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發文日期：中華民國111年04月21日

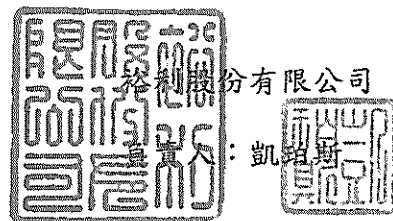
發文字號：111 裕字-第000627號

主旨：本公司銷售台灣默克股份有限公司之產品「REBIF 44 MICROGRAMS 立比扶注射劑 44MCG (衛署罕菌疫輸字第000002號)」仿單變更通知，詳如說明段。

說明：

- 一、本公司銷售台灣默克股份有限公司之產品「REBIF 44 MICROGRAMS 立比扶注射劑 44MCG (衛署罕菌疫輸字第000002號)」承蒙貴院採用，特此致謝。
- 二、接獲原廠通知，上述產品自即日起仿單內容變更，原核准資訊不變(藥品許可證字號、成份、含量等)。
- 三、仿單內容變更說明請見附件。新包裝批號自BA077945將陸續出貨至各醫療院所。
- 四、特此說明，敬請轉知 貴院相關單位，並請繼續支持本公司為禱。

附件：原廠公文、仿單變更對照表、中英文仿單、許可證



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受文者：裕利股份有限公司、吉程股份有限公司

發文日期：中華民國 111 年 04 月 18 日

發文字號：台灣默克藥字第 111042 號

速別：

密等及解密條件：普通

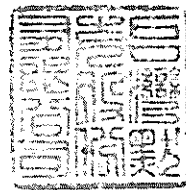
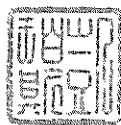
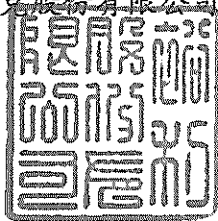
附件：藥品許可證、仿單、變更說明

主旨：「立比扶注射劑 44 mcg Rebif 44 micrograms」仿單變更通知。

說明：

- 一、自即日起台灣默克股份有限公司產品立比扶注射劑 44 mcg Rebif 44 micrograms，仿單內容變更，原核准資訊不變（藥品許可證字號、成份、含量等）。
- 二、仿單內容變更說明請見附件
- 三、新包裝批號自 BA077945 將陸續出貨至各醫療院所
- 四、特以此函通知 貴公司轉發至相關醫療院所，如有任何疑問，請電洽：

台灣默克股份有限公司

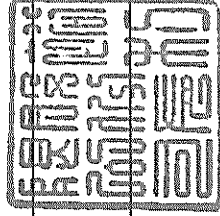


台灣默克股份有限公司

代表 負責人 李俊隆

立比扶注射劑 22 mcg & 44 mcg 中文仿單

	原核准版本	擬變更版本	備註及參考資料
警語與注意事項	<u>Benzyl alcohol</u> 本藥每 0.5 毫升單劑含 2.5 毫克 benzyl alcohol。 早產兒或新生兒不可投予 Rebif®。嬰幼兒及 3 歲以下孩童可能會造成毒性反應及過敏反應。	<u>賦形劑</u> <u>鈉含量</u> 本藥每一劑量含少於 1 mmol 鈉(23 毫克)，幾近於不含鈉。 <u>Benzyl alcohol</u> 本藥含 benzyl alcohol。Benzyl alcohol 可能會導致過敏反應。 監測 3 歲以下孩童的呼吸症狀。 應告知懷孕或哺乳的病人有潛在的風險來自於賦形劑 benzyl alcohol，可能會因為長時間的累積導致代謝性酸中毒。 應謹慎使用在肝或腎功能不全的病人，因為有潛在的風險來自於賦形劑 benzyl alcohol，可能會因為長時間的累積導致代謝性酸中毒。	請參閱 EMA SmPC 及 Excipient guideline
資料日期	2020 年 3 月	2021 年 5 月_EMA SmPC 07/01/2021_excipient	修正為仿單更新日期



