observed when up to 480 mg/kg was administered. Commonly in various animal species tested, changes suggesting effects on the digestive tract were observed with oral doses. The main findings were soft faeces, mucous faeces, accumulation of dark red materials (suggesting bleeding) in the gastro-intestinal tract, duodenal ulcers and vomiting. LD_{50} of intraperitoneal administration was 1,268 mg/kg in male mice, 1.8 g/kg in male rats, 1.6 g/kg in female rats and 823 mg/kg in male guinea-pigs. Intraperitoneal administration also showed changes suggestive of ribavirin's effect on the digestive tract.

A single dose study of ribavirin in combination with IFN α-2b was not implemented. The applicant stated the reason for this was that they believed that the toxicity seen with ribavirin in combination with IFN α-2b would be the same as ribavirin alone because no toxicity was demonstrated with IFN α-2b when mice, rats and monkeys received a single intramuscular administration at a dose level beyond 1,000-fold of the maximum clinical dose for humans.

Repeated-dose toxicity studies of ribavirin investigated oral administration for 1 to 12 months in rats and dogs. The results demonstrated that the main target organs of toxicity in rats and dogs were red blood cells (reductions at above 10 mg/kg) and bone marrows (hypoplasia at above 20 mg/kg). In addition, it showed effects on the digestive tract (enteritis at above 15mg/kg), thymus and lymph nodes (lymphopenia at above 20mg/kg). In all animal species, reductions in erythroid parameters (anaemia) were observed at the same dose level as the estimated clinical dose. In general, effects of ribavirin were more prominent in dogs than in rats.

A repeated dose toxicity study of ribavirin in combination with IFN α-2b was conducted using monkeys because responses to IFN α-2b are species-specific and primates show closest biological activities to humans. If IFN α-2b is administered to monkeys for over 1 month, neutralising antibodies will be produced and it will not be possible to make a correct toxicological assessments. Therefore, duration of administration in the combination dose study was set as 1 month. The result showed that anaemia was more pronounced in animals receiving ribavirin in combination with IFN α-2b than in animals receiving either of agents alone, but the effect was additive and they recovered after withdrawal. Other toxicological changes observed in the combination group were all found in the groups receiving either ribavirin or IFN α-2b alone and no new toxicity was found with the combination.

Ribavirin's reproductive and developmental toxicity were investigated in rats and rabbits, and prenatal and early pregnancy toxicity studies, organogenesis toxicity studies, and peri/postnatal toxicity studies were conducted. In addition, in order to investigate growth, development, behaviour and reproductive ability of the next generation, studies on development before and after parturition and functions of dams were conducted in rats. There was no finding indicating effects on reproductive ability of the parent animals, and growth, functional development and reproductive ability of the offspring. However, when ribavirin is administered during organogenesis period, suppressions of foetal development, increases in the post-nidation loss (embryonic/foetal fatality) and teratogenicity were observed with 1.0 mg/kg or over, which were far lower doses than the clinical dose (800 mg/day for humans with body weight of 60 kg or over corresponds to 13 mg/kg). In addition to those effects of

ribavirin, abortions were observed in pregnant rhesus monkeys receiving IFN α-2b. Therefore, the applicant concluded that reproductive and developmental toxicity of ribavirin in combination with IFN α-2b was self-evident and did not conduct a study investigating the toxicity of ribavirin in combination with IFN α-2b.

Genotoxicity of ribavirin was investigated in six sets of assays. Reverse mutation assays with bacteria, a chromosomal aberration assay with human lymphocyte and a rat dominant lethality assay gave negative results, but a gene mutation assay with mouse lymphoma, a cell transformation assay with BALB/c 3T3 and a mouse micronucleus assay gave positive results. Therefore, ribavirin was considered to have genotoxicity. It was believed that the mode of the action was in imbalance at the nucleic acid level, which was caused by a reduction of GTP in cells due to an inhibition of inosine monophosphate dehydrogenase (IMPDH), and it was assumed that direct DNA damage was not involved. Genotoxicity studies of ribavirin in combination with IFNα-2b were not conducted. This is because ribavirin showed genotoxicity, and reverse mutation assays with bacteria, DNA repair assays with bacteria and a mice micronucleus assay of IFNα-2b gave all negative results, suggesting that IFN α-2b was not likely to have a direct effect on DNA and chromosomal components.

Carcinogenicity studies of ribavirin were conduced in mice and rats, but no carcinogenicity was found. As IFN α-2b does not have biological activities in rodents and production of IFN α-2b neutralising antibodies was reported in a 4-week repeated dose study in rats, the applicant considered that no toxicological findings would be obtained with a long-term administration and did not conduct carcinogenicity studies of ribavirin in combination with IFN α-2b.

In an antigenicity study of ribavirin, active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PCA) tests in guinea pigs were carried out. All results were negative and ribavirin was considered to have no antigenicity. As IFN α-2b shows antigenicity in animals, no antigenicity study of IFN α-2n in combination with ribavirin was conducted.

The applicant did not conduct a single dose study of ribavirin in combination with IFNα-2b assuming that toxicity would not be enhanced when they were used concurrently, but they did not provide a rationale for this assumption. Therefore, the

Evaluation Centre requested the applicant to submit their view. The applicant's replies were as follows: (i) Toxicity of a single dose of ribavirin was low, for example, LD_{50} of a single oral dose of ribavirin was high in all tested animal species and effects were limited to the digestive tract in the all species. In addition, there was no single toxicity finding of IFN α-2b. (ii) Single and repeated doses of IFNα-2b did not show effect on the digestive tract, therefore, they suspected that toxicity of ribavirin and IFNα-2b manifested themselves differently. (iii) The result of the one-month repeated dose TK study of ribavirin in combination with IFNα-2b in the cynomolgus monkey suggested that ribavirin and IFN α-2b did not influence each other's pharmacokinetics. Therefore, the applicant believes that a single dose of ribavirin in combination with IFN α-2b will not enhance the toxicity. The Evaluation Centre cannot agree to the reply and believes that, ultimately, unless a combination study is carried out, it is not possible to assess toxicity of a single dose of ribavirin in combination with IFNα-2b. However, as toxicity of long-term use was determined in combination repeated dose studies, the Evaluation Centre agrees under constraint that they are not going to conduct a fresh investigation of single dose toxicity of ribavirin in combination with IFNα-2b.

In a one-month combination study in monkeys, the group receiving ribavirin in combination with IFNα-2b showed reductions in the blood pressure, body temperature and the heart rate. The Evaluation Centre asked the applicant about the relevance of those with the use of ribavirin and safety in human. The applicant made the following reply.

(i) The group of monkeys that received a single dose of 50mg/kg of ribavirin, which was approximately 3.8-times of the estimated clinical dose, did not show any differences in their blood pressure, body temperature and heart rates compared with the control group. Similar results were obtained in the general pharmacological study when rats received a single dose of 200mg/kg of ribavirin, which was approximately 15.4-times of the estimated clinical dose. The group of monkeys that received a single dose of 3.1 mg/m^2 (1 mg is applicable to approximately 2×10^8 IU) of IFN α-2b showed a slight reduction in the blood pressure, but no abnormalities in the heart rate or body temperature were observed. (ii) In monkeys, the high dose combination group

(ribavirin: 100 mg/kg, IFN α-2b: 3.1 mg/m^2) showed marked reductions in blood pressure, heart rates and body temperature and the low dose combination group (ribavirin: 50 mg/kg, IFN α-2b: 3.1mg/m^2), also showed mild reductions in blood pressure and body temperature. Those animals in the high dose and low dose combination groups showed strong systemic effects, and diarrhoea, loss of appetite, dehydration, body weight loss, etc., were observed in addition to moderate to severe anaemia in both combination groups. In particular, three animals in the high dose combination group, which died or were sacrificed due to deterioration of the general state, showed significant reductions in the blood pressure, heart rates and body temperature. However, in examinations at 4 weeks after withdrawal, no abnormality in the high dose combination group was observed and recovery was confirmed. Based on the above three points, the applicant believed that the reductions in the blood pressure, heart rates and body temperature observed in the one-month combination study in monkeys were not direct effects of ribavirin, but were secondary effects associated with deterioration of the general state. As recovery was confirmed after withdrawal, the applicant considered the risk in clinical use in humans was low. The Evaluation Centre accepted the reply.

In the rat oral dose toxicity study, cardiomyopathy was observed. The Evaluation Centre asked the applicant if it was considered to be equivalent to cardiomyopathy in human. The Evaluation Centre also asked the applicant to clarify the rationale for considering the cardiomyopathy as the secondary effect of intestinal necrosis and explain the rationale for considering the risk to the human was low based on the fact that cardiomyopathy was not observed in other animal species. To this, the applicant replied as follows.

(i) In the rat 30-days toxicity study, cardiomyopathy was observed in the high dose groups at 160 and 320mg/kg. A wide range of intestinal necrosis was also observed in all animals in these groups and systemic inflammations, such as alveolitis, inflammatory cell infiltration of lymph nodes and hepatic centrilobular necrosis, were found. Therefore, the applicant considered that administration of ribavirin was not the direct cause of cardiomyopathy found in the rats, but toxins and bacteria entering from wounds in the intestinal mucus membrane together with severe anaemia caused deterioration of the general status and stress which led to cardiomyopathy. Therefore,

they assessed that the cardiomyopathy in the rats was secondary and non-specific, and it was not relevant to cardiomyopathy in humans. The applicant argued that, when 120 mg/kg (the highest dose) was administered in the rat 28-days study, although anaemia was found, there was no digestive tract disorder and cardiomyopathy was not seen, which supported the conclusion that ribavirin was not directly responsible for the cardiomyopathy. (ii) In another 28-days study using a different animal species, the dog, 5 out of 6 animals in the highest dose group (60 mg/kg) died or were sacrificed due to deterioration of their general status, but no cardiomyopathy was observed. Also, a one-month combination (ribavirin in combination with IFN α-2b) study in monkeys xxxx, 3 animals in the highest dose group died or were sacrificed due to deterioration of general status, but no cardiomyopathy was observed. Based on the above two points, the applicant assessed that ribavirin administration was not a direct cause of cardiomyopathy in the rats, but it was caused by a secondary effect of serious digestive tract disorders, because cardiomyopathy was observed in no animal species other than rats and only found in rats in the repeated dose study that received so high dose levels that the general status was deteriorated. Therefore, the applicant believed that it did not suggest risks to humans.

The Evaluation Centre appreciated that cardiomyopathy in rats was not relevant to human cardiomyopathy and their mechanisms were different, but similar conditions were not found in dogs and monkeys despite the applicant assuming that the cause of cardiomyopathy in rats was deterioration of the general status or stress. Therefore, the Evaluation Centre has requested the applicant to discuss differences in the mechanisms by species, and to explain what the difference was between these and cardiomyopathy caused by septicaemia, if they assumed that they were cause by toxins and bacterial infections through the wounds on the intestinal mucus membrane.

As strong digestive tract disorders, such as diarrhoea, bleeding, inflammation, ulceration and necrosis, were found in oral dose toxicity studies in rats and dogs and digestive tract symptoms were also observed in humans as adverse drug reactions, the Evaluation Centre asked the applicant their view on risks of causing more serious digestive tract disorders in humans or risks when administering to patients with digestive tract disorders such as digestive tract ulcerations. The applicant replied as follows.

(i) The digestive tract disorders that were observed in the oral dose toxicity studies in rats or dogs were clearly seen in a short-term studies for 28 or 30 days (rats: 160 mg/kg or over, dogs: 15 mg/kg or over), but histopathological abnormalities were not seen in the highest dose groups in the 52-weeks studies (rats: 90 mg/kg. dogs: 20 mg/kg). In the dog 52-week study, diarrhoea was observed in the groups receiving an almost equivalent dose to the estimated clinical dose of ribavirin, 10 mg/kg, or above, but the incidence was reduced as the administration was continued, therefore it was assumed that the effect on the digestive tract was reversible. (ii) In the overseas clinical trials, digestive tract disorders that occurred in the combination groups at the incidence of 5% or more were diarrhoea, abdominal pain, nausea, vomiting, loss of appetite, abdominal pain or indigestion. However, the incidences of these were equivalent or only slightly increased compared with the IFN α-2b groups (from the prescribing information for the USA and Germany). (iii) On the other hand, digestive tract disorders that occurred at the incidence of 5% or more in the combination groups in the Japanese clinical trials were loss of appetite (72%), nausea, vomiting, gastritis and diarrhoea and the adverse drug reactions other than loss of appetite were very similar to reports from abroad. Digestive tract bleeding was observed in one patient (0.4%). Based on the above, the applicant replied, the section for important adverse drug reactions in ribavirin's prescribing information (draft) in Japan stated "Digestive tract bleeding (less than 1%): Observe carefully and if an abnormality is found, stop administration and take appropriate actions" calling for caution of physicians and patients. The Evaluation Centre accepted the reply.

E. Data on Pharmacology

No HCV infected cultured cell line that enables us to assess the effects of anti-viral agents against HCV with a good reproducibility has been established. Therefore, *in vitro* anti-viral effects of ribavirin were assessed using bovine viral diarrhoea virus (BVDV), which is a closely related to HCV. MDBK (bovine kidney) cells were infected with BVDV and two hours later, 0.2 to 200 μM of ribavirin (1μM = 0.244 ng/mL) was added to the culture. Between 1.56 and 6.25 μM, it dose-dependently inhibited cell damages by the virus with an IC_{50} value of 3μM. At a concentration

above 12.5 μM, a reduction in the vital cell count was observed, which was thought to be caused by the cell proliferation inhibitory effect of ribavirin. The BVDV RNA load was determined by the quantitative RT-PCR assay. It showed that the ribavirin reduced RNA level dose-dependently with IC_{50} of 1.5μM. In this study system, IFN α-2b dose-dependently inhibited cell damage by the virus at concentrations between 16 and 250 IU/mL. IC_{50} was 30 IU/mL. When ribavirin and IFN α-2b were used concomitantly in this study system, in the presence of 15.6 to 1000 IU/mL of IFN α-2b, the ribavirin concentration-effect curve shifted towards lower concentrations dependent on the IFN α-2b concentration and an increase in the vital cell count was observed. The interaction coefficient of the combination effect (Pharmacol. Rev., 47, 331, 1995) was determined to be 3.17, suggesting the increase in the effect was synergistic. With regard to ribavirin's effects on the cell proliferation, effects of concurrent IFN α-2b were not obvious. In addition, effects on the anti-viral activities of ribavirin with concurrent IFN alphas (IFN α-2b, IFN α-2a, consensus IFN α and IFN α-n3), IFN betas (IFN β-T1 and IFN β-1a) and IFN gamma were investigated. When 100 IU/mL and 500 IU/mL of IFN alphas, including IFN α-2b, were used in combination, anti-viral activities of ribavirin were enhanced, but when IFN betas or IFN gamma were used concurrently, no changes in the anti-viral activities of ribavirin were observed, even after increasing the concentration of the IFN to up to 500 IU/mL. This result indicated that depending on the type of IFN, the effect of a concurrent IFN differs.

Reference data on the spectrum of *in vitro* antiviral activity of ribavirin were submitted. According to the data, ribavirin showed antiviral activity against RNA viruses in *in vitro* studies, which used influenza virus type A (FluV A) and parainfluenza virus type 2 (PfluV 2) infected to a human malignant melanoma cell line (HMV-II), respiratory syncytial virus (RSV) infected to a glucose-dependent human endocervical carcinoma cell line (Gl-HeLa) and measles virus (MLSV) and mumps virus (MPSV) infected to an African green monkey kidney cell line (Vero), and their IC_{50} were 41, between 61 and 139, 342, 59 and 11 μM, respectively. In contrast, IFN α-2b only showed antiviral activities against MLSV and MPSV and their IC_{50} were 143 and 95 IU/mL, respectively. With regard to DNA viruses, both ribavirin and IFN

α-2b showed antiviral activity against human cytomegalovirus (CMV) infected to a human foetus lung cell line (MRC-5), and their IC_{50} were 267 μM and 13 IU/mL, respectively. However, they did not show activity against herpes simplex virus type 1 (HSV-1) infected to a human B lymphoma cell line (RPMI8226) or a human embryonic fibroblast cell line (HEF). With regard to effects on cell proliferations, ribavirin suppressed proliferation of HMV-II and RPMI8226 and their IC_{50} were 240 and 117 μM, respectively. IFN α-2b suppressed proliferation of RPMI8226 and IC_{50} was 76.0 IU/mL. According to the applicant, development of ribavirin tolerance was not reported.

Reference data on *in vivo* anti-viral activities of ribavirin in monkeys were submitted. According to this, squirrel monkeys were infected with Flu A through inhalation, then after six hours, received inhalation of approximately 13 mg/kg/day of ribavirin for 4 days. All animals in the untreated control group showed sneezing or coughing on day 1 to day 4, whereas 3 out of 4 animals in the group receiving ribavirin showed the symptoms. Looking at nasal discharge as an index, all animals in the untreated control group showed nasal discharge on day 1 to day 7, whereas no animals in the ribavirin group showed nasal discharge. Rhesus monkeys received subcutaneous injection of Lassa virus, and then received ribavirin from the date of infection to day 18 of infection (the prophylaxis group) or from day 5 to day 18 of infection (the treatment group). Ribavirin was given as subcutaneous doses, and the dose was 50mg/kg once a day on the first day of the treatment then 10mg/kg three times per day after that. Results showed that appearance of virus in serum was delayed until day 7 in the prophylaxis group and their highest serum viral load was lower than that of surviving animals in the untreated control group. Also, serum viral loads of animals in the treatment group did not increase like dead animals in the control group. The survival rate of the animals in the untreated control group was 40% (4 out of 10 animals), whereas the survival rate of animals in both groups receiving ribavirin was 100% (4 animals each). Furthermore, rhesus monkeys received intramuscular injection of Junin virus, and then the animals in the prophylaxis group received 60 mg/kg/day of ribavirin on day 0 to day 3, 30 mg/kg/day on day 4 to day 7 followed by 15 mg/kg/day on day 8 to day 17, all intramuscularly in two divided doses per day. The animals in the treatment group received 60mg/kg/day of ribavirin on day 6 and 15 mg/kg/day on day 7 to day 20, all

intramuscularly in two divided doses per day. All 4 animals in the control group that received the vehicle died by day 26, whereas on week 9 after infection, all 4 animals in the ribavirin prophylaxis group were surviving and 3 out of 4 animals in the treatment group died. In an experiment in rhesus monkeys receiving intramuscular injection of type 1 dengue fever virus, 50mg/kg of ribavirin or the vehicle was administered intravenously on a day before infection in a random and blind fashion. Then for the following 9 days, 10mg/kg of ribavirin was administered intramuscularly three times a day. Eight out of 10 animals in the control group which received the vehicle showed swelling of local lymph nodes and increases in rectal temperature to over 39.5 °C. The same symptoms were seen in 7 out of 10 animals in the ribavirin group, and there was no significant difference in serum virus loads, serum AST and ALT values of the group that received the vehicle and the group that received ribavirin.

It is not possible to say that the mechanism of antiviral activities of ribavirin is fully understood, but involvement of nucleic acid synthesis inhibitory action and induction of mutations is suspected. To verify these mechanisms of actions, the applicant investigated metabolism of ribavirin, effects on viral RNA synthesis, etc.