立比扶注射劑 66 mcg & 132 mcg 中文仿單			
	原核准版本	擬變更版本	備註及參考資料
成份	已知效能的賦形劑：7.5 mg benzyl alcohol。	已知效能的賦形劑：每 0.5 mL 注射液含有 benzyl alcohol 2.5 mg。	請參閱 EMA SmPC
警語與注意事項	<u>Benzyl alcohol</u> 本藥每 0.5 毫升單劑含 2.5 毫克 benzyl alcohol。早產兒或新生兒不可投予 Rebif®。嬰幼兒及 3 歲以下孩童可能會造成毒性反應及過敏反應。	<u>賦形劑</u> <u>鈉含量</u> 本藥每一劑量含少於 1 mmol 鈉(23 毫克)，幾近於不含鈉。 <u>Benzyl alcohol</u> 本藥含 benzyl alcohol。Benzyl alcohol 可能會導致過敏反應。 監測 3 歲以下孩童的呼吸症狀。 應告知懷孕或哺乳的病人有潛在的風險來自於賦形劑 benzyl alcohol，可能會因為長時間的累積導致代謝性酸中毒。 應謹慎使用在肝或腎功能不全的病人，因為有潛在的風險來自於賦形劑 benzyl alcohol，可能會因為長時間的累積導致代謝性酸中毒。	請參閱 EMA SmPC 及 Excipient guideline
資料日期	2020 年 3 月	2021 年 5 月_EMA SmPC 07/01/2021_excipient	修正為仿單更新日期



N0723050

MERCK

Rebif® 22 micrograms 44 micrograms

License No.000001
License No.000002

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms
Rebif 44 micrograms

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 ml) contains 22 micrograms (million IU) or 44 micrograms (million IU) of interferon beta-1a.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rebif is indicated for the treatment of relapsing multiple sclerosis. In clinical trials, this was characterized by two or more acute exacerbations in the previous two years (see section 5.1). Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity (see section 5.1).

4.2 Posology and method of administration

Rebif is available in two strengths: 22 micrograms and 44 micrograms.

The recommended posology of Rebif is 44 micrograms given three times per week by subcutaneous injection. A lower dose of Rebif 22 micrograms, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treatment specialist. Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

When first starting treatment with Rebif, in order to allow acclimatization to the drug, the recommended dose is 22 micrograms. After 2 weeks of treatment, it is recommended that patients should be evaluated at least every second year in the 4-year period after initiation of treatment with Rebif and a decision for longer term treatment should then be made on an individual basis by the treating physician.

There is very limited information on the use of Rebif in children under 16 years of age and therefore Rebif should not be used in this population.

Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to estimate febrile symptoms associated with Rebif administration.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif have not been demonstrated beyond 4 years of treatment. It is recommended that patients should be evaluated at least every second year in the 4-year period after initiation of treatment with Rebif and a decision for longer term treatment should then be made on an individual basis by the treating physician.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Patients should be informed of the most frequent adverse reactions associated with interferon beta administration, including symptoms of the flu-like syndrome (see section 4.6). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

Thrombotic microangiopathy (TMA)

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. If clinical features of TMA are observed, further testing of blood plasma levels, serum lactate dehydrogenase (LDH), schistocytes, erythrocyte fragmentation on a blood film and renal function is recommended. If TMA is diagnosed, prompt treatment (considering plasma exchange) and discontinuation of Rebif are required.

Depression and suicidal ideation

Rebif should be administered with caution to patients with previous or current depressive disorders in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Rebif should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Rebif and treated appropriately. Discontinuation of therapy with Rebif should be considered (see sections 4.3 and 4.4).

Seizure disorders

Rebif should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if this category is not adequately controlled with anti-epileptics (see sections 4.3 and 4.4).

Cardiac disease

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with interferon beta-1a. Symptoms of the flu-like syndrome associated with interferon beta-1a therapy may prove stressful to patients with cardiac conditions.

Injection site reactions

Injection site reactions (ISR) have been reported in patients using Rebif (see section 4.8). To minimize the risk of injection site reactions patients should be advised to:

- use an aseptic injection technique.
- rotate the injection sites with each dose.

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred.

If the patient experiences any break in the skin, which may be associated with swelling or damage of fluid from the injection site, the patient should be advised to consult with their physician.

Before commencing injections with Rebif, if the patient has multiple lesions, Rebif should be discontinued until healing has occurred. Patients with simple lesions may continue provided that the lesions are not too extensive.

Immunisation

In clinical trials with Rebif, asymptomatic elevations of hepatic transaminases (particularly alanine aminotransferase (ALT)) were common and 1-3% of patients developed elevations of hepatic transaminases above 5 times the upper limit of normal (ULN). In the absence of clinical symptoms, serum ALT levels should be monitored prior to the start of therapy. At months 1, 2, 3, 6 and 9 on therapy and periodically thereafter. If elevation of ALT should be considered if ALT was above 5 times the ULN, and gradually re-evaluated when enzyme levels have normalized. Rebif should be initiated with caution in patients with a history of significant liver disease. Clinical evidence of active liver disease, alcohol abuse or increased serum ALT > 2.5 times ULN. Treatment with Rebif should be stopped if clinical or other clinical symptoms of liver dysfunction appear.

Rebif, like other interferon beta, has a potential for causing severe liver injury including acute liver failure (see section 4.3). The majority of the cases of severe liver injury occurred within the first six months of the treatment. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. The overall incidence of these is slightly higher with Rebif 44 than Rebif 22 micrograms. Therefore, in addition to more laboratory tests normally required for monitoring patients with multiple sclerosis, liver enzyme monitoring and complete and differential blood cell counts and platelet counts are recommended at regular intervals (1, 2, and 6 months) following introduction of Rebif therapy and then periodically thereafter in the absence of clinical symptoms. Tests should be more frequent when initiating Rebif 44 micrograms.

Thyroid disorders

Patients being treated with Rebif may occasionally develop new or worsening thyroid abnormalities. Thyroid function testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If tests are normal at baseline, routine testing is not needed but should be performed if clinical findings of thyroid dysfunction appear (see section 4.3).

Caution must be taken to avoid severe myopathy

Caution should be used, and close monitoring considered when administering interferon beta-1a to patients with severe renal and hepatic failure and to patients with severe myopathy.

Interferon antibodies

Serum neutralizing antibodies against interferon beta-1a may develop. The presence of antibodies is not yet understood. Clinical data suggest that after 54-64 months of treatment with Rebif 22 micrograms and Rebif 44 micrograms, approximately 24% and 19% to 14% respectively of patients develop persistent serum antibodies to interferon beta-1a. The presence of antibodies has been shown to attenuate the pharmacodynamic response to interferon beta-1a (see 2.2 micrograms and 4.4 micrograms). Although the clinical significance of the detection of antibodies has not been fully elucidated, the development of neutralizing antibodies is associated with reduced efficacy on clinical and MRI variables. If a patient responds poorly to therapy with Rebif, and has neutralizing antibodies, the treating physician should reassess the benefit/risk ratio or continued Rebif therapy. The use of various assays to detect serum antibodies and differing definitions of antibody positivity limits the ability to compare heterogeneity among different products.

Other forms of antibody response

Only sparse safety and efficacy data are available from non-immunisation patients with multiple sclerosis. Rebif has not yet been investigated in patients with primary progressive multiple sclerosis and should not be used in such patients.

Excipients

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose. It is essentially 'sodium-free'.

Emulsifier

This medicinal product contains benzyl alcohol. Benzyl alcohol may cause allergic reactions. Monitor patients less than 3 years of age for respiratory symptoms.

Advise patients who are pregnant or breastfeeding of the potential risk from exogenous benzyl alcohol, which may accumulate over time and cause metabolic toxicity. The use with caution in patients with hepatic or renal impairment, because of the potential risk from exogenous benzyl alcohol which may accumulate over time and cause metabolic toxicity.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with interferon beta-1a in humans.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif in combination with medicinal products which have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. anti-epileptics and some classes of antidepressants.

The interaction of Rebif with corticosteroids or adrenocorticotrophic hormone (ACTH) has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive Rebif and corticosteroids or ACTH during relapses.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data (more than 1,000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was discontinued during pregnancy, and treatment likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Based on animal data (see section 5.3), there is a possibility of increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy.

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the clinical/physiological characteristics of interferon beta-1a, suggests that levels of interferon beta-1a excreted in human milk are low.

The benefit and potential risk of breastfeeding should be considered along with the patient's medical need for interferon beta-1a therapy.

Fertility

The effects of Rebif on fertility have not been investigated.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta (e.g. dizziness) might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The highest incidence of adverse reactions associated with Rebif therapy is related to flu-like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Approximately 70% of patients treated with Rebif can expect to experience the typical interferon flu-like syndrome within the first 48 hours after starting treatment. Approximately 30% of patients will also experience reactions at the injection site, predominantly mild inflammation or erythema. Asymptomatic increases in laboratory parameters of hepatic function and decreases in white blood cells are also common.

Theophylline and other reactions observed with interferon beta-1a are usually mild and reversible, and respond well to dose reductions. In case of severe or persistent undesirable effects, the dose of Rebif may be temporarily lowered or interrupted at the discretion of the physician.

Local administration

The adverse reactions associated have been identified from clinical studies as well as from post-marketing reports (see section 4.7). Indicated adverse reactions identified during post-marketing surveillance. The following definitions apply to the frequency terminology used hereafter.

Very common: >10% common: 1% to 10% uncommon: 0.1% to 1% rare: <0.1% very rare: <0.01% frequency not known: cannot be estimated from the available data.

Rebif 22 micrograms and Rebif 44 micrograms

Very common: Neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, pancytopenia.