To investigate metabolism of ribavirin in cells, the medium of the human hepatocellular carcinoma cell line HepG2 was replaced with a medium containing 41μM of ribavirin. The cells were collected from time to time and the metabolites were measured with HPLC. As a result, after uptake of ribavirin by the Hep G2 cells, ribavirin was immediately metabolised to ribavirin mono-phosphate (RMP), di-phosphate (RDP) and tri-phosphate (RTP), and unchanged ribavirin was undetectable. The intercellular GPT was reduced after the replacement with the medium containing ribavirin and it was reduced to 37% by 4 hours later. Effects of RMP on inosine monophosphate dehydrogenase (IMPDH) were investigated, as the tertiary structure of ribavirin was similar to guanosine. RMP showed an IMPDH inhibitory effect with a Ki value of 0.5μM. By adding guanosine, the antiviral action-concentration curve of RMP shifted towards the higher concentration, but the maximum activity was not lowered. RMP also showed an anti-viral effect on BVDV and IC_{50} was 3μM. In contrast, the Ki of a selective IMPDH inhibitor, mycophenolic acid (MPA), was 10μM, but it did not show a clear anti-viral effect against BVDV. Based on these results, the applicant stated that

although a reduction of intracellular GPT from an IMPDH inhibition may be involved in the mode of antiviral action of ribavirin, that could not account for everything.

To investigate suppressive action of RTP against incorporation of GTP into RNA, a study was conducted using six genotypes of RNA dependent RNA polymerase (RdRp) that were prepared from cDNA isolated from serum of chronic hepatitis C patients. The results showed that, with any types of RdRp, RTP suppressed incorporation of GPT into RNA by any types of RdRp. However, suppression of incorporation by genotype 1b was slightly weaker and IC_{50} was between 143 and 152μM. IC_{50} against other genotypes were between 49 and 111μM. RTP also suppressed incorporation of GTP into RNA by RdRp of BVDV with IC_{50} of 49μM. Using U7CC or G7CC as a RNA template, adenosine triphosphate (ATP), cytidine triphosphate (CTP) or RTP were added to RdRp from HCV. When uridine is used as a template, RTP was incorporated into RNA, but when guanosine is used as a temperate, RTP was not incorporated, suggesting that RTP was recognised as a nucleotide substrate by RdRp of HCV and incorporated into RNA. Both ribavirin and RTP did not affect internal ribosome entry site (IRES) dependent protein synthesis, which is the starting point of translation of HCV RNA. Ribavirin and 3 types of phosphorylated ribavirin did not affect the HCV's non-structural protein 3 (NS3) protease activities.

Furthermore, results of a study using poliovirus, which is also a single strand RNA virus as is HCV, were submitted as reference data. RTP was recognised as a substrate by RdRp of poliovirus, paired with cytidine and uridine in a RNA template, and incorporated into RNA. RTP was incorporated at a similar rate to cytidine and uridine, and RTP incorporated into RNA was used as a template for subsequent RNA synthesis. In order to investigate the effect on viral replication, cells infected with virus were treated with ribavirin for either 2 hours or 8 to 10 hours. The infectious viral load was reduced with few effects on translation and replication of viral RNA. Mutagenicity was assessed though treating virus-infected cells with ribavirin for 4 to 7 days. As a result, incidences of mutated virus were increased at concentration of 100μM or above, demonstrating a reduction in the infectious viral load. When cells infected with virus were treated with ribavirin for 10 hours, the rates of displacement of G with A and C with U were about 11 and 7 times higher than the untreated group,

respectively, suggesting that ribavirin induced these displacements. The applicant stated that the mutation of C to U could be explained with mutation of G to A, which was induced by incorporation of RTP in place of GTP when a RNA (-) strand was synthesised.

Of the six metabolites of ribavirin, pharmacological effects of three metabolites other than phosphorylated ribavirin ($TCONH_2$, RTCOOH and TCOOH) were investigated using BVDV infected MDBK cell line. None of them showed anti-viral effects. The suppressive effects on cell proliferation were also investigated using the human peripheral blood mononuclear cells and the human hepatocellular carcinoma cell line Hep G2. None of them suppressed cell proliferation within the dose range of up to 200μM.

General pharmacology studies of ribavirin investigated effects on the general conditions, the central nervous system, the automatic nervous system and smooth muscles, the respiratory and circulatory systems, the digestive system, and water and electrolyte metabolisms. No effects were seen other than reductions in passivity at posture change in 2 animals and reduced reactivity, crouching position, spasm of pinna and a weak atypical behavioural change in 1 animal out of 5 animals receiving 300 mg/kg (oral dose) in the investigation of the general conditions and a prolongation of anaesthesia which was observed when 200mg/kg (oral) were given in the investigation of anaesthetic effects.

The Evaluation Centre asked the applicant to explain homogeny of BDVD, which was used in assessment of the anti-viral effect, to HCV. The applicant replied that HCV and BVDV belonged to the Flavivirus family, and in the Hepatitis C Virus genus and the Pestivirus genus, respectively, and both were single strand (+) RNA viruses. Their base sequences of genome RNA were similar, showing a 21% match in the base sequences of the open reading frames of HCV (genotype 1a, 1b, 2a, 2b, 3a and 3b) and BVDV, and all viral proteins were produced from long polyproteins cleaved by the host or viral proteases. Also, both had protein domains with serine protease, helicase and RNA dependent RNA polymerase activities in polyproteins at similar locations. The Evaluation Centre requested the applicant to discuss the possibilities of ribavirin affecting DNA information by inducing mutations and the possibilities of producing mutated proteins. The applicant believed that ribavirin did not induce mutation to

DNA in the way that it did to RNA, as ribavirin did not suppress DNA dependent DNA polymerase (DdDp) α and β and incorporation of ribavirin into DNA was not observed *in vitro* and *in vivo*. The applicant explained that this maybe because ribavirin and phosphorylated ribavirin, which were not deoxygenated at the pentose, were not recognised as substrate by cellular DdDp that used deoxynucleotides as a substrate, and DdDp had accurate editing functions unlike RdRp. The Evaluation Centre requested the applicant to discuss reasons for ribavirin showing different degrees of additive effects depending on a type of IFN. The applicant stated that although the data shown did not show additive effects with IFN β and IFN γ, the comparison might not be accurate as the tests were conducted under conditions in which the same antiviral activity was not necessarily shown with all IFN. They also explained that, theoretically, it was not possible to explain the lack of additive effects with IFN β and IFN γ, but this may be clarified in clinical studies in future. The Evaluation Centre accepted the above responses.

F. Data on Absorption, Distribution, Metabolism and Excretion

In this application, data on ribavirin and ribavirin in combination with IFN α-2b are submitted.

(1) Results in Animals

1) Absorption

When male and female rats received a single oral dose of 0.3, 1.5, 7.5 or 40 mg/kg of ^{14}C-ribavirin in fasting condition, plasma radioactivity reached the maximum in 1 to 2 hours after the dosing and decreased with the half-life of 4 to 7 hours. Both C_{max} and AUC showed linearity and there was no obvious sex difference in any of the parameters. Radioactivity in red blood cells reached the maximum 2 hours after the administration and then decreased gradually. The ratio of radioactivity in red blood cells verses plasma was between 1.0 and 1.3 with C_{max} and 2.6 and 5.8 with C_{24hr}.

When male and female rats received repeated oral doses of 10, 20 or 40mg/kg of ribavirin in non-fasting condition once daily for 28 days, the accumulation indexes after

28 days against the initial administration, which was determined from $AUC_{0\text{-}24hr}$ of plasma ribavirin concentration, were between 1.2 and 2.1, but there was no obvious increase in C_{max} following the repeated doses. As the rate of an increase in $AUC_{0\text{-}24hr}$ was more than the increase in dosage, non-linearity was suggested. When plasma ribavirin concentrations in male and female rats were compared, in general, male rats had higher concentrations than female rats, suggesting sex differences in rats.

Male and female dogs received a single oral dose of 5 or 20 mg/kg of ^{14}C-ribavirin in fasting condition. The plasma radioactivity reached the maximum at 15 minutes to 1 hour after the administration and decreased with the half-life of 8.7 to 9.5 hours, suggesting linearity of both C_{max} and $AUC_{0\text{-}24hr}$. The radioactivity in the red blood cells reached the maximum at 1 to 2 hours after the administration then decreased gradually. The ratio of radioactivity in the red blood cells verses plasma was low, 0.5 to 0.6, at C_{max}, but was high, 6.9 to 9.2, at C_{48hr}, showing an increase with time after administrations. Sex differences were not observed with any of the parameters.

When male and female dogs received repeated oral doses of 5, 10 or 20 mg/kg of ribavirin once daily for 28 days in non-fasting condition, plasma ribavirin concentrations at 24 hours after each administration stopped showing clear increases after day 7 of treatment and it was considered that steady-state was achieved sometime before this. In male and female animals, the plasma ribavirin concentrations after the initial administration reached the maximum at 0.5 to 0.75 hours after dosing then decreased with the half-life of between 7.43 and 10.1 hours. The plasma ribavirin concentrations after the final administration in male and female animals reached the maximum at 0.5 to 0.75 hours after the administration then decreased with the half-life of 8.54 to 12.9 hours. Linearity in C_{max} and AUC was observed and the accumulation indexes determined from $AUC_{0\text{-}24hr}$ were between 1.14 and 1.50. When plasma ribavirin concentrations in male and female animals were compared, no clear sex differences in any of the parameters on the initial and final dosing days were observed.

Transfer of ribavirin to the blood cells was investigated in a pharmacokinetic study in which male monkeys received a single oral dose of 20 mg/kg of ^{14}C-ribavirin in fasting condition. The plasma radioactivity reached the maximum at 10.7 hours after the dosing then decreased rapidly at a steady rate. After 96 hours of dosing, it was below

the quantitation limit. In contrast, the radioactivity of the whole blood reached the maximum at 18.7 hours after the dosing then decreased gradually with the half-life of 180 hours. The concentration at 168 hours after dosing was approximately 60% of C_{max}. In a comparison of AUC_{0-t}, the radioactivity of the whole blood was approximately 20-times higher than the plasma radioactivity. Transfer of radioactivity to the blood cells was increased with time after dosing. It was 54% at 0.5 hours after dosing, whereas it was near to 100% at 72 hours after dosing.

Effects of the combination use of IFN α-2b on pharmacokinetics of ribavirin were investigated in male and female monkeys which received either a daily dose of 50mg/kg of ribavirin alone or daily doses of 50 or 100 mg/kg of ribavirin in combination with repeated subcutaneous dose of IFN α-2b (3,105 $\mu g/m^2$ once every 2 days). After the repeated oral dose in non-fasting condition, effects of concomitant IFN α-2b on plasma ribavirin kinetics were not observed after the initial and the final administration. The elimination half-life after the final dose was 195, 175 and 160 hours in the 50 mg/kg ribavirin group, the 50 mg/kg combination group and the 100 mg/kg combination group, respectively. The accumulation indexes determined from AUC_{0-24hr} were 3.80, 4.40 and 3.38 in the 50 mg/kg ribavirin group, the 50 mg/kg combination group and the 100 mg/kg combination group, respectively. The serum IFN α-2b concentrations, which were measured at the same time, were not affected by the dosed amount of concomitant ribavirin after the initial and the final administrations. After the initial administration, the serum IFN α-2b concentration reached the maximum at 2 hours after dosing in all groups, then rapidly decreased with the half-life of approximately 3 hours. After the final administration, the serum IFN α-2b concentration reached the maximum at 4 to 8 hours after dosing. The accumulation indexes determined from $AUC_{0-24hrs}$ of serum IFN α-2b concentration were 2.99 and 2.10 when 50 and 100 mg/kg of concomitant ribavirin was administered, respectively.

In view of the interactions with other drugs, the Evaluation Centre questioned the possibility of drug interactions through (i) sodium dependent nucleotide transporter (N1 transporter) involved in absorption of ribavirin in the upper small intestine and (ii) equilibrative nucleoside transporter (es-transporter) involved in distribution of ribavirin into tissue cells.

The applicant replied that they could not rule out (i) the possibility of competitive inhibitions of NI transporter by other nucleosides or nucleoside analogs and (ii) the possibility of drugs with inhibitory effects on cell membrane transport of nucleosides or nucleoside analogs to inhibit uptake of ribavirin into cells by es-transporter. They stated that although there was no study investigating these in detail, non-clinical and clinical data reported so far did not suggest these drug interactions.

The Evaluation Centre accepted the reply.

2) Distribution

When male and female rats received a single oral dose of 20 mg/kg of ^{14}C-ribavirin in non-fasting condition, tissue radioactivity reached the maximum at 2 or 8 hours after dosing in all tissues, including the digestive tract. All male and female animals showed extensive distribution of radioactivity to all tissues. Radioactivity in tissues other than the digestive tract was the highest in the liver, and then followed by the kidneys, the heart and the bladder. In the brain, the spinal code, the bones, the eyeballs and fat, the radioactivity was constantly lower than in plasma. Apart from reproductive organs, no clear sex differences in distribution of radioactivity and the elimination patterns were observed.

When male and female rats received repeated oral doses of 20mg/kg of ^{14}C-ribavirin once daily for 21 days in non-fasting condition, tissue radioactivity reached near steady-state on day 14 for the blood cells and after day 7 for the most of other tissues, in male and female animals. After the final administration (on day 21), tissue radioactivity reached the maximum at 2 or 8 hours after dosing in all tissues in male and female animals and the distribution patterns were almost the same as those after a single dose. Radioactivity in tissues other than the digestive tract was the highest in the liver, and then followed by the kidneys, the heart and the bladder. Relatively high radioactivity was observed in the skeletal muscles, the lungs, the spleens, the pancreas, the mesenteric lymph nodes, the prostates, the bladder and the bone marrows. As was with the single dose, apart from reproductive organs, no clear sex differences in distribution of radioactivity and the elimination patterns were observed.

When 18 days pregnant rats received a single oral dose of 20mg/kg of ^{14}C-ribavirin in fasting condition, tissue radioactivity of the dams reached the maxim at 2 to 8 hours after dosing. The level in the uterus, the placenta and the amniotic membrane were about the same as plasma radioactivity. Radioactivity in the foetus tissues reached the maximum at 8 hours after dosing and radioactivity in all tissues was either roughly the same as plasma radioactivity of dams or about twice that level. From these, high migration of ribavirin or the metabolites through the placenta was suggested.

When ^{3}H-ribavirin was added to plasma of the rat, the monkey and the human, the plasma protein binding rates were very low in any of these species and in the monkey and the human, no binding of ribavirin to plasma protein was observed.

3) Metabolism

As metabolism pathways of ribavirin, (i) reversible phosphorylation and (ii) deribosylation → hydrolysis of amide were recognised. As metabolites after (i) reversible phosphorylation, three types of phosphorylated ribavirin (RMP, RDP and RTP) were identified. As metabolites after (ii) deribosylation → hydrolysis of amide, $TCONH_2$, RTCOOH and TCOOH were identified.

When male rats received a single oral dose of 20mg/kg of ^{14}C-ribavirin in fasting condition, $TCONH_2$ in the plasma and urine, $TCONH_2$ and RTP in the red blood cells, and phosphorylated ribavirin (RMP, RDP and RTP) in the liver were identified as their main metabolites. When male monkeys received a single oral dose of 20 mg/kg of ^{14}C-ribavirin in fasting condition, $TCONH_2$ in the plasma and urine, TCOOH and $TCONH_2$ in the faeces, and phosphorylated ribavirin (mainly RMP) in the red blood cells were identified as their main metabolites. When humans received a single oral dose of 604 mg (a capsule) of ^{14}C-ribavirin in fasting condition, as well as unchanged ribavirin, radioactive TCOOH and $TCONH_2$ were identified in the urine. In rats, monkeys and humans, no phosphorylated ribavirin was found in the extracellular fluids (plasma and urine).

An *in vitro* metabolism study using human and rat liver preparations suggested that cytochrome P450 (CYP) was not involved in ribavirin metabolism. Therefore, it was

believed that concomitant use of ribavirin with other drugs was not likely to cause, at least, pharmacokinetic interactions involving CYP enzymes. Neither in humans nor rats, effects of additional IFN α-2b on *in vitro* metabolism of ribavirin were observed.

When rats received repeated oral doses of ribavirin up to 120 mg/kg once daily for 7 days in non-fasting condition, no effects on drug-metabolising enzyme systems in the liver were observed.

4) Elimination

When ^{14}C-ribavirin was administered orally in rats, dogs and monkeys, the main elimination path way was urine excretion in all species and they did not show sex differences in the elimination patterns of radioactivity in all species. When male and female rats received repeated oral doses of 20 mg/kg of ^{14}C-ribavirin in non-fasting condition once daily for 21 days, the cumulative elimination ratio up to 168 hours after the final administration was 95% (male) and 92% (female) of radioactivity in the urine, and 7.4% (male) and 8.2% (female) of radioactivity in the faeces. When male and female dogs received a single oral dose of 5 or 20 mg/kg of ^{14}C-ribavirin in fasting condition, the cumulative elimination ratio up to 48 hours after dosing was 93 to 94% (male) and 94 to 95% (female) in the urine, and 1.9 to 2.0% (male) and 2.0 to 2.1% (female) of radioactivity in the faeces. When male monkeys received a single oral dose of 20 mg/kg of ^{14}C-ribavirin in fasting condition, the radioactivity elimination ratio up to 168 hours after dosing was 70% in the urine, and 17% in the faeces. The cumulative elimination ratio in the faeces was roughly constant after 72 hours of dosing, but the cumulative elimination ratio in the urine was gradually increasing even after 168 hours of dosing, suggesting that elimination of the dosed radioactivity from the body was very slow in monkeys.

When bile duct cannulated male rats received a single oral dose of 20 mg/kg of ^{14}C-ribavirin in fasting condition, the rate of radioactivity elimination in the bile was extremely low, a cumulative value up to 48 hours from dosing being 0.771%. The cumulative elimination ratio of radioactivity in the urine and faeces at the same time point was 87% and 4%, respectively. Based on a total of the residual rates in the bile,

urine and body (4.7%), the absorption rate of ribavirin from the digestive tract in rats was estimated at over 90%.

When weaning rats on the 11th day from the parturition received a single dose of 20 mg/kg of ^{14}C-ribavirin in non-fasting condition, transfer of ribavirin or metabolites to milk was confirmed. The rate of radioactivity in the milk against the plasma radioactivity (milk/plasma) was 0.55, 0.68, 0.62, 0.77 and 1.3 at 0.5, 2, 4, 8 and 24 hours after dosing, respectively.

(2) Results in Humans

The following studies described in 1) to 8) were conducted abroad and the studies described in 9) and 10) were conducted in Japan.

1) Pharmacokinetics of ^{14}C-ribavirin (Overseas Study)

When healthy non-Japanese adult male volunteers received a single oral dose of a 604 mg capsule of ^{14}C-ribavirin in fasting condition, radioactivity in the red blood cells, blood (whole blood) and plasma reached the highest levels at 35, 33 and 1.5 hours after dosing, respectively. The radioactivity levels in the red blood cells and whole blood changed roughly parallel to each other and gradually fell until 28 days from dosing. In contrast, elimination of plasma radioactivity was rapid and radioactivity was below the quantitation limit at 24 hours after dosing. As the level of radioactivity in the red blood cell was about 2 times of the level of radioactivity in the whole blood, most of radioactivity in the whole blood was thought to be present in the red blood cells. As the level of radioactivity in the plasma was below the quantitation limit (<0.16 μq eg./mL) at 24 hours after dosing, it was not possible to follow the kinetics. However, near the peak, a similar level to the ribavirin concentration was seen. The plasma ribavirin concentration reached the maximum at 1.75 hours after dosing, and then decreased at the half-life of 62 hours.

The cumulative elimination ratio of radioactivity in the urine and faeces up to day 14 of dosing was 61% and 12%, respectively, which was measured at the same time. The

elimination rate of ribavirin in the urine at the same time-point was 17%, and approximately 27% of radioactivity eliminated in the urine was ribavirin.

2) Absolute Bioavailability (Overseas Study)

Healthy non-Japanese adult male volunteers received rapid intravenous injection of a 150mg solution of $^{13}C_3$-ribavirin, and then received an oral dose of 400 mg (two 200mg capsules) of ribavirin one hour later in fasting condition. The absolute bioavailability determined in the same volunteers was 64% in average. The apparent distribution volume at steady state and total body clearance after intravenous administration was 241 L and 40.5 L/hr, respectively.