Endocrine disorders

Uncommon: Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism.

Immune system disorders

Rare: Anaphylactic reactions.

Neurological disorders

Very common: Asymptomatic transaminase increase. Common: Severe elevations in transaminases. Uncommon: Headache, dizziness or vertigo. Rare: Seizures.

Psychiatric disorders

Rare: Depression, insomnia. Suicide attempt.

Respiratory system disorders

Very common: Headache. Uncommon: Seizures. Frequency not known: Transient neurological symptoms (e.g. hypotension, muscle spasm, paraesthesia, difficulty in walking, muscular stiffness that may mimic multiple sclerosis exacerbations).

Cardiovascular disorders

Uncommon: Thrombotic events. Rare: Myocardial infarction, stroke, peripheral vascular disease, hypertension, atherosclerosis, coronary artery disease, obstructive renal artery or vein.

Other disorders

Uncommon: Thrombotic events. Rare: Myocardial infarction, stroke, peripheral vascular disease, hypertension, atherosclerosis, coronary artery disease, obstructive renal artery or vein.

Rebif 22 micrograms and Rebif 44 micrograms

Uncommon: Thrombotic events. Rare: Myocardial infarction, stroke, peripheral vascular disease, hypertension, atherosclerosis, coronary artery disease, obstructive renal artery or vein.

Rebif 22 micrograms and Rebif 44 micrograms

Uncommon: Thrombotic events. Rare: Myocardial infarction, stroke, peripheral vascular disease, hypertension, atherosclerosis, coronary artery disease, obstructive renal artery or vein.

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Rebif 22 micrograms and Rebif 44 micrograms

Uncommon: Thrombotic events. Rare: Myocardial infarction, stroke, peripheral vascular disease, hypertension, atherosclerosis, coronary artery disease, obstructive renal artery or vein.

Etiological response markers (e.g. T2-T2-DS activity, response, and beta 2 microglobulin) are induced by interferon beta-1a following subcutaneous doses administered in healthy volunteer subjects. Time to peak concentrations following a single subcutaneous injection were 24 to 48 hours for neopterin, beta 2 microglobulin, and T2-DS, 12 hours for IL-6 and 24 hours for IL-10 and IL-12. Peak concentrations of similar height and time were observed for most of these markers after first and sixth administration.

The precise mechanism of action of Rebif in multiple sclerosis is still under investigation.

Rebif 22 micrograms and Rebif 44 micrograms

The safety and efficacy of Rebif has been evaluated in patients with relapsing-remitting multiple sclerosis at doses ranging from 11 to 44 micrograms (1-12 million IU) administered subcutaneously three times per week. In a controlled study, Rebif 22 micrograms and Rebif 44 micrograms have been demonstrated to decrease the incidence (approximately 30% over 2 years) and severity of clinical relapses in patients with at least 2 exacerbations in the previous 2 years and with an EDSS of 6-8.5 at entry. The proportion of patients with disability progression, as defined by at least one point increase in EDSS confirmed three months later, was reduced from 58% (placebo) to 20% (Rebif 22 micrograms) and 27% (Rebif 44 micrograms). Over 4 years, the reduction in the mean exacerbation rate was 22% in patients treated with Rebif 22 micrograms, and 30% in patients treated with Rebif 44 micrograms. In a comparison with a group of patients treated with placebo for 2 years and then either Rebif 22 micrograms or Rebif 44 micrograms for 2 years.

Secondary progressive multiple sclerosis

In a 3-year study in patients with secondary progressive multiple sclerosis (EDSS 3-6.5) with evidence of clinical progression in the preceding 2 years and who had not experienced relapses in the preceding 8 weeks, Rebif had no significant effect on progression of disability, but reduced rate was reduced by approximately 30%. If the patient population was defined by two subgroups (those with and those without relapses in the 2 year period prior to study entry), there was no effect on disability in patients without relapses, but in patients with relapses, a proportion with progression in disability at the end of the study was reduced from 70% (placebo) to 57% (Rebif 22 micrograms) and 44 micrograms (combined). These results obtained in a subgroup of patients a posteriori should be interpreted cautiously.

Primary progressive multiple sclerosis

Rebif has not yet been investigated in patients with primary progressive multiple sclerosis, and should not be used in such patients.

5.3 Pharmacokinetic properties

Absorption

In healthy volunteers after intravenous administration, interferon beta-1a exhibits a sharp multiphasic decline with serum levels proportional to the dose. Subcutaneous and intramuscular administrations of Rebif produce equivalent exposure to interferon beta.

Distribution

Following repeated subcutaneous injections of 22 and 44 micrograms doses of Rebif maximum concentrations were typically observed after 8 hours, but this was highly variable.