3) Effect of Food on Bioavailability (Overseas Study)

Healthy non-Japanese adult volunteers received a single oral dose of 600 mg of ribavirin with or without a meal using a crossover design. When administered with a meal, bioavailabilites as both C_{max} and AUC were increased by approximately 70%. Furthermore, the start of absorption was delayed when administered after a meal and the absorption speed was lower.

4) Effect of Anti-acids on Bioavailability (Overseas Study)

Healthy non-Japanese adult volunteers received 600 mg of ribavirin alone or with an anti-acid agent without a meal. When administered with an anti-acid, AUC_{0-t} showed a 14% reduction, but plasma concentration profiles, including $T_{max,}$ did not show clear difference.

The Evaluation Centre asked the applicant whether the healthcare professionals needed to be informed of the reduction in AUC_{0-t} when an anti-acid was used concomitantly.

The applicant replied that they will describe the result of this study in 3) Effect of concomitant use of magnesium hydrate or aluminium hydrate, under the section for drug interactions in the prescribing information.

The Evaluation Centre accepted the reply.

5) Pharmacokinetic Interactions with Concomitant IFN α-2b (Overseas Study)

Non-Japanese chronic hepatitis C patients received repeated oral doses (the first and the last dose were administered without a meal) of ribavirin (600 mg twice daily, 1200 mg/day) alone or in combination with IFN α-2b ($3x10^6$ IU, subcutaneously three times per week). When administered in combination with IFN α-2b, bioavailability (C_{max}, AUC) of ribavirin was increased by 14 to 23% after the first dose and 4 to 13 % after the last dose. Considering inter-subject variations (90% confidence interval), the applicant concluded that the difference was not clinically significant. The accumulation index determined from $AUC_{0\text{-}12hr}$ was 6.84 and 5.57 after monotherapy and combination therapy, respectively. There was no clear difference in T_{max} and the elimination half-life of monotherapy and combination therapy.

Serum INF α-2b concentrations were measured at the same time, and it showed an increase of 18 to 25% after the first dose and a decrease of 8 to 20% after the last dose. The applicant concluded that the difference was not clinically significant, considering the inter-subject variations (90% confidence interval) in the same way as the ribavirin concentration. There was no clear difference in T_{max} and the elimination half-life after monotherapy and combination therapy. The accumulation index determined from $AUC_{0\text{-}12hr}$ was 2.69 and 1.89 after monotherapy and combination therapy, respectively.

The Evaluation Centre accepted that the variations in serum concentrations were within a range of inter-subject variations when ribavirin and IFN α-2b were used in combination, but believe that neither presence nor absence of interactions have been demonstrated. However, adverse drug reactions of combination use were investigated in the submitted documentation. Considering the conclusion, the Evaluation Centre judged that, at the present moment, there was no need for further investigation of the pharmacokinetics of the combination use.

6) Pharmacokinetics in Hepatically Impaired Patients (Overseas Study)

When healthy non-Japanese adult volunteers and patients with mild, moderate and severe hepatic impairment received a single oral dose of 600 mg ribavirin without a meal, C_{max} of plasma ribavirin was increased according to the severity of hepatic impairment, but no clear differences in T_{max} and AUC were observed. In addition, as kidney clearance of ribavirin was not altered according to the severity of hepatic impairment, it was assessed that there was no significant change in drug absorption and clearance.

The Evaluation Centre asked for the reason for providing the statement in the contraindication section, "(7) Patient with Severe Hepatic Function Failure [An increase in the blood ribavirin concentration may cause serious adverse drug reactions]" and contraindicating to the patients with severe hepatic function impairment in this application, although ribavirin was not contraindicated to patients with hepatically impaired patients in the USA, on the basis of this study result. The applicant replied that they judged that they should have a stricter standard in Japan than in the USA and set a contraindication because it was contraindicated to "patients with severe hepatic function impairment or non-compensated cirrhosis" in Germany unlike in the USA, and an increase in C_{max} seen in patients with severe hepatic function impairment may affect the safety. The applicant, however, amended the statement to the more appropriate, "(7) Patients with Serious Hepatic Function Disorder [An increase in the blood ribavirin concentration may cause serious adverse drug reactions.]"

The Evaluation Centre accepted the response.

7) Pharmacokinetics in Renally Impaired Patients (Overseas Study)

When healthy non-Japanese adult volunteers (CLcr: ≥ 90 L/min), or patients with mild (CLcr: 61 to 90 mL/min), moderate (CLcr: 31 to 60 mL/min) and severe (CLcr: 10 to 30 mL/min) chronic renal impairment received a single oral dose of 400 mg ribavirin without a meal, C_{max} and AUC_{0-t} of the plasma ribavirin level showed an increase dependent on the severity of renal function impairment. Total clearance (CL/F) was

decreased in contrast. In patients with renal impairment, the renal clearance of ribavirin showed a decline according to the severity of renal impairment and a correlation to CLcr was observed.

Non-Japanese chronic renal failure patients received a single oral dose of 400 mg of ribavirin without a meal and then underwent artificial dialysis 7 to 10 hours after dosing. During dialysis (7 to 10 hours after dosing), no clear differences in plasma ribavirin concentrations of the vein and artery were observed, suggesting that the plasma ribavirin concentration was essentially unaffected by artificial dialysis. In patients with dialysis-dependent renal failure, little un-changed ribavirin was eliminated in the urine (a cumulative elimination ratio of 0 to 48 hours: 0.30% of dose), but dialysis clearance (4.04 L/hr) was almost identical to renal clearance (4.31 L/hr) of patients with mild renal impairment (CLcr: 61 to 90 mL/min).

The Evaluation Centre asked the applicant to provide the rationale of choosing 50 mL/min in a contraindication statement of ribavirin, "(6) Patients with chronic renal failure or renal function impairment whose creatinine clearance is 50 mL/min or less."

The applicant's response was as follows. Patients with moderate chronic renal impairment (31 to 60 mL/min) were classified in two categories, CLcr between 31 and 50 mL/min and CLcr between 51 and 60 mL/min and investigated their ribavirin pharmacokinetic parameters (C_{max}, AUC_{0-t}, CL/F). Patients with CLcr between 31 and 50mL/min showed an increase in the average AUC_{0-t} values and a decrease in CL/F in a similar way as patients with CLcr between 10 and 30 mL/min. As ribavirin was not removed by haemodialysis, the applicant judged that patients with this level of renal function impairment should not receive ribavirin (considering ribavirin induced anaemia). Therefore, the applicant used 50 mL/min in Japan which was the same as overseas prescribing information (CLcr of 50 mL/min or below is classified as a "marked reduction" according to the Japanese society of nephrology and "phase 2: renal function impairment" according the Seldin, et al). In addition, the applicant believed that the healthcare professionals needed to be cautious with patients with mild or moderate renal function impairment and elderly patients. Therefore, they added "(6) Patients with mild or moderate renal dysfunction" in the Administer with Care section of the prescribing information and a new section for elderly patients was

created in order to state that ribavirin should be administered with care to elderly patients.

The Evaluation Centre accepted the response.

8) Sex difference in Pharmacokinetics of Healthy Adult Volunteers (Overseas Study)

When healthy non-Japanese adult volunteers received a single oral dose of 400, 800 or 1200 mg of ribavirin without a meal, no clear sex differences in any of pharmacokinetic parameters were observed in the 400 mg group. However, in the groups which received 800 mg and 1200 mg, C_{max} and AUC of the female subjects were generally higher, and on average, they were 1.4 to 1.6 times higher. There were no clear sex differences in T_{max} and the cumulative urine elimination ratio of 0 to 168 hours after dosing.

The Evaluation Centre asked the applicant what the reason was for the sex differences in ribavirin's pharmacokinetics observed at higher doses.

The applicant replied as follows. The average doses per body weight (Dose/BW) of the group received 400, 800 and 1200 mg were 5.74, 10.7 and 16.2 mg/kg for male subjects, respectively, and 6.84, 13.3 and 22.3 mg/kg for female subjects, respectively, and compared to male subjects, female subjects received higher dose on the whole. In a regression analysis of male and female combined data, significant linear relationships were observed between C_{max} and Dose/BW, and AUC_{0-t} and Dose/BW, and a trend of high blood concentrations in subjects who received higher Dose/BW was observed regardless of the sex. The applicant concluded that the reason for higher plasma ribavirin concentrations in females were mainly derived from differences in male and female body weight, and the differences in the concentrations were within a range of inter-subject variations in both sexes and would not cause clinical problems.

Although the Evaluation Centre accepted that the sex differences seen in the high dose groups were caused by the differences in bodyweight and they were within a range of inter-subject variations, the Evaluation Centre considers that there is a possibility that efficacy and safety in patients who have high AUC may be different in patients who have low AUC. However, the Evaluation Centre decided that the dose amount did not

need to be changed depending on sex at the present moment because no specific problems were seen from the submitted data and dose reductions in case of adverse drug reactions were prescribed.

9) Phase I Single Dose Study (Japanese Clinical Study)

When healthy Japanese adult male volunteers received a single oral dose of 200, 400, 600, 800, 1000 or 1200 mg of ribavirin without a meal, plasma ribavirin concentration reached the maximum at 1.4 to 2.2 hours after dosing then decreased in a biphasic fashion. The half-life for the distribution phase, $t_{1/2\alpha}$, and the half-life for the elimination phase, $t_{1/2\beta}$, was 0.95 to 2.6 hours and 28 to 49 hours, respectively, and no clear difference with the dosed amounts was observed. In contrast, linearity was observed with C_{max} within a dose range of between 200 and 800 mg and with $AUC_{0\text{-}t}$, within 200 and 1000 mg. With a higher dose, the increase reached a plateau, suggesting non-linearity of pharmacokinetics caused by saturation of absorption.

The cumulative rates of ribavirin elimination in the urine from 0 to 72 hours after dosing, which were measured at the same time, were between 7.7 and 15.9%, which were roughly constant regardless of the increased dose in the groups receiving 400 mg or more.

10) Pharmacokinetics of Repeated Doses in Chronic Hepatitis C Patients (Japanese Clinical Study)

When Japanese chronic hepatitis C patients received repeated oral doses of 400 mg of ribavirin twice daily (800 mg/day) for 24 weeks after a meal in combination with an IFNα-2b preparation ($6x10^6$ three times per week, intramuscularly), C_{min} of the serum ribavirin concentration was not increased after 8 weeks from the start of the dosing, thus it was estimated that the patients had reached steady state. The accumulation indexes for C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ taken after the initial and the final dosing were 5.24, 14.2 and 8.11, respectively. At the final dosing, the elimination half-life was about 10 times longer (29.3 hours to 295 hours), and the actual elimination phase of the initial dosing could be below the quantification limit, therefore, it was considered

difficult to predict the steady state of repeated doses from ribavirin single dose pharmacokinetic data. T_{max} did not show effect of repeated doses and was roughly the same after the initial and final dosing.

The serum IFNα-2b concentration was measured at the same time. It reached the maximum at 5.7 hours after both the initial and final dosing then decreased rapidly. The accumulation indexes determined from C_{max} and $AUC_{0\text{-}12hr}$ were 2.04 and 2.27, respectively.

(3) Similarity of Pharmacokinetics in Japanese and Non-Japanese

The dosage and administration methods used in Japanese clinical studies were chosen referring to the results of the overseas optimum dose study and considering differences in bodyweight of Japanese and overseas populations. Therefore, before referring to data from overseas studies, the relationship of pharmacokinetics in the Japanese and overseas population needs to be clarified. Concerning this, the applicant compared the studies described in the above 8) Sex difference in Pharmacokinetics of Healthy Adult Volunteers (overseas clinical study) and 9) Phase I Single Dose Study (Japanese Clinical Study); and the studies described in the above 5) Pharmacokinetic Interactions with Concomitant IFN α-2b (Overseas Study) and 10) Pharmacokinetics of Repeated Doses in Chronic Hepatitis C Patients (Japanese Clinical Study). They concluded that there was no big difference in pharmacokinetics of Japanese and non-Japanese.

With the data presented, the Evaluation Centre assess that it is appropriate to consider pharmacokinetics in Japanese to be not largely different from non-Japanese, taking the differences in bodyweight into account, although those clinical studies used for the comparison were not planned for investigation of similarities in pharmacokinetics and do not necessarily allow accurate comparisons as the conditions of Japanese and overseas studies, such as the amounts and timing of ribavirin administration, sampling points, the matrix of measurements (plasma/serum) and meals, were different.

G. Clinical Data

(1) Overview of Clinical Study Results Submitted

Data from four clinical studies in Japan in 480 subjects in total were submitted with the application; they are a phase I study in 54 healthy adult male volunteers xxxxxxx, a study investigating the effect of ribavirin in combination with IFN α-2b in 126 chronic hepatitis C patients who were IFN non-responders or relapse patients xxxxxxxxxxxx, a dose selection study in 272 chronic hepatitis C patients with "genotype 1b and a high viral load" xxxxxxxxxxx, and a pharmacokinetic study in 28 chronic hepatitis C patients with "genotype 1b and a high viral load" xxxxxxx. A phase III clinical study and an optimum dose study implemented abroad, which were used as references when selecting the dosage and administration methods for Japanese clinical studies, were submitted as reference data.

1) Phase I Study

Safety and pharmacokinetics of a single oral dose of 200, 400, 600, 800, 1000 and 1200 mg of ribavirin was investigated in 54 healthy adult male volunteers. With regard to safety, adverse events of temporal headache (assessed as "not relevant") in 1 subject in the 400mg group and headache (assessed as "relevant") in 1 subject in the 1200 mg group were observed, but both are mild and disappeared without medical interventions. In blood biochemistry tests, high CPK values in 3 subjects in the 200 mg group and a high neutral fat level in 1 subject in the 600 mg group were observed, but all of them were assessed as "not relevant" to ribavirin. One subject in the 1000 mg group showed occult blood in the urine, which was assessed as "probably not relevant". From the above, the applicant concluded that safety of a single dose of ribavirin up to 1200 mg per day was demonstrated.

A repeated dose study in healthy volunteers was not conducted for reasons including that non-clinical reproductive development toxicity studies of ribavirin showed reduced sperm counts and morphological changes in the testis and sperms, results of gene toxicity studies were positive, and elimination from the body took about 6 months.

The applicant stated that they had decided to continue clinical trials in patients cautiously, as comparisons with the overseas single dose study results showed that pharmacokinetics in Japanese and Caucasians did not differ largely, as there were no pharmacokinetic interactions of ribavirin in combination with IFNα-2b, considering that overseas clinical trials had been conducted in many patients already, and based on the outcome of the clinical trial consultation with the Organisation for Pharmaceutical Safety and Research.

Please refer to Section F "(2) Data in Humans" for the pharmacokinetic findings.

2) Study Investigated Effects of Ribavirin in Combination with IFN α-2b in Chronic Hepatitis C Patients (IFN non-responders or relapse patients)

In a double-blinded, parallel-groups comparative study in 126 chronic hepatitis C patients who were IFN non-responders and who had relapsed after successful IFN treatment, 6 million IU of IFN α-2b was intramuscularly administered for 6 times per week for 2 weeks, and then 3 times per week for 22 weeks in combination with placebo or ribavirin (600 mg or 800 mg daily, divided into two doses) for 24 weeks. In this study, 62 patients were allocated to the IFN α-2b + ribavirin group (hereinafter referred to as I/R Group) and 64 patients were allocated to the IFN α-2b + placebo group (hereinafter referred to as I/P Group).

With regard to efficacy, the primary endpoint was the rate of response defined as the virological improvement (the rate of patients with undetectable virus) on 24 weeks after the end of treatment. In full analysis set, the response rate of patients with "genotype 1b and a high viral load" was 9.8% (4/41) in the I/R Group and 0% in the I/P Group (0/40) and in patients other than "genotype 1b and a high viral load", the response rate was 75.0% (15/20) in the I/R Group and 28.6% (6/21) in the I/P Group. Common efficacy differences in each stratum were checked using the Breslow-Day test (for interaction). The result was p=0.434, showing no interactions. Therefore, two groups with strata combined were compared with the Cochran-Mantel-Haenszel test. As a result, the I/R Group was significantly superior to the I/P Group (p=0.001).

Safety was investigated in 126 patients registered (62 in the I/R Group and 64 in the I/P Group). The incidence of adverse drug reactions was 100% for both I/R Group and I/P Group, showing no difference. As subjective symptoms and objective findings, depilation and pruritus were observed in 43.5% and 43.5%, respectively, in the I/R Group and 31.3% and 28.1%, respectively, in the I/P Group, and the incidences were higher in the I/R Group. Clinical lab test abnormalities were decreased haemoglobin and reticulocytosis in 71.0% and 71.0%, respectively, in the I/R Group and 0% and 4.7%, respectively, in the I/P Group, which occurred at higher rates in he I/R Group. However, they all recovered with dose reductions or withdrawal of ribavirin. Apart from those, the applicant stated that there was no clinically remarkable problem. Adverse drug reactions observed more frequently in the I/R Group (adverse drug reactions concerning subjective symptoms and objective findings or lab tests: with the incidence of 10% or over and at the same time, more than twice as high as the I/P Group or over 10% differences in incidences) were events concerning lab tests such as leukopenia, reticulocytosis and decreased haemoglobin and subjective symptoms and objective findings of rash, pruritus and anaemia. Two out of 15 patients had dose reductions and then were withdrawn because of decreased haemoglobin and anaemia, but they recovered or improved with a dose reduction or withdrawal of ribavirin. Twelve patients experienced 35 serious adverse events (10 patients with 33 events in the I/R Group, 2 patients with 2 events in the I/P Group) and more events were seen in the I/R Group. Most of the events occurred during treatment and patients completely recovered or improved during the observation period. Of 33 serious adverse events seen in the I/R Group, 30 were assessed as adverse drug reactions, with 1 case of colon cancer, which was an unexpected adverse drug reaction. Of 2 serious adverse events in the I/P Group, 1 was assessed as an adverse drug reaction.

3) Comparative Study of IFN α-2b in Combination with Ribavirin and IFN α-2b Alone in Chronic Hepatitis C Patients with "Genotype 1b and a High Viral Load"

In chronic hepatitis C patients with "genotype 1b and a high viral load" (1 Meq./mL or over with the d-DNA probe assay or 10^5 copies/mL or over with the RT-PCR assay), a placebo controlled double-blinded parallel groups comparative study was carried out. The study investigated three groups; IL/R Group with 90 patients receiving IFN α-2b

(6 million IU: 6 times a week for 2 weeks + 3 times a week for 22 weeks) + ribavirin 600 or 800 mg/day for 24 weeks, IH/R Group with 94 patients receiving IFN α-2b (10 million IU: 6 times a week for 2 weeks + 6 million IU: 3 times a week for 22 weeks) + ribavirin 600 or 800 mg/day for 24 weeks, and IH/P Group with 88 patients receiving IFN α-2b (10 million IU: 6 times a week for 2 weeks + 6 million IU: 3 times a week for 22 weeks) + placebo for 24 weeks.

With regard to efficacy, in FAS, the primary endpoint, which was virological improvement (at 24 weeks after the final administration) with the baseline viral load (by a d-DNA probe assay) as covariant, was significantly superior in the IL/R Group + IH/R Group (the ribavirin combination therapy group) compared with the IH/P Group (p=0.004, logistic regression analysis). The IL/R Group and the IH/R Group were also significantly superior to the IH/P Group respectively (p=0.002, p=0.013, logistic regression analysis). When the patients were divided into 3 categories of baseline viral loads of less than 1 Meq./mL, 1 to less than 5 Meq./mL, and 5 Meq./mL or over, the higher the HCV RNA level, the lower was virological improvement (at 24 weeks after the final administration). Furthermore, the response rate with virological improvement (at 24 weeks after the final administration) which did not account the baseline viral load as covariant was 20.7% in the IL/R Group, (18/87), 16.0% in the IH/R Group (15/94) and 2.4% in the IH/P Group (2/85), showing the IL/R Group + IH/R Group was significantly superior to the IH/P Group (p=0.003, logistic regression analysis). The IR/R Group and the IH/R Group were also significantly superior to the IH/P Group respectively (p=0.002, p=0.007, logistic regression analysis). A stratified analysis by effects of past IFN treatment showed that the response rate of relapse patients and non-responders in the IH/P Group was 0%, whereas in the IL/R Group + IH/P Group, 16% of relapse patients and 18% of non-responders showed response.

With regard to safety, the incidence of adverse drug reactions in all groups, the IL/R, the IH/R and the IH/P was 100%. Adverse drug reactions that were observed at high frequency in the combination group (incidences of 10% or over) which were more than twice the incidence in the IH/P Group or with a difference of over 10% were lab test result abnormalities suggestive of disorders of red blood cells, such as increased reticulocyte and decreased haemoglobin, and subjective symptoms and objective findings such as pruritus and rash. Of 32 patients who had dose reductions or

withdrawal because of decreased haemoglobin or anaemia, 5 patients were withdrawn after a reduction of ribavirin. All of them were completely recovered from decreased haemoglobin and anaemia or improved after ribavirin reduction or withdrawal. Furthermore, 55 serious adverse events were observed in 30 patients (13 events in 29 patients in the IL/R Group, 11 events in 20 patients in the IH/R Group, 6 events in 6 patients in the IH/P Group). Of those 55 serious adverse events, 49 events were assessed as adverse drug reactions (27 in the IL/R Group, 19 in the IH/R Group, 31 in the IH/P Group). More serious adverse events (including adverse drug reactions) were observed with combination therapy than monotherapy. Most of the events appeared during the treatment period and the outcome in all but 2 cases was complete recovery or improvement. Symptoms of 2 patients with persistent adverse drug reactions were hyperglycaemia and a weight decrease in 1 patient and hypothyroidism in another patient and all symptoms were assessed "marked". An unexpected adverse drug reaction (bladder tumour) was observed in 1 patient in the IL/R Group. Also, death of 1 patient who was in the IL/R Group from liver failure was confirmed. Trial treatment of this patient was withdrawn on day 19 of the clinical trial because of an incident of haemorrhage of the digestive tract (malaena). The patient was diagnosed with small intestine ulcer and received an operation. After the operation, the patient developed a complication of pneumonia and on 12 days after the operation, the patient had liver failure. On 71 days from the liver failure, the patient died. It was judged that there was no causal relationship.

4) Pharmacokinetics

Pharmacokinetics of IFNα-2b in combination with ribavirin was investigated in 28 chronic hepatitis C patients with "genotype 1b and a high viral load" (1 Meq./mL or over with the d-DNA probe assay or 10^5 copies/mL or over with the RT-PCR assay).

With regard to safety, the incidence of adverse drug reactions was 100%. There were 4 cases with lymphopenia, 15 cases with thrombocytopenia, 1 case with microscopic haemauria and 3 cases with a CRP elevation, but all of them were moderate to mild. One patient was withdrawn due to serious adverse events (assessed to be adverse drug reactions; decreased haemoglobin, nausea, muscle pain, malaise).

For pharmacokinetics, please refer to section F.

5) Overseas Dose Selection Study

A study comparing IFN α-2b monotherapy and IFN α-2b + ribavirin combination therapy in (IFN naïve) chronic hepatitis C patients (an overseas dose optimisation study (Study number: C96-114)):

In Europe and USA, four studies in total were implemented in hepatitis C patients who had relapsed after IFN treatment and who had no previous IFN treatment. Compared with IFN α-2b monotherapy, ribavirin 1000 or 1200mg per day (a dose was selected based on bodyweight of the subject) in combination with IFNα-2b was significantly more effective in terms of bringing hepatitis C virus to below limit of detection. Following this, efficacy and safety of lower doses of ribavirin were investigated comparing with the 1000 or 1200 mg group. Targeting IFN naïve chronic hepatitis C patients, the safety and efficacy was investigated in 4 IFN α-2b + ribavirin groups (4 groups were; I/R(400) Group: a group receiving 3 million IU of IFN α-2b + 400mg of ribavirin, I/R(600) Group: a group receiving 3 million IU of IFN α-2b + 600mg of ribavirin, I/R(800) Group: a group receiving 3 million IU of IFN α-2b + 800mg of ribavirin, and I/R(1000/1200) Group: a group receiving 3 million IU of IFN α-2b + 1000 or 1200mg of ribavirin), and I/P Group (million IU of IFN α-2b + placebo).

The study consisted of two stages. In the first stage, patients were randomised and allocated to the groups, including the placebo group, and received treatment for 24 weeks, and then were followed for 24-weeks for observation after the treatment. The dosage of ribavirin in the second stage was determined on the basis of the haemoglobin level in week 4 of the treatment and changes in the HCV RNA level. In the first stage, 228 patients were randomised and 223 patients initiated the treatment. There were 44 in the I/R (400) Group, 44 in the I/R (600) Group, 44 in the I/R (800) Group, 46 in the I/R (1000/1200) Group and 45 in the I/P Group.

The changes in the HCV RNA levels in all groups were similar for 48 hours from the start of treatment, but after that, the HCV RNA levels were dose-dependently decreased until week 4 of the treatment. The I/R (1000/1200) Group showed a

biggest fall in HCV RNA level up to week 4, and the next biggest fall was seen in the I/R (800) Group. The reduction from the baseline level (log 10) was –2.09 in the I/R (800) Group and –2.22 in the I/R (1000/1200) Group. With regard to the changes in the haemoglobin levels in each group, reductions in haemoglobin (haemolysis), which were dependent on the dosed amount of ribavirin, were observed. The reduction from the baseline level was 1.7 g/dL in the I/R (800) Group, 2.2 g/dL in the I/R (1000/1200) Group. More than 3 g/dL reductions of haemoglobin were observed in 7% of patients in the I/R (800) Group and 32% in the I/R (1000/1200) Group.

The dose amount of the second stage was chosen based on results on week 4 of the treatment in the first stage, as a lower dose of ribavirin, 800mg/day was selected. This is because, compared with 400 mg/day or 600 mg/day, 800 mg/day showed a closer degree of HCV RNA reduction to 1000 or 1200 mg/day, and at the same time, with 800 mg/day, fewer patients showed reductions in the haemoglobin level (haemolysis) than with 1000 or 1200 mg/day.

In the second stage, in addition to the 135 patients who were in the I/R (800) Group, the I/R (1000/1200) Group and the I/P Group in the first stage, 378 new patients were randomised (128 were allocated to the I/R (800) Group, 124 to the I/R (1000/1200) Group and 126 to the I/P Group). Efficacy and safety assessments were carried out by combining patients in the first stage; 172 patients in the I/R (800) Group, 170 patients in the I/R (1000/1200) Group and 171 patients in the I/P Group. The number of patients withdrawn was 21 in the I/R (800) Group, 23 in the I/R (1000/1200) Group and 14 in the I/P Group.

All items analysed were significantly superior in the I/R (800) Group and the I/R (1000/1200) Group, comparing with the I/P Group. Viral clearance at the end of treatment was seen in 49% of patients in the I/R (1000/1200) Group, which was higher than the I/R (800) Group, 45%. Similarly, 27% of patients sustained negative virus for 24 weeks after treatment, which was higher than the I/R (800) Group, 23%. HCV RNA of 82 to 88% of patients who sustained negative virus in I/R (combination) Groups was negative on week 4 of treatment. However, among patients whose HCV RNA became negative for the first time on week 12 of treatment, 26% in the I/R (800) Group and 42% in the I/R (1000/1200) Group remained negative. Also, among

patients with HCV genotype 1 and over 20 million copies/mL, the rate of patients who maintained negative HCV-RNA was higher in the I/R (1000/1200) Group than in the I/R (800) Group. With regard to reductions in hepatitis core (Knodell HAI score), the I/R (1000/1200) Group (-5.0) showed bigger reduction than the I/R (800) Group (-4.4) and improvement in hepatic fibrosis was also superior in the I/R (1000/1200) Group (22%) than the I/R (800) Group (17%).

With regard to safety, details, degrees and incidences of adverse events were similar to those seen in previous studies and they were a good reflection of characteristics of safety of both ribavirin and IFN α-2b. Most of the adverse events were mild or moderate and did not restrict the treatment. No patients in the I/R (800) Group were withdrawn due to anaemia and 1% in the I/R (1000/1200) Group were withdrawn due to anaemia. Two treatment groups did not show a large difference in withdrawals, 10% in the I/R (800) Group, 13% in the I/R (1000/1200) Group. The commonest reason for withdrawal was psychoneurological disorder. The percentage of patients who required a dose reduction was 16% in the I/R (800) Group and 28% in the I/R (10000/1200) Group. A dose reduction due to anaemia was 2% in the I/R (800) Group and 9% in the I/R (1000/1200) Group.

Incidences of serious adverse events were similar in three treatment groups, 14% in the I/R (800) Group, 9% in the I/R (1000/1200) Group and 9% in the I/P Group. One patient in the I/P Group died from spontaneous aortic dissection, which was unrelated to the drugs. Incidences of cardiovascular and psychoneurological adverse events were low in all three groups, 7% in the I/R (800) Group, 6% in the I/R (1000/1200) Group and 5% in the I/P Group.

From the above stage II results, efficacy observed in the I/R (800) Group and the I/R (1000/1200) Group was significantly superior to the I/P Group. Many efficacy endpoint gave better results in the I/R (1000/1200) Group than in the I/R (800) Group. Safety of the I/R (800) Group and the I/R (1000/1200) Group was roughly the same and the I/R (800) Group was not any safer than the I/R (1000/1200) Group. Therefore, it was concluded that the I/R (1000/1200) Group showed almost same safety but slightly higher efficacy compared with the I/R (800).

6) Summary of Clinical Studies Abroad (Study Number: C 95-144, I95-145, C95-132, I95-143)

Clinical studies in chronic hepatitis C patients which targeted relapse patients (C95-144, I95-145) and treatment-naïve patients (C95-132, I95-143) were submitted as reference data.

With regard to efficacy, IFNα-2b in combination with ribavirin (hereinafter referred to as combination therapy) was more effective than IFN α-2b alone (hereinafter referred to as monotherapy), regardless to whether the patient was treatment-naïve or relapsed and independent of genotypes or viral loads. Particularly, in patients with genotype 1 or a virus load of over 2 million copies/mL, the difference from monotherapy was significant. Combination therapy's significant effect was also observed in patients who had bridging fibrosis in liver tissues. Ninety one to 96% of patients who showed HCV-RNA clearance had sustained normal ALT, showing a high correlation.

With regard to safety, adverse drug reactions observed with combination therapy were those observed with each drug alone and no reactions occurred synergistically by combination use. Haemolysis, which was a characteristic adverse drug reaction of ribavirin, can be controlled by following the protocol concerning decrease in haemoglobin levels. Therefore, combination therapy was considered to be not inferior to monotherapy from a safety point of view. Adverse drug reactions observed with combination therapy were generally mild or moderate and adverse events that would impair safety of combination therapy in chronic hepatitis C patients were considered to be absent.

(2) Outline of Evaluation by the Evaluation Centre

The Evaluation Centre summarised the outcome of the evaluation as follows.

1) Current Status and Various Guidelines

In Japan, the number of HCV infected patients is estimated at between 1 to 2 million. They are likely to progress to chronic hepatitis and cirrhosis then develop hepatocellular cancer (said to be at a yearly rate of 7%). With chronic hepatitis C, it is

rare for sustained infection to clear naturally. The objective of treatment is to achieve virological improvement in order to stop progress of the disease and to inhibit development of cirrhosis and hepatic cancer. Therefore, eradication of the virus is essential, the treatment is highly important and the prime task considering the number of patients we have.

Guidelines (consensus) for hepatitis C have been published in the USA (NIH), Europe (EASL) and Asia-Pacific region (APASL). Ribavirin was not mentioned in the American guideline as it was produced before FDA approved ribavirin, however, the European and Asia-Pacific guidelines already recognise the need.

According to the Asia-Pacific guideline (Journal of Gastroenterology and Hepatology, 15, 825-841, 2000), IFN + ribavirin combination therapy is the first choice treatment for treatment-naïve chronic hepatitis C patients. It also states that patients with genotypes 2 and 3, or patients with genotype 1 and a low viral load (2×10^6 virus equivalents/mL or less) will require a 6 month treatment and patients with genotype 1 or 4 with a high viral load (2×10^6 virus equivalents/mL or above) will require a 12 month treatment. Patients who had relapsed after achieving ETR (end of treatment response) with the previously believed best treatment (IFN 3 million IU/3 times a week, 6 months) should receive combination therapy of IFN (3 million IU/3 times a week) and ribavirin (800 to 1200 mg/day, adjusting the dose according to the bodyweight) for 6 months or, if giving IFN monotherapy, stronger IFN should be used and either the dose should be higher or treatment should be longer.

According to the European guideline (Journal of Hepatology, 30, 956-961, 1999), apart from contraindicated patients, all patients who are treated for the first time should receive IFN + ribavirin combination therapy. The period of treatment is determined by genotype and the viral load and it recommends a 6 month treatment to patients with genotype 2 and 3 regardless of the viral load. To patients with genotype 1, if the viral load is low (less than 2 million copies/mL), a 6 month treatment is recommended, and if the viral load is high (2 million copies/mL or over), a 12 month treatment is recommended. It recommends two treatments to patients who had relapsed after IFN treatment. They were IFN + rivabirin combination therapy for 6 months, if ribavirin is not contraindicated, or high dose IFN therapy (an amount above

3 million IU or 9μg three times per week) for 12 months. With both treatments, HCV RNA should be measured at 3 months from the start of the treatment and if positive, treatment should be stopped. It also states that there are no clear data showing re-treatment is effective in patients who did not respond to IFN monotherapy or IFN + ribavirin combination therapy.

Recently, the British guidelines (clinical guidelines on the management of hepatitis C, *Gut*, vol 49, Suppl. I, 2001) were published. According to this, IFN + ribavirin combination therapy is the first choice of treatment for treatment-naïve chronic hepatitis C patients and chronic hepatitis C patients who had relapsed after IFN monotherapy.

2) Efficacy

(i) Administration of ribavirin to IFN naïve patients who are not "with genotype 1b and a high viral load"

Clinical studies carried out in Japan targeted intractable patients, i.e., the combination study was in relapse patient and the dose selection study was in patients with genotype 1 b and a high viral load. The Evaluation Centre asked the opinion of the applicant regarding the fact that they did not limit the indication to intractable patients in this submission.

The applicant stated that although they did not conduct a clinical study in 'IFN naïve patients other than those "with genotype 1b and a high viral load"' in Japan, they could expect the following, concerning safety and efficacy of the combination therapy.

With regard to safety, a clinical study in IFN naïve patients (xxxx *N. Eng. J.Med.*, 339, 1485-1492, 1998, xxxx *Lancet*, 352, 1426-32, 1998) and a clinical study in relapse patients xxxx were conducted. Safety in patients other than intractable patients was inferred by comparing these results. Adverse events seen relatively more often in the clinical study in IFN naïve patients were insomnia, fatigue, depression, pruritus, anorexia and coughing, but no qualitative differences in overall adverse events were seen. The applicant replied that they did not believe that incidences of serious adverse events had led to increased withdrawal.

With regard to efficacy, the percentage of IFN non-responders and relapse patients calculated from the percentages of patients who had sustained negative virus load after IFN monotherapy in 'treatment naïve chronic hepatitis C patients other than those "with genotype 1b and a high viral load"' (47%, 650/1396) was 53%, according to the results published by the MHW 'Non-A Non-B Hepatitis' Study Groups (MHW 'Non A Non B Hepatitis' Study group, 1995 study report, 72-73, 1995). According to the Japanese clinical studies, 76.2% (16/21) of IFN non-responder or relapse patients other than those "with genotype 1b and a high viral load" and who received IFN α-2b + ribavirin combination therapy had sustained negative virus. Therefore, a response rate when non-responders or relapse patients received the combination therapy is estimated at 53×7.62 = about 40%. By adding this to that for IFN monotherapy, 47%, the applicant expects to see sustained negative virus in 87% of patients in total.

The Evaluation Centre believes that it is questionable to discuss efficacy based on hopeful speculations. However, the Evaluation Centre would like to make a decision on whether the combination therapy should be given to patients other than intractable patients, based on the expert review including whether we should refer to results of an overseas clinical study in treatment naïve patients which were cited by the applicant for safety discussion.

(ii) Appropriateness of dosage of ribavirin and IFN α-2b in Japan

As a ribavirin dose selection study was not conducted in Japan for this submission, the Evaluation Centre asked the applicant to explain the appropriateness of the dose selected for Japan.

The applicant replied that the average bodyweight of chronic hepatitis C patients in overseas large-scale studies was 77 kg and ribavirin dose per bodyweight was between 10 and 16 mg/kg, based on the minimum dose of 800mg/day and the maximum dose of 1200 mg/day. In Japanese clinical trials in chronic hepatitis C patients with IFN α-2b, the average bodyweight of patients was approximately 60 kg. Therefore, it will be applicable to 600 to 1000 mg/day with a bodyweight conversion. Safety of a single dose of 1200mg ribavirin was demonstrated in the Japanese phase I study. Therefore, it was possible to choose 600 to 1000 mg/day of ribavirin for clinical studies in chronic

hepatitis C patients, but considering that the dose of IFN α-2b was higher and more frequent at an initial stage than abroad, the applicant decided to choose a slightly lower upper limit for ribavirin. Thus they have chosen 600 mg/day (3 capsules /day) for patients weighing less than 60 kg and 800 mg/day (4 capsules/day) for patients who weigh more than 60 kg, i.e. roughly 10 to 13 mg/kg. With regard to the dosage of IFN α-2b, overseas clinical studies used lower doses, i.e., 3 million IU 3 times a week, and did not have initial successive dosing, unlike Japanese IFN treatment. However, to focus on bringing the virus below determination limit, the applicant chose 6 to 10 million IU everyday for 2 weeks, then 3 times per week for 22 weeks. This is a commonly used dosage regime in Japan, which is believed to maintain minimum safety and eradicate the virus most effectively.

The Evaluation Centre asked the applicant to explain the differences in thinking processes when choosing the dosage of ribavirin and IFN α-2b. The applicant replied that the results of the overseas studies showed that the occurrences of adverse drug reactions were not synergistic when ribavirin was used concomitantly with IFN α-2b. Considering this, the applicant judged that there was no need to change the dosage and administration of IFN α-2b currently used in the therapy, so that as high as possible a treatment effect could be investigated. With regard to ribavirin, the applicant judged that the dose should be extrapolated with bodyweight because of the limitation on safety (anaemia due to reductions in haemoglobin). Based on this, the doses were selected and the clinical trials were conducted. The ribavirin dose per 1kg bodyweight and the percentage of patients with sustained negative virus on 24 weeks after the final dose showed differences at a threshold of 10.6 mg/kg both in Japan and abroad, and the optimum dose per 1kg of bodyweight was the same. Concerning safety, the percentage of patients who had dose reductions because of decreased haemoglobin in the Japanese studies was 19.1%, higher than abroad, which was 5.6%. Although the severity of decreased haemoglobin showed a tendency of worsening over 13 mg/kg, this can be controlled by following the dose-reduction and withdrawal criteria. Other adverse drug reactions did not show a tendency of deterioration in the severity with a dose increase of ribavirin. Therefore, the applicant judged that the doses selected for Japan, i.e. 800 mg (over 60 kg) and 600 mg (less than 60 kg) were appropriate.