Elimination

After repeated subcutaneous doses in healthy volunteers, the main PK parameters (C_{max} and C_{trough}) increased proportionally to the increase in dose from 22 micrograms to 44 micrograms. The estimated apparent half-life is 50-60 hours, which is in line with the accumulation observed after multiple dosing.

Metabolism

Interferon beta-1a is equally metabolized and excreted by the liver and the kidneys.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, and genotoxicity.

Rebif has not been investigated for teratogenicity. Actual embryo-fetal toxicity in monkeys showed a reduction of reproductive outcomes. Based on observations with other alpha and beta interferons, an increased risk of abortions cannot be excluded. No information is available on the effects of the interferon beta-1a on male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Glycerol
Lactose
Limonene
Polysorbate 80
0.01M Sodium acetate buffer pH 4.7

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Describe on box.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C) away from the cooling element. Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

One ml type 1 glass syringe, with a stainless steel needle, containing 0.5 ml solution.

Rebif 22/44 micrograms is available as a package of 1, 3, or 12 syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This solution for injection in a pre-filled syringe is ready for use. It may be administered with a suitable auto-injector.

For single use only. Only clear to appearance solution without particles and without visible signs of deterioration should be used.

Any unused product or waste material should be disposed of in accordance with local requirements.

Date of information

May 2021, EMA SmPC 070/02021, excipients

Manufacturer

Merck Serono S.p.A.
Address: Via Delle Mignole 15, Zona Industriale in Montebello, 20026 Meda, Italy

Market Authorized Holder

Merck Ltd. Taiwan
Address: Of. No. 82, Sec. 2, Tiding Blvd., Taipei (11043), Taiwan
Tel: 822 2612-1111

行政院衛生署 疫苗學製成品 細菌學免 許可證

案審文件號碼：DHA02200000202

衛生署菌疫輸字第 000002 號

中文名稱：立比扶注射劑 44mcg

英文名稱：Rebif 44 micrograms

類別：本藥限由醫師使用

劑型：注射劑

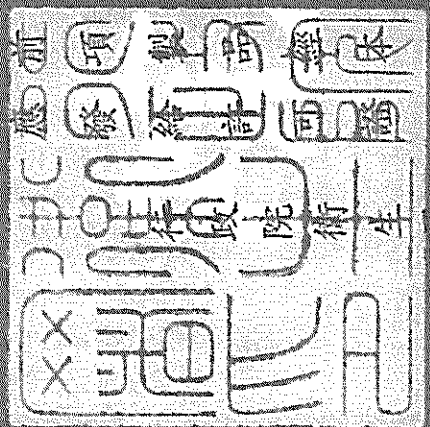
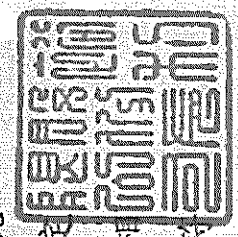
包裝種類：0.5ml 預充填注射針筒裝，預充填注射針 100支以下盒裝。

含量或單位：Each 0.5ml contains: Interferon β -1a.....44mcg

藥商名稱：新加坡商雪蘭諾股份有限公司臺灣分公司
製造廠名稱：Vetter Pharmafertigung GmbH & Co. KG manufacture for Industria
製造廠地址：Farmaceutica Serono S.p.A. (P)Vetter: Schutzenstrasse 99/101, D-88212 Ravensburg, Germany (O)Serono: Zona Industriale Modugno Bari, Italy.



適應症：復發型多變性硬化症。

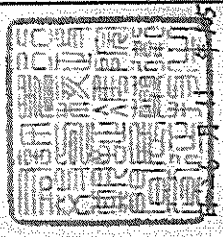


審核與藥事法之規定相符
實證明

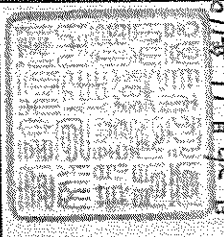
李明亮

發證日期 玖拾 年 拾壹 月 貳拾陸 日
有效期間 壹佰 年 拾壹 月 貳拾陸 日

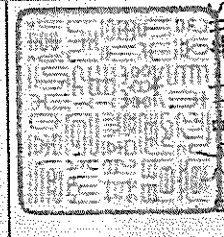
至 展 准 核



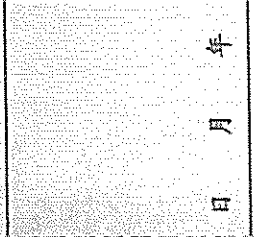
905039



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藥師

日 月 年