The Evaluation Centre considers this response generally appropriate as a rationale for the dose selection. However, in patients whose bodyweight is between 60 and 62 kg, ribavirin will be more than 13 mg/kg, and may lead to safety problems. Therefore, the Evaluation Centre would like to make a decision based on the expert review.

(iii) Regarding ribavirin administration method

Ribavirin's dosage and administration is "usually for adult, orally administer 600 mg or 800 mg per day of ribavirin in two divided doses after breakfast and evening meals every day." "If the patient weighs more than 60 kg, the daily dose should be 800 mg, if the patient weights less than 60 kg, the daily dose should be 600 mg." The Evaluation Centre asked how to take 600 mg in two divided doses (200 mg/capsule, 3 capsules).

The applicant replied that although they have not carried out detailed investigation, ribavirin's half-life was long, 300 hrs, and it was highly cumulative. Therefore, as long as the dose per day was the same, C_{max} and trough concentration at steady state was not likely to be affected by the divided dose. The applicant believes that both 200mg in mornings and 400 mg in evenings or 400 mg in mornings and 200 mg in evenings would not cause pharmacokinetic problem. In the overseas clinical trials, when the dose was reduced to 600 mg/day, patients received 200 mg in mornings and 400 mg in evenings. In the Japanese clinical studies, when 600 mg/day was given, the patients received 200 mg in mornings and 400 mg in evenings. Considering that efficacy and safety of 600mg/day was only confirmed with 200 mg in mornings and 400 mg in evenings both in Japan and abroad, the applicant stated that they were going to add "when administering 600 mg/day, administer 200 mg after breakfasts and 400 mg after evening meals" to the dosage and administration section.

The Evaluation Centre accepted the reply.

(iv) Mode of action of the combination therapy

The Evaluation Centre asked the reason for ineffectiveness of ribavirin monotherapy and the mode of action of combination effect of ribavirin with existing IFN therapy.

The applicant replied that the anti-viral effect of ribavirin monotherapy against chronic hepatitis C was weak and it showed no change or only a trend of decrease during treatment. It is reported that negative HCV RNA was hardly seen after treatment or during treatment (*Hepatology*, 16, 649-654, 1992, *J. Hepatol.*, 25, 591-598, 1996, *Hepatology*, 26, 473-477, 1997, *Ann. Intern. Med.*, 123, 897-903, 1995, etc.) They suspected that the combination effect of IFN α-2b + ribavirin was not an additive effect but a synergistic effect. The applicant also said that it was confirmed *in vitro* that a combination of INF α and ribavirin had a synergistic effect on suppression of cell damage by the virus (the BVDV infection study in MDBK cells, please refer to Section E).

(v) Necessity of liver histology tests

The Evaluation Centre asked the applicant's view on a necessity of liver histology tests before starting ribavirin combination therapy in order to confirm histological progress, which is a factor that defines efficacy.

The applicant replied that the liver histological tests were carried out before starting trial treatment in clinical studies in order to investigate the degree of fibrosis and the response and to eliminate cirrhosis with certainty. It was not a treatment requirement. The effect of IFN α-2b + ribavirin combination therapy was also seen in patients with progressed hepatic fibrosis. Therefore, the applicant argued, there was no need to conduct a liver biopsy in order to decide treatment policy. The applicant introduced the following specialists' opinions. Liver biopsy was done in order to diagnose chronic hepatitis histologically. In clinical practice, it was fully possible to diagnose chronic hepatitis (eliminate cirrhosis) with blood and biochemical tests and diagnostic imaging. IFN α-2b monotherapy did not require liver biopsy, so there was no need to perform biopsy before starting ribavirin combination therapy. Furthermore, it was possible to distinguish chronic hepatitis from cirrhosis with platelet and the hepatic standby capacity and considering the risk of liver histology tests, they did not think it needed to be essential. The specialists sincerely hoped that ribavirin combination therapy would be used widely. The Evaluation Centre would like to decide the necessity of liver histological tests based on the expert review.

(vi) Differences in HCV-RNA assay in Japan and abroad

The Evaluation Centre asked the applicant that if the definition of a high viral load with HCV-RNA assay was the same as the definition abroad. The applicant pointed out that the method used in Japanese clinical studies (d-DNA probe) and the method used in overseas clinical studies (q-PCR) were reported to show high correlation ($r=0.7446$, $p<0.001$, $n=260$). According to the regression line, 1 Meq./mL with the d-DNA probe assay was expected to be applicable to 1 million copies/mL in q-PCR. Therefore, 1.0 Meq./mL with the d-DNA probe assay was not largely different from 2 million copies/mL in q-PCR, which was used in overseas clinical trials. The applicant also said that categories of HCV RNA loads used in investigations of the relationship with IFN treatment effect in Japan and abroad were in good agreement and there was no problem in drawing a dividing line of a high virus load at 100k copies/mL in RT-PCR, 1.0 Meq./mL with the d-DNA probe assay and 2 million copies/mL with the q-PCR assay. Even when the conversion formula was used, the viral loads which were used as border values in Japanese and overseas clinical trials did not precisely agree. However, the Evaluation Centre believed that the applicant's explanation, i.e., there was no big difference in categories used in Japanese and overseas clinical trials, was appropriate, considering that those assay methods were semiquantitative and there were problems with the precision, and viral loads showed biological changes. The Evaluation Centre would like to confirm this decision in the expert review.

(vii) Divergence of FAS and PPS

In the combination effect study in Japan xxxxx, the numbers of patients in the full analysis set (FAS) and per protocol set (PPS) were 122 and 73, respectively, and in the dose selection study xxxxx, the number of patients in FAS and PPS were 266 and 137, respectively, showing large differences in the numbers of patients in two analysis sets. Therefore, the Evaluation Centre requested the details of patients excluded in PPS. The applicant replied that they were going to describe exclusions in the Gaiyo. The Evaluation Centre also requested the applicant to show analysis results of PPS and time changes in viral load in FAS and PPS.

With regard to PPS analysis results, the applicant replied that, in the combination effect study xxxx, 3.8% of patients in the I/R Group and 0% in the I/P Group belonged to A stratum ("genotype 1b and a high viral load"), and 84.6% in the I/R Group and 33.3% in the I/P Group belonged to B stratum (other than "genotype 1b and a high viral load"). The Cochran-Mantel-Haenszel test showed significance (p=0.007). In the dose selection study xxxxx, as it was not possible to calculate the maximum likelihood estimate, analysis was done with Cochran-Mantel-Haenszel test. As a result, the IL/R Group + the IH/R Group, the IL/R Group and the IH/R Group were respectively superior to the IH/P Group (p=0.001, p=0.001, p=0.003, respectively). The applicant concluded that the result of PPS analysis was the same as FAS analysis and there was no difference in the conclusions from the two analyses.

The Evaluation Centre checked that there was no large difference in the time changes of efficacy in FAS and PPS and accepted the response.

One of the reasons for the difference in the numbers of patients in FAS and PPS was that many patients used prohibited concomitant drugs in order to treat original diseases in both the combination effect study and the dose selection study. The Evaluation Centre asked the applicant what the reason was for use of the prohibited drugs and resultant outcome of the patients. The applicant was also asked to investigate how it affected the results.

The applicant submitted information on patients who used the prohibited drugs, i.e., treatment groups, used prohibited drugs, timing of the use, ALT values just before the use of the drug. With regard to the effect to the analysis results, the applicant replied that although they regarded the virological improvement and ALT improvement not assessable and excluded all these patients from the analysis according to the protocol, IFN was the only drug effective for HCV and use of the prohibited drugs would not affect virus clearance. Most of the prohibited drugs were used when liver function was exacerbated following ALT elevations, with a hope to improve it. Therefore, in order to separately investigate how much effect patients who violated the protocol and took the prohibited drugs had on ALT improvement, an analysis was carried out, excluding patients with these protocol violations from FAS. The applicant stated that the result was in agreement with FAS analysis.

The Evaluation Centre asked the applicant to show time-changes of viral loads and ALT of the applicable patients. The Evaluation Centre confirmed that improvements of ALT from administration of concomitant drugs were not necessarily dependent on the viral loads, and accepted the reply.

3) Safety

(i) Adverse drug reactions observed in Japanese clinical trials

Safety in the Japanese clinical studies xxxx was summarised as follows. Adverse drug reactions in all 246 patients who received administration of ribavirin (adverse drug reactions observed in 28 patients in the pharmacokinetic study was excluded from this analysis) were analysed. Adverse drug reactions with subjective symptoms and objective findings showing incidences of over 50% were fever, malaise, headache, anorexia, joint pain and rash. Of those, incidences of reactions other than rash were over 50%, even with IFN α-2b monotherapy. Pruritus, rash and alopecia were seen at higher incidences with ribavirin combination therapy compared with monotherapy (incidences were over 10% and more than twofold of incidences with IFN α-2b monotherapy or more than 10% difference). There was no big difference in the degree of reaction with monotherapy and combination therapy. Adverse drug reactions involving lab test values that were seen in more than 50% were leukopenia, neutropenia, thrombocytopenia, haemoglobin decreased, reticulocytosis, haematocrit value decreased and iron metabolism disorder. Of those, thrombocytopenia, neutropenia and leukopenia were over 50% even with IFN α-2b monotherapy. Adverse drug reactions that were observed at higher incidences with ribavirin combination therapy than monotherapy (incidences were over 10% and more than twofold of incidences with IFN α-2b monotherapy or more than 10% differences) were leukopenia, haemoglobin decreased, reticulocytosis, haematocrit value decreased, RBC decreased, iron metabolism disorder, haemoglobin increased, serum iron increased, indirect bilirubin increased, hyperuricaemia and direct bilirubin increased. They were mainly caused by leukopenia and red blood cell disorders due to ribavirin. Forty-seven patients out of 246 patients (19.1%) had dose reductions because of the characteristic adverse drug reaction of ribavirin, haemoglobin decreased, and of those,

13 patients (5.3%) were withdrawn (including those withdrawn from reasons other than haemoglobin decreased). Two patients were withdrawn without having a dose reduction. The haemoglobin values were recovered with withdrawal and no patients required other treatment. Leukopenia was seen frequently with IFN monotherapy, but the incidence was increased when ribavirin was used in combination. The leukocyte count at the end of treatment was about 4,100/mm^3 with IFN monotherapy, but it was lower, about 3,300/mm^3, with ribavirin combination therapy. One patient was withdrawn due to leukopenia. With this patient, the leukocyte count was lowest in week 4 and week 16 of treatment, 2,000/mm^3, and altered below 3,000/mm^3 from week 2 till withdrawal. After withdrawal, the value recovered to the pre-treatment level in 2 weeks and no other treatment was required.

(ii) Concerning a lack of repeated dose study in healthy volunteers

In the phase I study xxxx, only a single dose of 200 to 1200mg of ribavirin was investigated, but no repeated dose study was carried out. The Evaluation Centre understood that the applicant did not carry out repeated dose in healthy volunteer for ethical reasons, as strong toxicity of ribavirin was obvious from findings such as effects on reproductive organs in non-clinical studies and positive gene toxicity study results.

(iii) Mode of actions for haemoglobin decrease and reticulocytosis

In the combination effect study xxxx, the group receiving combination therapy had more serious adverse events and as characteristic adverse events of ribavirin, haemoglobin decrease and reticulocytosis (red blood cell disorders, so called haemolytic anaemia), occurred at high incidences with ribavirin combination therapy, which were hardly seen with IFN α-2b monotherapy. The Evaluation Centre asked the applicant what was the ribavirin's mode of action for this, was it reversible and did it affect haematogenesises (effect on bone marrows).

The applicant replied that the increase in reticulocytes was a normal compensatory response to anaemia and thought to be a result of normal haematogenesises. Results of a study in which 15 mg/kg of ribavirin was intramuscularly administered to monkeys

for 10 days showed that anaemia with ribavirin was not affecting erythroblast stem cells, but thought to have caused by reversible inhibition of red blood cells release from bone marrows, inhibition of maturity of erythroblast precursor cells or extravascular haemolysis. The applicant believed that the lifespan of normal red blood cells of monkeys was about 95 days, but after ribavirin administration, the lifespan was shortened to roughly 60 days. In a study administering IFN α-2b and ribavirin concomitantly for 1 month to monkeys, about 4 weeks from withdrawal, haemoglobin was returned normal. In clinical studies, at around week 4 of treatment, haemoglobin was reduced then reached steady state after that. Parallel to this, compensatory reticulocytosis was observed, and after the treatment all patients showed recovery in haemoglobin values in 4 to 8 weeks. The applicant stated that, therefore, as seen in the monkey study, the lifespan of red blood cells was thought to have shortened with ribavirin administration in humans and then normalised after the treatment. Therefore, it was reversible and there was no effect on bone marrows.

The Evaluation Centre accepted the study results presented, but IFN is known to cause bone marrow suppressions, aplastic anaemia in patients who received ribavirin combination therapy was reported abroad, and a high proportion of patients in the combination therapy group in the Japanese clinical studies showed leukopenia. Therefore, the Evaluation Centre believes that the possibility of bone marrow suppression with the combination therapy cannot be ruled out. The Evaluation Centre thinks cautions should be given and there is a need to pay attention on safety. In the prescribing information of ribavirin in the USA, bone marrow suppression in combination therapy with IFN α-2b is described under “Warning”.

Furthermore, the Evaluation Centre asked the applicant to explain whether dose reduction criteria based on decreased haemoglobin was appropriate because 24.6% (15/61) of patients in the combination effect study xxxxx and 17.4% (32/184) of patients in the dose selection study xxxxx had ribavirin dose reductions because of decreased haemoglobin.

The applicant replied that in these clinical studies, they established dose reduction and withdrawal criteria of ribavirin and IFN α-2b using haemoglobin values as an index, which was used in overseas clinical studies. The haemoglobin value in the criterion,

10g/dL, which was used in overseas clinical trials, was chosen considering the residual effect of ribavirin after withdrawal and the long half-life. They believed that, even if the study medications were withdrawn before transfusion was necessary, the haemoglobin value might decrease further, so if the ribavirin dose was reduced when the haemoglobin value was 10g/dL, they thought they could avoid transfusion or withdrawal of the study medications. As a result, haemoglobin values of patients who had a 200mg/day reduction of ribavirin were recovered and also there were patients who had sustained negative virus, the applicant believed the dose reduction criteria were appropriate. The Evaluation Centre assessed that the above responses were appropriate.

(iv) Dyspnea and sputum

The Evaluation Centre asked the applicant's interpretation of the adverse events, dyspnea and sputum increase, which were seen more frequently in the IFN α-2b + ribavirin combination therapy group than the IFN α-2b monotherapy group and the same trend was seen in both the combination effect study xxxx and the dose selection study xxxx.

The applicant replied that dyspnea was observed in 12.2% (30/246) in the ribavirin combination therapy group, and 2.6% (4/152) in the monotherapy group. Sputum increase was 8.1% (20/246) and 2.6% (4/152), respectively. Breakdown of 30 patients with dyspnea in the combination therapy group was 6 patients with dyspnea and 24 patients with breathlessness, and the breakdown of 4 patients with dyspnea in the monotherapy group was 1 patient with dyspnea and 3 patients with breathlessness. In the combination therapy group, incidences of dyspnea and breathlessness were higher than in the monotherapy group. As most of patients in the combination therapy group showed haemoglobin decreased, these adverse events were thought to be related to red blood cell disorders caused by ribavirin. Of those patients, one patient with breathlessness had withdrawal of ribavirin. The patient received no other treatment but breathlessness had disappeared on 127 days from the occurrence. In most of the other patients, the events disappeared without treatment and most of them were mild in severity in both groups. The breakdown of 20 patients with increased sputum in the

combination therapy group was 16 patients with increased sputum and 4 patients with sputum. The breakdown of the monotherapy group was 3 patients with increased sputum and 1 patient with sputum. The applicant stated that increased sputum, including sputum, was mild in severity but the incidence was higher in the combination therapy group than in the monotherapy group. The Evaluation Centre would like to refer to the expert review for the need to call for caution on respiratory diseases.

(v) Details of serious adverse drug reactions

Of serious adverse drug reactions reported abroad, the Evaluation Centre asked the applicant to provide the details of deaths other than suicide, especially cardiovascular diseases.

The applicant stated that in a total of 3126 patients who received IFN α-2b and ribavirin concomitantly in overseas clinical studies, 4 deaths (0.13%) were reported. Of them, 3 (0.10%) died for reasons other than cardiovascular disorders and 1 (0.03%) died from a cardiovascular disorder. The patient who died of a cardiovascular disorder was diagnosed with myocardial infarction. This patient was a 56 years old obese man, who had complications of diabetes and hypertension, and a history of myocardial infarction, angina and drug abuse. In one month from the start of IFN α-2b + ribavirin combination therapy, he developed anaemia (the lowest value was 9.3g/dL), so ribavirin was reduced to a half. Three months later, he had a myocardial infarction and died. The death was during treatment and could not rule out the relevancy. In the total of 3,126 patients who received IFN α-2b and ribavirin concomitantly in overseas clinical studies, only 1 patient (0.03%) died from a cardiovascular adverse drug reaction, so the applicant considered it was not a high incidence. However, the applicant replied that they cannot rule out the effect of the main adverse drug reaction of ribavirin, anaemia, on cardiac function and the cardio vascular system, so they would call for a caution. The Evaluation Centre accepted the response.

(vi) Rationale for creatinine clearance in the contraindication section

A pharmacokinetic study in non-Japanese patients with renal impairment showed that the pharmacokinetics of ribavirin were largely affected by the severity of renal impairment. The Evaluation Centre asked the applicant's opinion of whether the guideline for patients with renal impairment was set up appropriately. For the details on this, please refer to section F 7) "Pharmacokinetics in patients with renal impairment (overseas clinical study)".

(vii) Reproductive toxicity

The Evaluation Centre asked the applicant's view on reproductive toxicity of repeated dose, safety during clinical trials and provision of information after launch.

The applicant replied that in the clinical trials, female subjects with childbearing potential were pregnancy tested just before start of treatment, on week 12 and week 24 of treatment, 12 weeks and 24 weeks after cessation of treatment with common pregnancy testing agents. Also after trials, investigators surveyed if male subjects' sexual partners became pregnant or gave birth. As a result, one patient in the combination effect study had a sexual partner who delivered a baby naturally one year and 9 months after the treatment. The applicant stated that there was no abnormality in the newborn.

As an after launch measure, in the prescribing information, it has already contraindicated. However, in addition to this, the applicant was intending to produce patient leaflets, in order to provide information on ribavirin's reproductive toxicity, call for complete contraception and encourage a full discussion with doctors regarding how to act in the event that pregnancy was found, and would provide them in medical establishments and pharmacies. The Evaluation Centre accepted the response.

(viii) Safety investigation in special populations

Safety investigation in special populations, such as elderly or paediatric patients, pregnant, parturient and breastfeeding women, was not carried out, but in the

prescribing information (draft), it was contraindicated to pregnant (including those with childbearing potential) and breastfeeding women.

The Evaluation Centre believed this was appropriate considering reproductive toxicity of ribavirin. However, the Evaluation Centre also thought caution for the elderly population was required and asked the applicant if a special caution was required. The applicant replied that they were going to put a new section on "elderly patients" and state that cautious treatment was required as renal function of elderly patients was often compromised and reduced renal function may lead to an increase in the ribavirin blood concentration. The Evaluation Centre accepted the reply. Please refer section F 7) for the ribavirin pharmacokinetics with renal function impairment.

4) Prescribing Information (Draft)

(i) Reason for contraindicating to male patients whose partners are pregnant or possibly pregnant

The Evaluation Centre asked the applicant's view concerning the statement under the contraindication of the prescribing information, 'male patients whose partners are pregnant or possibly pregnant', which could be interpreted as 'male patients whose partners are pregnant cannot receive the treatment'.

The applicant replied that they thought they can arouse caution more if ribavirin was contraindicated to 'male patients whose partners are pregnant or possibility pregnant' and put warnings like in the USA, rather than allow ribavirin administration with descriptions of contraception methods like in Germany. Chronic hepatitis C patients have symptoms of chronic hepatitis for a long time then progress to hepatocellular cancer via cirrhosis. The period taken for each step is said to be 10, 20 or 30 years. Therefore, the applicant believed that there will be no clinically significant problem in male chronic hepatitis C patients who have not got cirrhosis but whose partners are pregnant or possibly pregnant to receive symptomatic treatment of liver function abnormalities, etc., and to wait IFN α-2b and ribavirin combination therapy until the

partner has given birth. The Evaluation Centre would like to assess how to deal with applicable patients based on the expert review.

(ii) IFN α-2b monotherapy

The Evaluation Centre asked the applicant in what sort of circumstance, IFN α-2b may be used alone.

The applicant replied that monotherapy will be given to patients with a history of hypersensitivity to ingredients of ribavirin or other nucleoside analogues, patients with uncontrolled heart disorders, patients with haemoglobinopathy (thalassemia, sickle cell anaemia etc.,) or patients with chronic renal failure or renal dysfunction with below 50 mL/min creatinine clearance. The also replied that pregnant women or women with childbearing potential, lactating female and male patients whose partners were pregnant or possibility pregnant should consider combination therapy with ribavirin as the first choice after the patient had a baby, after finishing or stopping breast feeding or after the partner had a baby.

(iii) Description of adverse drug reactions

The Evaluation Centre requested the applicant to describe mainly IFN α-2b monotherapy's adverse drug reactions in the prescribing information of IFN α-2b, as the submitted prescribing information (draft) of IFN α-2b described adverse drug reactions when it was used with ribavirin. The Evaluation Centre confirmed that appropriate amendments were made.

3. Overall assessment

The Evaluation Centre believes that this submission contains the following problems based on the data submitted.

- Two Japanese clinical studies (the combination effect study and the dose selection study) had very many protocol violations.

- Efficacy and safety in treatment naïve patients other than those “with genotype 1b and a high viral load” are not investigated.
- A ribavirin dose selection study in Japanese was not implemented.
- The overseas clinical studies used as reference data used different doses of both ribavirin and IFN α-2b.

In addition, the number of clinical studies implemented in Japanese patients was limited to 3 including the pharmacokinetic study. Also, the dose of IFN α-2b in the overseas clinical studies was 3 million IU and lower than the planned dose in Japan. Considering these, we cannot say safety information of the dosage and administration in the submission was collected fully.

However, considering that this combination therapy is for chronic hepatitis C, to which we have social obligation to supply more effective treatment urgently, the Evaluation Centre thinks this combination therapy could be approved based on the submitted data taking the following points into account.

- The two Japanese clinical studies showed that the ratio of negative HCV-RNA at 24 weeks after the end of treatment, which was the primary endpoint, was significantly higher with ribavirin combination therapy than IFN α-2b alone. This is in agreement with the results of the overseas clinical trials that were submitted as reference data.
- Combination therapy of IFN α-2b + ribavirin was shown to be effective in intractable patients, such as “genotype 1b and a high viral load” and patients that had relapsed.
- With the combination therapy, haemoglobin reduction and reticulocytosis (red blood cell disorders, so called haemolytic anaemia) occurred at characteristically high incidences, which are hardly seen with IFN α-2b monotherapy. However, it was shown that by paying full attention and with appropriate dose reduction or withdrawal, they recovered.

- Apart from haemoglobin reduction, no large difference in quantity and quality of safety was seen compared with IFN α-2b.

18 September 2001

REVIEW REPORT (2)

1. Application Products

Proprietary name	Rebetol Capsules 200 mg
Generic name	Rivavirin
Applicant	Schering Plough Co. Ltd
Date of application	27 April 2001

Proprietary name	Intron A Injection 300, 600, 1000
Generic name	Interferon-alpha 2b (recombinant)
Applicant	Schering Plough Co. Ltd
Date of application	27 April 2001

2. Overview of Review

The Review Center sought responses mainly about the following points and conducted the investigation on the basis of consultation with experts.

(1) Data on Specifications and Test Methods

The Review Center asked the applicant why moisture content had been set as a test method for the product. When told that this specification had now been deleted because no change in moisture content had been noted in the stability tests, they accepted this.

(2) Data on Safety

The applicant had submitted test results for 18 months storage (PTP packaging) in the long term product storage tests on the product. As hardly any change had been found in any of the test items, the applicant wanted to extend the expiration period for the PTP packaged product to 18 months. The Review Center judged the specification for

the expiration period to be valid. Long term storage tests on PTP packaged product up to 36 months are currently ongoing.

(3) Data on Toxicology

Regarding the cardiomyopathy which had occurred at 160 and 320 mg/kg in the 30 day toxicity study in rats, the Review Center asked the applicant to explain further why they claimed that this phenomenon was unrelated to human cardiomyopathy and had developed due to the administration of high doses of rivavirin to the rats. The applicant gave the following reply.

In groups exposed to these dose levels, morphological changes had been seen throughout the body beginning with the gut and it could be inferred that endotoxins secreted by cells invading from the G-I tract had led to septicaemic shock. Based on WHO classification, cardiomyopathy can be seen as [1] idiopathic cardiomyopathy of unknown cause and [2] specific myocardial disease seen in association with a disease state. As the phenomenon noted at high doses of rivavirin in rats was very similar to the cardiomyopathy induced by bacteremia and septicaemic shock in the latter category, it seemed to have arisen due to complex interrelations between the rivavirin toxicity, shock, infection, inflammation, tissue damage and repair. As no cardiomyopathy was seen in dogs or monkeys and cardiomyopathy has been reported to occur spontaneously in rats, this would seem to be a species difference.

The Review Center accepted this response.

(4) Data on Pharmacology

The Expert had confirmed that rivavirin inhibits virus proliferation by causing mutation in viral RNA. However, the point was made that even after viral elimination, it could not be thought that virus with the mutation would be fully driven out of the body, and in non-responders especially, there had been no investigation of how mutant virus left in the hepatocytes would behave in the body. As the presence or otherwise and nature of mutation in virus left in the body had not been clarified in non-responders on combination therapy, the Review Center asked the applicant to survey this as part of the post-marketing surveillance program etc. The applicant responded to this as follows.

There are various hypotheses about viral infection rates of hepatic tissue in hepatitis C patients. Lau et al. (J. Hepatol. 24, 48, 1996) investigated this using *in situ* hybridization and antibody detection methods and found parenchymal cell infection rates of 5% and 10% respectively. Infection rates varied markedly depending on the indicator of histologic activity for the hepatitis and it has been reported that no virus could be detected by electron microscopy in human chronic hepatitis C (Hepatology 28, 573, 1998). Moreover, in order to confirm the virus population, it would seem necessary to track mutation in the virus over the treatment period both in temporal and quantitative terms and determine the base sequence of the genome, but as the site of mutation in the genome is thought not to be fixed, the whole length of the genome would need to be analyzed. Accordingly, in order to analyze the rate at which mutation is induced, a technique to determine the base sequence of the whole length of the genome quickly and on a large scale would be needed and at the present time, this is not technically feasible. Doing repeated liver biopsies also subjects the patient to risk such as bleeding from the site. In non-responders on combination therapy, it may be imagined that mutant virus retaining infectivity is present in the cells and blood, but the effects of such mutant virus on the disease are not clear at the present time. Nevertheless, despite the fact that a diverse virus population clearly emerges over the spontaneous course of chronic hepatitis C, the population relevant to deterioration of the disease (aggravation, promoting progression to hepatic cirrhosis and hepatic carcinoma) is unclear at the present time.

The Review Center accepted the response of the applicant that this is not technically feasible at this stage.

(5) Clinical Data

1) Quality of Japanese clinical studies

In that the proportion of cases excluded from the PPS had been as high as 50% in the results submitted this time, the experts had pointed out that the quality of the Japanese clinical studies had been very poor. The main reasons for PPS exclusion had been had been the non-performing of the tests relating to entry criteria and issues relating to the concomitant medication rules. Inadequate provision of monitoring had been pointed out in the GCP review by Kiko and there had been judged to be problems pertaining to

the organization of the trials by the applicant. However, as the Japanese results did not in any way contradict the largely settled clinical findings from Europe and America and that examination of the trial content raised no problems such as any great change in the conclusions depending on the handling of the non-PPS cases, they had concluded that it would be difficult to reject these study findings. The Review Center informed the applicant that the experts had also had a very poor opinion of the quality of the trials and warned the applicant to improve in future, but in view of the clinical imperative, they decided to accept the results of the Japanese studies.

2) Setting of dose and administration for this combination therapy

[1] Handling of foreign study findings

The dose finding study for rivavirin conducted overseas had been submitted as reference data with the present application. As the dosage and administration for IFNα-2b in the said study differed from those in the application for Japan, the Review Center stressed that this could be viewed as no more than reference data. As the foreign and Japanese pharmacokinetics could be judged to be virtually equivalent, they concluded that it would be possible to evaluate the results of studies conducted setting the dosage and administration used in Japan with reference to the findings of the foreign dose finding study on rivavirin.

[2] Dosage and administration of rivavirin and IFNα-2b

The opinion given by the experts regarding the fact that the Japanese dosage and administration of rivavirin had been set without conducting a dose finding study, was that if the pharmacokinetics were assumed to be similar, it would be reasonable to set the dose based on body weight calculation. On the other hand, they acknowledged that as the dose of IFNα-2b was different overseas, there might possibly be some problems in using the foreign results as they were. At the time of the application, the two dose levels of rivavirin had been set taking body weight of 60kg as the dividing line, but as the body weight of most of Japanese patients is concentrated around 60 kg, they also took the view that this division might cause confusion in the therapeutic setting and so was not appropriate. The furthermore voiced the opinion that setting

600 mg as the dose for those weighing less than 65 kg might also be more appropriate in safety terms.

The Review Center judged that as only one combination of rivavirin dose levels based on body weight had been used in the clinical studies, and no evidence had been demonstrated in terms of efficacy or safety to justify changing this dividing line, it would be difficult to change the dose of rivavirin just for the sake of clinical convenience. Moreover, they held that safety could be assured by providing the information demonstrating the grounds for this dividing line, that is to say, that the incidence of decreased haemoglobin rises if the dose of rivavirin exceeds 13 mg/kg and in real practice by reducing the dose as appropriate whilst monitoring for adverse reactions.

With reference to the above opinions from the experts, the Review Center judged that the application administration and dose could be seen as valid as no difference in efficacy and safety had been demonstrated in the foreign and Japanese studies.

3) Handling of untreated patients classed as 'other than of genotype 1b and with high virus titre'

In the data submitted for the present application, no study looking at untreated Japanese patients classed as 'other than of genotype 1b and with high virus titre' had been conducted and the experts had offered two opinions about accepting this patient group for this combination therapy. One was that as the effect of superimposing concomitant rivavirin had not been investigated in these patients, a patient group which had not been included in clinical trials should not yet be designated as a target bearing in mind the adverse reactions which might result from such co-administration. The other view was that as long as adverse events were not of a degree to pose problems, because the foreign results had demonstrated efficacy of 53-86% in non-genotype 1 cases in ##, and IFNα monotherapy is known to be effective in non-genotype 1 Japanese patients (generally about 60%), increased levels of efficacy could be anticipated. Moreover as IFNα monotherapy places a considerable physical and economic burden on the patient over a long period of time, it would impose a huge

burden on the patient not to be able try combination therapy until his or her condition had been proved to be refractory.

4) Safety of this combination therapy

[1] Adverse drug reactions in Japanese clinical trials

The safety of this combination therapy in all the Japanese clinical trials conducted in patients was reviewed in the light of the final results for pharmacokinetic study ## in Japan.

Upon tabulating the adverse reactions in the total of 271 patients given rivavirin, those found at a higher incidence in the rivavirin co-administration group than with IFNα-2b monotherapy (incidence 10% or more, difference in incidence from IFNα-2b monotherapy 10% or more) were eruption (50.9%), hair loss (alopecia) (49.8), itching (pruritus) (30.3%), and anaemia (10.3%). As the incidence of adverse reactions related to laboratory values, those showing a higher frequency with the co-administration of rivavirin than in monotherapy (incidence 10% or more, difference in incidence from IFNα-2b monotherapy 10% or more) comprised decreased white blood cells (leukopaenia) (86.7%), decreased haemoglobin (63.1%), impaired iron metabolism (55.0%), decreased haematocrit (54.2%), decreased red cells (51.3%), hyperuricemia (19.6%), rise in bilirubin (17.0%) and rise in indirect bilirubin (14.8%). Those amongst these whose incidence exceeded 50% were decreased white blood cells (leukopaenia), decreased haemoglobin, decreased haematocrit, impaired iron metabolism and decreased red cells. Decreased haemoglobin was noted in 57/271 cases (21.0%) of whom 13 cases (4.8%) discontinued the drug (however, the reasons for discontinuation included reasons other than the decreased haemoglobin). Two cases were discontinued without reducing the dose. The haemoglobin levels recovered upon withdrawal and no patient required other forms of treatment.

From the above results, adverse reactions which clearly appeared or increased as a result of co-administration were confirmed to be decreased white cells and those caused by erythrocyte damage by rivavirin. Decreased haemoglobin was an adverse reaction particular to the co-administration group seen hardly at all with IFNα-2b monotherapy, but as it was seen to reverse upon withdrawing the drug, an approach

such as conducting appropriate laboratory tests during co-administration and reducing the dose or withdrawing the drug would seem to be effective. A high incidence of leukopaenia is also noted with IFNα-2b but in that the frequency of this rose upon co-administration and there have been reports of pernicious anaemia overseas, care would seem to be needed, such as by conducting appropriate laboratory tests in the same way as for haemoglobin and reducing the dose or withdrawing the rivavirin or IFNα-2b. In the 'Precautions and Warnings regarding dosage and administration', the applicant has provided criteria for dose reduction or drug withdrawal if decreases are seen in haemoglobin, white cell count and platelet count. The Review Center judged that these warnings were reasonable.

[2] Teratogenicity of rivavirin

As rivavirin was confirmed to be teratogenic in the nonclinical studies, preventing the use of this combination therapy prior to pregnancy and the risk of foetal abnormalities as a result of pregnancy was considered to be of the utmost importance in subjects in whom rivavirin is contraindicated or in whom caution is required. The package insert (draft) states that 'contraindicated' subjects include 'male partners of women who are pregnant or of childbearing potential'. The experts took the view that even though the possibility of rivavirin passing into semen cannot be ruled out, its use would be possible if measures were taken to prevent the female being exposed to rivavirin, such as by using condoms. Bearing in mind the seriousness of this disease, it would be undesirable contraindicate it or limit the patients to whom it can be given on no clear grounds. In the light of the experts' opinion, the Review Center removed 'male partners of women who are pregnant or of childbearing potential' from the contraindicated subjects, and asked for the package insert to advocate caution in the said subjects and 'women of childbearing potential and their male partners' and describe the measures to be taken.

[3] Malignant tumours

Malignant tumours had been found as adverse reactions to this combination therapy in two patients in the Japanese clinical study. Mutagenicity had been noted in the nonclinical studies on rivavirin, but given that the pharmacological studies had

confirmed that it is not taken up into the DNA and all the results from the carcinogenicity study had been negative, there are no data suggesting any direct link between rivavirin and the presentation of malignant tumours at the present point in time. The Review Center instructed that as well as outlining the manifestation of cancers the package insert, data pertaining to safety should be collected in the postmarketing phase.

[4] Respiratory adverse reactions

As the incidence of respiratory adverse reactions in the Japanese trials had been higher with combination therapy group than with IFNα-2b monotherapy, the Review Center sought the opinion of the experts as whether special warnings were needed about respiratory disease. The experts stated that in gradually progressive anaemia with haemoglobin down to about 10 g/dL, exhibiting dyspnoea or shortness of breath is not usual and as there is also no increase in sputum in anaemia, the respiratory symptoms would appear to have been due to some action separate from the anaemia. However, as interstitial pneumonia is known to appear with IFNα, they felt attention should be drawn to this. The Review Center asked for the possibility of dyspnoea and increased sputum to be include as major adverse reactions in the adverse reactions sections of the 'Precautions and Warnings'.

[5] Positioning of this combination therapy in the treatment of chronic hepatitis C

Quoting from foreign guidelines and the like, the Applicant took the view that this combination therapy should be seen as a first line choice in the treatment of chronic hepatitis C using IFNα-2b. However, in that no benefit from combining rivavirin had been demonstrated in any of the chronic hepatitis C patients during the Japanese clinical studies as stated above, and that new adverse reactions such as anaemia occurred as a result of the combination, the Review Center decided that there was insufficient information at the present time to set it as a first line approach for all chronic hepatitis C and that the choice of either IFNα-2b monotherapy or combination therapy should be made on a case by case basis at the clinical level with reference to the trial results described in the package insert. The experts also supported this decision.

[6] Need for histological examination of the liver prior to therapy

As patients with cirrhosis of the liver had not been targeted in the present clinical studies, efficacy and safety in such patients is unclear. The experts were asked about the need for this to be differentiated by liver biopsy prior to initiating combination therapy in the post-marketing situation. The experts held that nowadays the degree of liver fibrosis or presence of liver cirrhosis can be estimated to some degree on the basis of clinical parameters and considered that biopsy was unnecessary. However, although not imposing a duty for liver biopsy, they felt that this combination therapy does need to be conducted under the supervision of a liver specialist.

In view of the above expert opinion, the Review Center judged that on the understanding that this combination therapy would be conducted under the supervision of a hepatitis specialist, histological examination of the liver would not always be necessary.

[7] Effect of different HCV-RNA assay methods in Japanese and foreign studies on virus titre assessment

Different HCV-RNA assay methods had been used in the Japanese and foreign clinical studies and so the opinion of the experts was sought as to the validity of a comparative evaluation of the findings of those studies. The experts stated that the development of several assay methods for viruses was being pursued and that in the present circumstances, such a comparison was possible, supporting the view of the Review Center. The success rate of IFN monotherapy is normally inversely proportional to virus titre, but therapeutic effects different from monotherapy are being obtained by this combination therapy, such as not seeing a correlation between success rate and virus titre. Based on the advice from the experts, the Review Center judged that as long as the success rates at different virus titres for this combination therapy were set out in the package insert, it would be appropriate to leave the choice for individual patients to be made by the clinic.

[8] Postmarketing surveillance

In the proposed postmarketing surveillance program (draft), the applicant stated that in addition to an immediate postmarketing survey, a special survey would be conducted in order to gather information about efficacy and safety. In the light of the results of the review and consultation with the experts, the Review Center asked for the following points to be incorporated into the structure to ensure that the special survey would be meaningful.

1) Confirming efficacy and safety in untreated patients 'other than of ‘genotype 1b and with high virus titre' in whom the efficacy of the combination therapy has not been confirmed in clinical trials

2) Setting the number of patients to give sufficient for analysis in each category in stratified analysis by genotype and virus titre

3) Conducting a safety analysis based on the dose of rivavirin per unit body weight (mg/kg)

3. Data compliance report by Kiko and judgement by Review Center

(1) Review Center judgement of documentation compliance review result

As a result of the review by Kiko the documentation based on the provisions of Article 14 Clause 4 of the Pharmaceutical Affairs Law, non-compliance had been found in parts (deviation from the protocol in some of the results, text in the data for approval review etc. failing accurately to reflect the basic data). The main things pointed out by Kiko were that monitoring had not been carried out at the right times at many of the centres and that there had been many deviations from the study plan in the assessment of adverse reaction severity. As regards the latter, the applicant has conducted a fresh analysis based on the Study Protocol and presented the results of this. Upon evaluating the results of the re-analysis, the Review Center judged that no change had arisen in the results for review. In the light of the above survey result, the Review Center judged that there was no obstacle to conducting the review on the basis of the data for approval review.

(2) Judgement by Review Center of GCP on site survey result

As a result of the GCP evaluation meeting, some deviations from the Study Protocol were found and three cases were non-compliant with GCP and were excluded from the application data. The Review Center judged that there was no obstacle to conducting the review on the basis of the submitted data for approval review once these cases had been excluded.

4. Revisions to Review Report (1)

In the light of the compliance survey result and corrections etc. to the application data, Review Report (1) is amended as follows. No change to the results for review will arise due to these changes. (The amended parts are underlined).

- p25, line 27 "(7) Patients with serious hepatic dysfunction [the blood level of the drug may rise and serious adverse reactions may occur]"
  is amended to
  "(7) Patients with serious hepatic dysfunction [<u>there is a possibility of diminished hepatic spare capacity</u> and serious adverse reactions may occur]".

- p27, line 27 "By the time of the final dose, the elimination half life had lengthened about ten fold (29.3→295 hours)"
  is amended to
  "By the time of the final dose, the elimination half life had lengthened about ten fold (29.3→<u>291</u> hours)".

- p28, line 29 "One case of temporal headache in the 400 mg group (assessed as not related)"
  is rendered as
  "One case of temporal headache in the 400 mg group (<u>placebo treated case</u>) (assessed as not related)".

- p28, line 32 "An elevated value for neutral lipids was noted in one case in the 600 mg group …"

is rendered as

"An elevated value for neutral lipids was noted in one case in the 600 mg group (placebo treated case)".

- p29, line 18 "In cases other than 'genotype 1b and with high virus titre', 75.0% (15/20) in the I/R group …"
  is rendered as
  "In cases other than 'genotype 1b and with high virus titre', 70.0% (14/20) in the I/R group …".

- p29, line 20 "Breslow-Day tests on the common potency difference in each class (examination of interaction) gave p=0.434 and no interaction was noted"
  is rendered as
  "Breslow-Day tests on the common potency difference in each class (examination of interaction) gave p=0.383 and no interaction was noted".

- p29, line 26 "Amongst the subjective and objective concomitant symptoms, hair loss and itching (pruritus) occurred at a higher incidence with I/R, being seen respectively at 43.5% and 43.5% in the I/R group and 31.3% and 28.1% in the I/P group. Amongst the abnormal variations in laboratory values, decreased haemoglobin and reticulocytosis were manifested more with I/R, being seen respectively at 71.0% and 71.0% in the I/R group and 0% and 4.7% in the I/P group, but both recovered upon reducing the dose or withdrawing the rivavirin. There was held to be nothing else posing any major clinical problem. The adverse reactions seen at a high frequency in the I/R group (subjective and objective concomitant symptoms or adverse reactions related to laboratory values: incidence 10% or more and frequency of twice or more or difference of 10% or more compared to I/P group) were those related to laboratory values such as decreased leukocytes (leukopaenia), reticulocytosis or decreased haemoglobin and those due the symptoms and signs of eruption, itching (pruritus) and anaemia."
  This is amended as follows.

"Amongst the subjective and objective concomitant symptoms, hair loss and eruption occurred at a higher incidence with I/R, being seen respectively at 45.2% and 46.8% in the I/R group and 35.9% and 28.1% in the I/P group. Amongst the abnormal variations in laboratory values, decreased haemoglobin was manifested more with I/R, being seen at 72.6% in the I/R group and 1.6% in the I/P group, but it recovered upon reducing the dose or withdrawing the rivavirin. There was held to be nothing else posing any major clinical problem. The adverse reactions seen at a high frequency in the I/R group (subjective and objective concomitant symptoms or adverse reactions related to laboratory values: incidence 10% or more and frequency of twice or more or difference of 10% or more compared to I/P group) were those related to laboratory values such as decreased leukocytes (leukopaenia), reticulocytosis or decreased haemoglobin and those due subjective and objective concomitant symptoms such as eruption, itching (pruritus) and anaemia."

- p29, line 30 "There was held to be nothing else posing any major clinical problem. The adverse reactions seen at a high frequency in the I/R group (subjective and objective concomitant symptoms or adverse reactions related to laboratory values: incidence 10% or more and frequency of twice or more or difference of 10% or more compared to I/P group) were those related to laboratory values such as decreased leukocytes (leukopaenia), reticulocytosis or decreased haemoglobin and those due the subjective and objective concomitant symptoms of eruption (pruritus) and anaemia."
  This text is amended as follows.
  "There was held to be nothing else posing any major clinical problem. The adverse reactions seen at a high frequency in the I/R group (subjective and objective concomitant symptoms or adverse reactions related to laboratory values: incidence 10% or more and frequency of twice or more or difference of 10% or more compared to I/P group) were those related to laboratory values such as decreased leukocytes (leukopaenia) and decreased haemoglobin and those due the subjective and objective concomitant symptoms of eruption (pruritus) and anaemia."

- p30, line 8 “3) Comparative study on IFNα-2b and rivavirin co-administration and IFNα-2b monotherapy in chronic hepatitis C patients of ‘genotype 1b and with high virus titre’

  A placebo-controlled, double blind comparative study was conducted in chronic hepatitis C patients of ‘genotype 1b and with high virus titre’ (that is, 1 Meq/mL or more by b-DNA probe method or 10^5 copies/mL or more by RT-PCR). This study was conducted in three groups comprising 90 cases treated with IFNα-2b (6 million IU: 6/ week x 2 weeks + 3/week x 22 weeks) + rivavirin 600 or 800 mg/day x 24 weeks ('IL/R group'), 94 cases treated with IFNα-2b (10 million IU: 6/week x 2 weeks + 6 million IU: 3/week x 22 weeks) + rivavirin 600 or 800 mg/day x 24 weeks ('IH/R group') and 88 cases treated with IFNα-2b (10 million IU: 6/week x 2 weeks + 6 million IU: 3/week x 22 weeks) + placebo x 24 weeks ('IH/P group').

  Efficacy was significantly superior in the IL/R + IH/R (rivavirin co-administration) group to the IH/P group in terms of the degree of improvement in viraemia (24 weeks after completing treatment) taking the pre-treatment virus titre (b-DNA probe method) which constituted the primary endpoint in the FAS as the covariable (logistic regression analysis p=0.004). The IL/R and IH/R groups were both separately superior to the IH/P group (logistic regression analysis p=0.002, p=0.013). Dividing the baseline virus titres into three bands of less than 1 Meq/mL, 1 to less than 5 Meq/mL and 5 Meq/mL and over, the degree of improvement in viraemia 24 weeks after completing the treatment was also seen to fall as the HCV RNA level rose. Moreover, taking the degree of improvement in viraemia 24 weeks after completing treatment analyzed without taking the baseline virus titre as the covariable, efficacy was respectively 20.7% (18/87 cases) in the IL/R group, 16.0% (15/94 cases) in the IH/R group and 2.4% (2/85 cases) in the IH/P group and again the IL/R + IH/R group was significantly superior to the IH/P group (logistic regression analysis p=0.003). The IL/R and IH/R groups were again both separately superior to the IH/P group (logistic regression analysis p=0.002, p=0.007). Stratified analysis by the efficacy of past IFN therapy indicated that whereas efficacy in the IH/P group

was 0% for both relapsed cases and non-responders, it was 16% and 18% for the respective cases in the IL/R + IH/R group.

As regards safety, the incidence of adverse reactions was 100% in the IL/R, IH/R and IH/P groups. Those adverse reactions encountered at a high frequency (10% and over) during the study in the co-administration group and with twice or more or a difference of 10% or more in frequency from the IH/P group included abnormal variations in laboratory values indicating erythrocyte impairment such as reticulocytosis or decreased haemoglobin and subjective and objective concomitant symptoms such as pruritus or eruption. Amongst the cases whose dose was reduced or the drug withdrawn due to decreased haemoglobin or anaemia, 5/32 cases stopped the rivavirin having first reduced the dose. The decreased haemoglobin or anaemia disappeared or lessened upon reducing the dose or withdrawing the rivavirin in all these cases. Serious adverse events occurred as 55 episodes in 30 cases (IL/R: 29 episodes in 13 cases, IH/R: 20 episodes in 11 cases, IH/P: 6 episodes in 6 cases). Of these 55 episodes, 49 were judged to have been adverse reactions (IL/R: 27 episodes, IH/R: 19 episodes, IH/P: 3 episodes) and there were therefore more serious adverse events (including adverse reactions) with co-administration than with monotherapy. They occurred during the treatment period in most cases and as regards outcome, they disappeared or lessened in all but two cases. The two cases in whom adverse reactions persisted comprised one case of hyperglycaemia and weight loss, and one of decreased thyroid function (hypothyroidism), both judged to be severe. An unforeseen adverse reaction (bladder tumour) occurred in one case from the IL/R group. One death due to liver failure was also confirmed in the IL/R group. Administration of the study drug to this patient had been stopped following the appearance of gastrointestinal bleeding (per-rectal bleeding) on day 19 of rivavirin treatment and surgery was performed following a diagnosis of ulceration of the small bowel. Pneumonia also developed postoperatively and the patient went into liver failure 12 days after surgery and died 71 days after the appearance of the liver failure. There was judged to have been no causality by the drug."

This text is amended as follows.

“3) Comparative study on IFNα-2b and rivavirin co-administration and IFNα-2b monotherapy in chronic hepatitis C patients of ‘genotype 1b and with high virus titre’

A placebo-controlled, double blind comparative study was conducted in chronic hepatitis C patients of ‘genotype 1b and with high virus titre’ (that is, 1 Meq/mL or more by b-DNA probe method or 10^5 copies/mL or more by RT-PCR). This study was conducted in three groups comprising 89 cases treated with IFNα-2b (6 million IU: 6/ week x 2 weeks + 3/week x 22 weeks) + rivavirin 600 or 800 mg/day x 24 weeks ('IL/R group'), 92 cases treated with IFNα-2b (10 million IU: 6/week x 2 weeks + 6 million IU: 3/week x 22 weeks) + rivavirin 600 or 800 mg/day x 24 weeks ('IH/R group') and 88 cases treated with IFNα-2b (10 million IU: 6/week x 2 weeks + 6 million IU: 3/week x 22 weeks) + placebo x 24 weeks ('IH/P group').

Efficacy was significantly superior in the IL/R + IH/R (rivavirin co-administration) group to the IH/P group in terms of the degree of improvement in viraemia (24 weeks after completing treatment) taking the pre-treatment virus titre (b-DNA probe method) which constituted the primary endpoint in the FAS as the covariable (logistic regression analysis p=0.003). The IL/R and IH/R groups were both separately superior to the IH/P group (logistic regression analysis p=0.002, p=0.012). Dividing the baseline virus titres into three bands of less than 1 Meq/mL, 1 to less than 5 Meq/mL and 5 Meq/mL and over, the degree of improvement in viraemia 24 weeks after completing the treatment was also seen to fall as the HCV RNA level rose. Moreover, taking the degree of improvement in viraemia 24 weeks after completing treatment analyzed without taking the baseline virus titre as the covariable, efficacy was respectively 21.2% (18/85 cases) in the IL/R group, 16.3% (15/92 cases) in the IH/R group and 2.4% (2/85 cases) in the IH/P group and again the IL/R + IH/R group was significantly superior to the IH/P group (logistic regression analysis p=0.002). The IL/R and IH/R groups were again both separately superior to the IH/P group (logistic regression analysis p=0.002, p=0.007). Stratified analysis by the efficacy of past IFN therapy indicated that whereas efficacy in the IH/P group

was 0% for both relapsed cases and non-responders, it was 16% and 18% for the respective cases in the IL/R + IH/R group.

As regards safety, the incidence of adverse reactions was 100% in the IL/R, IH/R and IH/P groups. Those adverse reactions encountered at a high frequency (10% and over) during the study in the co-administration group and with twice or more or a difference of 10% or more in frequency from the IH/P group included abnormal variations in laboratory values indicating erythrocyte impairment such as decreased haemoglobin or decreased red blood cells and subjective and objective concomitant symptoms such as pruritus or eruption. Amongst the cases whose dose was reduced or the drug withdrawn due to decreased haemoglobin or anaemia, 5/32 cases stopped the rivavirin having first reduced the dose. The decreased haemoglobin or anaemia disappeared or lessened upon reducing the dose or withdrawing the rivavirin in all these cases. Serious adverse events occurred as 54 episodes in 29 cases (IL/R: 19 episodes in 10 cases, IH/R: 20 episodes in 11 cases, IH/P: 6 episodes in 6 cases). Of these 54 episodes, 47 were judged to have been adverse reactions (IL/R: 27 episodes, IH/R: 17 episodes, IH/P: 3 episodes) and there were therefore more serious adverse events (including adverse reactions) with co-administration than with monotherapy. They occurred during the treatment period in most cases and as regards outcome, they disappeared or lessened in all but two cases. The two cases in whom adverse reactions persisted comprised one case of hyperglycaemia and weight loss, and one of decreased thyroid function (hypothyroidism), both judged to be severe. An unforeseen adverse reaction (bladder tumour) occurred in one case from the IL/R group. One death due to liver failure was also confirmed in the IL/R group. Administration of the study drug to this patient had been stopped following the appearance of gastrointestinal bleeding (per-rectal bleeding) on day 19 of rivavirin treatment and surgery was performed following a diagnosis of ulceration of the small bowel. Pneumonia also developed postoperatively and the patient went into liver failure 12 days after surgery and died 71 days after the appearance of the liver failure. There was judged to have been no causality by the drug."

- p36, line 23 "On the safety front, the percentage of cases in the Japanese study whose dose was reduced due to decreased haemoglobin was much higher, at 19.1%, than the rate of 5.6% seen overseas."
  is amended to
  "On the safety front, the percentage of cases in the Japanese study whose dose was reduced due to decreased haemoglobin was much higher, at 13.6%, than the rate of 5.6% seen overseas."

- p38, line 23 "⑦ On the question of disparity between the FAS and PPS, there were respectively 122 and 73 cases in the full analysis set (FAS) and the per protocol set (PPS) in the study on the efficacy of co-administration conducted in Japan ## and respectively 266 and 137 cases in the FAS and PPS in the dose-finding study ##. There was thus a large disparity between the number of cases in the two analysis sets. The Review Center therefore asked for details of the cases excluded from the PPS and the applicant replied that the details of the exclusions were set out in the Gaiyo. The Review Center also asked for analysis results for the PPS and the time course of virus titres in the FAS and PPS to be shown.
  Regarding the results of PPS analysis, the applicant stated that efficacy in the co-administration efficacy study ## for class A ('genotype 1b and with high virus titre') was 3.8% with I/R and 0% with I/P, for class b ('other than 'genotype 1b and with high virus titre') was 84.6% with I/R and 33.3% with I/P and was significantly superior by the Cochran-Mantel-Haenszel test (p=0.007); moreover in the dose finding study ##, as a result of switching the analysis to the Cochran-Mantel-Haenszel because no optimum estimate could be calculated, the IL/R + IH/R group, IL/R and IH/R groups were all significantly superior to IH/P (respectively p=0.001, p=0.001, p=0.003). The results of analyzing the PPS were therefore very similar to the results of FAS analysis and there was no difference in the conclusions from the two analyses.
  The Review Center confirmed that there was no great difference between the FAS and PPS in the time course of efficacy and accepted this response."
  This text is amended as follows:

"⑦ On the question of disparity between the FAS and PPS, there were respectively 122 and 73 cases in the full analysis set (FAS) and the per protocol set (PPS) in the study on the efficacy of co-administration conducted in Japan ## and respectively 262 and 131 cases in the FAS and PPS in the dose-finding study ##. There was thus a large disparity between the number of cases in the two analysis sets. The Review Center therefore asked for details of the cases excluded from the PPS and the applicant replied that the details of the exclusions were set out in the Gaiyo. The Review Center also asked for analysis results for the PPS and the time course of virus titres in the FAS and PPS to be shown.
Regarding the results of PPS analysis, the applicant stated that efficacy in the co-administration efficacy study ## for class A ('genotype 1b and with high virus titre') was 4.0% with I/R and 0% with I/P, for class b ('other than 'genotype 1b and with high virus titre') was 78.6% with I/R and 33.3% with I/P and was significantly superior by the Cochran-Mantel-Haenszel test (p=0.014); moreover in the dose finding study ##, as a result of switching the analysis to the Cochran-Mantel-Haenszel because no optimum estimate could be calculated, the IL/R + IH/R group, IL/R and IH/R groups were all significantly superior to IH/P (respectively p=0.002, p=0.002, p=0.004). The results of analyzing the PPS were therefore very similar to the results of FAS analysis and there was no difference in the conclusions from the two analyses.
The Review Center confirmed that there was no great difference between the FAS and PPS in the time course of efficacy and accepted this response."

- p41, line 11 "The Review Center asked the applicant to explain further whether or not the criteria for dose reduction of the trial drug due to decreases in haemoglobin had been valid in view of the fact that the dose of rivavirin had been reduced for this reason in 24.6% (15/61 cases) in the co-administration efficacy study and in 17.4% (32/184 cases) in the dosage and administration finding study"
  is amended to
  "The Review Center asked the applicant to explain further whether or not the criteria for dose reduction of the trial drug due to decreases in haemoglobin had

been valid in view of the fact that the dose of rivavirin had been reduced for this reason in 24.6% (15/61 cases) in the co-administration efficacy study and in 17.7% (32/181 cases) in the dose finding study"

- p41, line 26 "④ Trends for dyspnoea, sputum: The Review Center asked the applicant how they could explain the fact that increases in dyspnoea and sputum amongst the adverse events had been more frequent in the IFNα-2b + rivavirin group than in the IFNα-2b monotherapy group and that a similar trend had also been seen in both the co-administration efficacy study ## and dose finding study ##.

  The applicant replied that dyspnoea had been noted in 12.2% (30/246 cases) in the rivavirin co-administration group and 2.6% (4/152 cases) in the monotherapy group. Moreover, increased sputum was held to have occurred respectively 8.1% (20/246 cases) and 2.6% (4/152 cases). Of the 3 co-administration cases showing dyspnoea, there were 6 cases of dyspnoea and 24 of shortness of breath and in the 4 cases in the monotherapy group, 1 of dyspnoea and 3 of shortness of breath. That is, there was a higher frequency of dyspnoea and shortness of breath in the low dose group".

  This text is amended as follows.

  " ④ Trends for dyspnoea, sputum: The Review Center asked the applicant how they could explain the fact that increases in dyspnoea and sputum amongst the adverse events had been more frequent in the IFNα-2b + rivavirin group than in the IFNα-2b monotherapy group and that a similar trend had also been seen in both the co-administration efficacy study ## and dose finding study ##.

  The applicant replied that dyspnoea had been noted in 11.9% (29/243 cases) in the rivavirin co-administration group and 2.6% (4/152 cases) in the monotherapy group. Moreover, increased sputum was held to have occurred respectively 8.2% (20/243 cases) and 2.6% (4/152 cases). Of the 29 co-administration cases showing dyspnoea, there were 5 cases of dyspnoea and 24 of shortness of breath and in the 4 cases in the monotherapy group, 1 of dyspnoea and 3 of shortness of breath. That is, there was a higher frequency of dyspnoea and shortness of breath in the low dose group."

5. Overall Judgement

The Japanese clinical results presented with this application were obtained for a limited patient group and range of dosage and administration. Nevertheless, to the extent of the data submitted, IFNα-2b and rivavirin combination therapy provided significantly higher response rates than IFNα-2b monotherapy in terms of virus elimination in the viraemia of chronic hepatitis C. This combination therapy is held to be the treatment of choice in untreated and recurrent chronic hepatitis C patients in EU and Asian Pacific guidelines and the results of the trials conducted overseas and those conducted in Japan show similar trends. In view of the seriousness of the disease and the therapeutic exigency, we judge that this combination therapy can be approved for the following uses in the following regimen with the approval conditions set out below and that it would be appropriate for it to be discussed by the First Subcommittee for new drugs and the Pharmaceutical Affairs Scientific Subcommittee. As for the uses for this combination therapy, because the clinical studies in Japan did not include efficacy and safety in untreated patients other than 'genotype 1b and with high virus titre' and efficacy and safety upon altering the rivavirin dose has not been confirmed in Japan, we judge that postmarketing survey will be needed to evaluate patients and amend the information about efficacy and safety as necessary. We also judge that the drug substance and products of rivavirin are powerful drugs and the re-examination period for these uses of rivavirin and IFNα-2b should be set at six years.

Rebetol Capsules 200 mg

[Uses]

The improvement of viraemia in chronic hepatitis C in combination with interferon alpha-2b (recombinant)

[Dosage and administration]

Rebetol capsules must be used in combination with interferon alpha-2b (recombinant). Adults normally take 600~800 mg as rivavirin in a day divided into two oral doses daily after breakfast and the evening meal. If the patient weighs less than 60 kg, the dose is 600 mg per day, and if more than 60 kg, the dose is 800 mg per day. If the

daily dose is 600 mg, 200 mg is taken after breakfast and 400 mg after the evening meal.
Interferon alpha-2b (recombinant) is given as a single dose of 6~10 million IU in a day by intramuscular injection six or three times per week.

[Approval conditions]
As therapeutic results by serotype (genotype) and virus titre cannot be stated with certainty, postmarketing surveillance including postmarketing clinical studies must be conducted so as quickly to gather therapeutic results by serotype (genotype) and virus titre. These must be reported without delay and reflected as appropriate in the package insert etc.

Intron A Injection 300, 600, 1000

[Uses]

- The improvement of viraemia in chronic hepatitis C
- The improvement of viraemia in HBe antigen positive and DNA polymerase positive chronic active hepatitis B
- Renal carcinoma, chronic myeloid leukaemia, multiple myeloma

[Dosage and administration]

- The improvement of viraemia in chronic hepatitis C
  HCV RNA must be confirmed to be positive for this use.

1) If Intron A is used as monotherapy (excluding situations with high serum HCV RNA levels)[Note 1)]
   Adults normally are given a single dose in a day of 6~10 million IU as interferon alpha-2b (recombinant)[Note 2)] by intramuscular injection six or three times per week.
2) If used in combination with rivavirin[Note 1)]
   Adults normally are given a single dose in a day of 6~10 million IU as interferon alpha-2b (recombinant) by intramuscular injection six or three times per week. They take 600~800 mg per day as rivavirin divided into two oral doses per day after breakfast and the evening meal. If the patient weighs less than 60 kg, the

dose of rivavirin is 600 mg per day, and if more than 60 kg, the dose is 800 mg per day. If the daily dose is 600 mg, 200 mg is taken after breakfast and 400 mg after the evening meal Note 1).

- The improvement of viraemia in HBe antigen positive and DNA polymerase positive chronic active hepatitis B
  Adults are normally given a daily dose of 6~10 million IU as interferon alpha-2b (recombinant)Note 2) in the first week and a daily dose of 6 million IU from the second week by intramuscular injection. However, a one day dose of 3 million or 6 million IU is given on the first day of administration.

- Renal carcinoma, chronic myeloid leukaemia, multiple myeloma
  Adults are normally given a daily dose of 3~10 million IU as interferon alpha-2b (recombinant)Note 2) in the first week and a daily dose of 6 million IU from the second week by intramuscular injection.
  The dose may be adjusted as appropriate to age and symptoms.

When administering interferon alpha-2b (recombinant)Note 2), it is used dissolved in the 1 mL of Japanese Pharmacopoeia 'Water for injections' provided per vial.

Note 3) Additional dosage and administration associated with new use

Note 4) Adjustment of text regarding existing uses

[Approval conditions]

- The improvement of viraemia in chronic hepatitis C in combination with rivavirin
  As therapeutic results by serotype (genotype) and virus titre cannot be stated with certainty, postmarketing surveillance including postmarketing clinical studies must be conducted so as quickly to gather therapeutic results by serotype (genotype) and virus titre. These must be reported without delay and reflected as appropriate in the package insert etc.

'Purged' text

24th October 2001

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau

Evaluation Report (2)

Product name	Rebetol Capsule 200mg
Non-proprietary name	Ribavirin
Applicant	Schering-Plough KK
Date of submission	27th April 2001

Product name	Intron A Injection 300, 600 and 1000
Non-proprietary name	Interferon alpha-2b, recombinant
Applicant	Schering-Plough KK
Date of submission	27th April 2001

[Outcome of Evaluation]

1. Safety of Combination Therapy

The Evaluation Centre asked the applicant to investigate patients in relation to pregnancies and haemotoxicities including bone marrow suppressions which have been reported after launch abroad, and reviewed the submitted safety data.

(1) Teratogenicity

This combination therapy is contraindicated to pregnant female, and both male and female patients are warned and told to take contraception measures during and 6 months after the treatment in overseas countries. However, since it was launched abroad, 713 cases of pregnancies before and after the combination therapy were reported by 31st March 2001 (refer to table 1).

Table 1: Female patients or male patients with female partners who were found to be pregnant before, during or within 6 moths from the end of the combination therapy in overseas clinical trials or post-marketing surveillance*

Outcome of pregnancy	Female patients (161 cases)	Male patients with female partners (552 cases)
Delivered healthy babies	25 (16%)	129 (23%)
Congenital anomaly	2 (1%)	7 (1%)
Infant diseases	-	1 (<1%)
Foetal death**	19 (11%)	39 (7%)
Abortion	39 (24%)	72 (13%)
Still pregnant	34 (21%)	109 (20%)
Unknown	42 (26%)	195 (35%)

* After the treatment, patients are to be followed for 6 months and if pregnancy is found by the end of the 6 months, the patients are to be followed for 1 year after delivery.
** Excluding congenital anomaly

Many pregnancies were aborted and according to the applicant's survey, some abortions were induced intentionally because of a congenital anomaly, but they were unable to specify the reason for abortions in most of the cases (the abortions because of congenital anomalies were counted as congenital anomalies in table 1).

The Evaluation Centre believes that patients have to be fully reminded about contraception and information on teratogenicity has to be collected, as congenital anomalies were found in some cases, many pregnancies were intentionally aborted, although the reasons are unknown, and pregnancies have been reported, although precautions are provided in the prescribing information (draft), including in the warning section, for example, overseas prescribing information states that the combination therapy is contraindicated to pregnant females and both male and female patients need to practice contraception.

Specifically, it was assessed that, as well as pregnant females being contraindicated in the prescribing information (draft), patients have to be notified to practice contraception and male patients have to be told to use condoms, they have to be very

thorough in drawing attention to this in the information sheet for patients and the information sheet for healthcare professionals. Furthermore, after Japanese launch, if a pregnancy is reported during or within 6 months from the end of the combination therapy, the pregnancy needs to be investigated at least by following-up during pregnancy and after delivery. Data including overseas data have to be collected and analysed. The applicant replied that they would address the above.

(2) Haematological Toxicity

The cumulative numbers of patients with haematological toxicities in past three years are as shown in table 2.

Table 2: Haematological serious adverse drug reactions occurred with IFN α-2b monotherapy and ribavirin combination therapy

(From 1st October 1998 till 30th September 2001)

Adverse Drug Reaction	Treated disease	IFN α-2b monotherapy in Japan	IFN α-2b monotherapy Abroad	In combination with Ribavirin Abroad
		Number of cases	Number of cases	Number of cases
Leukopenia	Chronic hepatitis C	5	6	61
	Chronic hepatitis B	0	1	-
	Renal cancer	0	0	-
	Multiple myeloma	2	1	-
	Chronic myeloid leukaemia	1	7	-
	Melanoma	-	16	-
	Unknown/others	0	2	5
	Total	8	33	66
Erythropenia	Chronic hepatitis C	2	9	329
	Chronic hepatitis B	0	0	-
	Renal cancer	0	0	-
	Multiple myeloma	0	5	-
	Chronic myeloid leukaemia	0	16	-
	Melanoma	-	14	-
	Unknown/others	0	11	65
	Total	2	55	394
Thrombocytopenia	Chronic hepatitis C	12	26	34
	Chronic hepatitis	0	1	-

	B			
	Renal cancer	0	0	-
	Multiple myeloma	0	4	-
	Chronic myeloid leukaemia	0	21	-
	Melanoma	-	31	-
	Unknown/others	0	8	7
	Total	12	91	41
Aplastic anaemia	Chronic hepatitis C	0	0	4
	Chronic hepatitis B	0	0	-
	Renal cancer	0	0	-
	Multiple myeloma	0	0	-
	Chronic myeloid leukaemia	0	1	-
	Melanoma	-	0	-
	Unknown/others	0	0	0
	Total	0	1	4
Myelosuppression	Chronic hepatitis C	0	0	1*
	Chronic hepatitis B	0	0	-
	Renal cancer	0	0	-
	Multiple myeloma	0	0	-
	Chronic myeloid leukaemia	0	0	-
	Melanoma	-	0	-
	Unknown/others	0	0	0
	Total	0	0	1
Pancytopenia	Chronic hepatitis C	0	1	10
	Chronic hepatitis B	0	0	-
	Renal cancer	0	1	-
	Multiple myeloma	0	1	-
	Chronic myeloid leukaemia	0	2	-
	Melanoma	-	11	-
	Unknown/others	0	1	2
	Total	0	17	12

* Erythropenia and thrombocytopenia are listed as events.

The ratio of estimated numbers of patients who received monotherapy and combination therapy in the last year is reported to be 1:1.8, but this includes patients who received the monotherapy for diseases other than chronic hepatitis C. When the treated diseases are different, profiles of adverse drug reactions may differ and straightforward comparison may not be appropriate, but as expected from the results of the Japanese clinical studies, erythropenia was seen at a higher incidence in

combination therapy than monotherapy. With other adverse drug reactions, 4 patients had aplastic anaemia. In the prescribing information (draft), the applicant has already mentioned myelosuppression including aplastic anaemia under the sections for "Important Basic Cautions" and "Severe Adverse Drug Reactions", and stated that precaution was required. Since the combination therapy was approved abroad, about x0,000 patients are estimated to have received the combination therapy so far. We believe that the fact that 4 cases of aplastic anaemia have been reported out of these patients has to be communicated to healthcare professions appropriately in writing and the applicant has to explain specifically that they need to be fully aware of this when treating patients. With regard to erythropenia, leukopenia and thrombocytopenia, as they were also seen in clinical studies, the applicant has called for cautions in "precautions for use concerning dosage and administration" to carry out periodical tests and to reduce the dose or stop treatment depending on the outcome of the tests. We believe that when it is launched in Japan, the applicant has to draw sufficient attention of healthcare professionals, so that they will conduct blood tests appropriately. The applicant agreed that they would describe the above in the information sheets for healthcare professionals and provide information.

2. Indications and Related Issues

As the above mentioned concerns on safety were raised in the meeting of the 1st Committee on Drugs (on 3rd October 2001), it was assessed that the indications of the combination therapy should be patients with genotype 1b and a high viral load, who had not been satisfactory treated with existing IFN treatment, considering risk and benefit.

As the 1st Committee on Drugs pointed out and as stated in above "1. Safety of Combination Therapy", the Evaluation Centre believes that the combination therapy should only target limited patients for the time being, considering the risk and benefit.

In the Japanese clinical studies, superiority of the combination therapy over the IFN α-2b monotherapy was demonstrated in the following two groups of patients.

- The combination effect study: Patients who had not responded to previous IFN treatment and who had relapsed
- The dose selection study: Patients with genotype 1b or serogroup 1 and a high virus load (100K copies/mL or over with RT-PCR assay or 1 Meq./mL or over with b-DNA assay)

With regard to virus types, the inclusion criterion of the dose selection study was genotype 1b or serogroup 1. Serogroup 1 includes genotype 1a and genotype 1b, and of 272 patients in the study, 3 patients were with genotype 1a (all in IH/R Group) and the rest of them were with genotype 1b. Genotype 1a is regarded to be intractable as is genotype 1b and in current medical practice, it is common to determine serogroups. Genotypes are not necessarily determined when finding out virus types. Considering this, it was judged that the target of the combination therapy should be based on the above patient populations and as follows.

- Patients with serogroup 1 and a high virus load (100K copies/mL or over with RT-PCR assay or 1 Meq./mL or over with b-DNA assay)
- Patients who did not respond to previous IFN treatment or patients who relapsed after IFN treatment

It was assessed that the indications and the precaution concerning the indications should be amended as follows. In addition, the statements on the dosage and administration were amended.

<u>Indications of Rebetol Capsule 200 mg:</u>

Virological improvement of chronic hepatitis C in combination with interferon alpha-2b, recombinant.

1. Patients with serogroup 1 and a high blood HCV RNA level
2. Patients who did not respond to interferon monotherapy or patients who relapsed after interferon monotherapy

   <Precaution for use concerning indications>

   Rebetol should be used in combination with interferon alpha-2b, recombinant (refer to [Clinical Results]). Rebetol monotherapy is not effective in chronic hepatitis C patients.

When carrying out the combination therapy for chronic hepatitis C, confirm that HCV RNA is positive, it is not other chronic liver diseases such as autoimmune hepatitis and alcoholic hepatitis, it is not chronic hepatitis accompanying cirrhosis and it does not accompany hepatic failure. When using Rebetol for chronic hepatitis C that is serogroup 1 and with a high blood HCV RNA level, confirm that the blood HCV RNA level is 10^5 IU/mL or over with RT-PCR assay or 1 Meq./mL or over with b-DNA assay.
Furthermore, confirm chronic hepatitis by tests including histology, hepatic standby capacity and platelets.

<u>Indications of Intron A Injection 300, 600 and 1,000:</u>

Virological improvement of the following chronic hepatitis C

1. Intron A Injection alone
   (1) Patients whose blood HCV RNA level is not high
2. In combination with ribavirin
   (1) Patients with serogroup 1 and a high blood HCV RNA level
   (2) Patients who did not respond to interferon monotherapy or patients who relapsed after interferon monotherapy

   [The rest is omitted]

   <Precaution for use concerning indications>

   1. When using Intron A Injection for virological improvement of chronic hepatitis C, When using Intron A Injection for virological improvement of chronic hepatitis C (*translator's note: The phrase is repeated in the original)*, confirm that HCV RNA is positive, it is not other chronic liver diseases such as autoimmune hepatitis and alcoholic hepatitis, it is not chronic hepatitis accompanying cirrhosis and it does not accompany hepatic failure.

      Furthermore, confirm chronic hepatitis by tests including histology, hepatic standby capacity and platelets.
   2. When using Intron A Injection in combination with ribavirin for chronic hepatitis C which is serogroup 1 and with a high blood HCV RNA level,

confirm that the blood HCV RNA level is 10^5 IU/mL or over with RT-PCR assay or 1 Meq./mL or over with b-DNA assay.

3. When Intron A Injection alone was used for virological improvement of chronic hepatitis C, the amount of HCV RNA eradication with Intron A Injection was 10.8% (4/37) in patients whose HCV RNA level was over 10^8 copies/mL with CRT-PCR assay, and of these, it was 0.0% (0/27) in patients with genotype II (1b) (serogroup 1). In patients whose HCV RNA level was over 10^9 copies/mL, the eradication rate of HCV RNA with Intron A Injection was 0.0% (0/3).

Dosage and Administration of Intron A Injection 300, 600 and 1,000:

- Virological improvement of chronic hepatitis C

Treatment should be started after confirming that HCV RNA is positive.
Usually in adults, administer 6 million to 10 million IU of interferon alpha-2b, recombinant once daily for six times per week for three weeks intramuscularly.
When ribavirin is used in combination, orally administer 600 mg to 800 mg per day of ribavirin in two-divided doses after breakfast and evening meals. If the bodyweight of the patient is 60kg or less, the daily dose of ribavirin should be 600 mg and if the bodyweight is over 60 kg, it should be 800mg. When administering 600 mg/day, 200mg should be administered orally after breakfast and 400 mg after evening meals.

5th November 2001
Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau

Evaluation Report (3)

Product name	Rebetol Capsule 200mg
Non-proprietary name	Ribavirin
Applicant	Schering-Plough KK
Date of submission	27th April 2001

Product name	Intron A Injection 300, 600 and 1000
Non-proprietary name	Interferon alpha-2b, recombinant
Applicant	Schering-Plough KK
Date of submission	27th April 2001

[Outcome of Evaluation]
Based on opinions given in the Pharmaceutical Affairs Council Meeting of the Pharmaceutical Affairs and Food Sanitation Council on 5th November 2001, the above products can be approved with the following alterations to the indications.

Rebetol Capsule 200 mg

[Indications]
Virological improvement of <u>any of the following</u> chronic hepatitis C in combination with interferon alpha-2b, recombinant.

1. <u>Patients with a high blood HCV RNA level</u>
2. Patients who did not respond to interferon monotherapy or patients who relapsed after interferon monotherapy

<Precaution for use concerning indications>
Rebetol should be used in combination with interferon alpha-2b, recombinant (refer to [Clinical Results]). Rebetol monotherapy is not effective in chronic hepatitis C patients.

When carrying out the combination therapy for chronic hepatitis C, confirm that HCV RNA is positive, it is not other chronic liver diseases such as autoimmune hepatitis and alcoholic hepatitis, it is not chronic hepatitis accompanying cirrhosis and it does not accompany hepatic failure. When using Rebetol for chronic hepatitis C with a high blood HCV RNA level, confirm that the blood HCV RNA level is 10^5 IU/mL or over with RT-PCR assay or 1 Meq./mL or over with b-DNA assay.

Furthermore, confirm chronic hepatitis by tests including histology, hepatic standby capacity and platelets.

Intron A Injection 300, 600 and 1,000

[Indications]

- Virological improvement of any of the following chronic hepatitis C
  1. Intron A Injection alone
     (1) Patients who are not with a high blood HCV RNA level
  2. In combination with ribavirin
     (1) Patients with a high blood HCV RNA level
     (2) Patients who did not respond to interferon monotherapy or patients who relapsed after interferon monotherapy
     [The rest is omitted]
     <Precautions for use concerning indications>
     3. When using Intron A Injection for virological improvement of chronic hepatitis C, When using Intron A Injection for virological improvement of chronic hepatitis C (*translator's note: The phrase is repeated in the original)*, confirm that HCV RNA is positive, it is not other chronic liver diseases such as autoimmune hepatitis and alcoholic hepatitis, it is not chronic hepatitis accompanying cirrhosis and it does not accompany hepatic failure.

        Furthermore, confirm chronic hepatitis with tests including histology, hepatic standby capacity and platelets.

4. When using Intron A Injection in combination with ribavirin for chronic hepatitis C with a high blood HCV RNA level, confirm that the blood HCV RNA level is 10^5 IU/mL or over with RT-PCR assay or 1 Meq./mL or over with b-DNA assay.

5. When Intron A Injection alone was used for virological improvement of chronic hepatitis C, the amount of HCV RNA eradication with Intron A Injection was 10.8% (4/37) in patients whose HCV RNA levels was over 10^8 copies/mL with CRT-PCR assay, and of these, it was 0.0% (0/27) in patients with genotype II (1b) (serogroup 1). In patients whose HCV RNA levels were over 10^9 copies/mL, the eradication rate of HCV RNA with Intron A Injection was 0.0% (0/3).

(Underlined parts were altered)