

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Extavia 250 microgram/ml powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Extavia contains 300 microgram (9.6 million IU) of recombinant interferon beta-1b per vial*.

After reconstitution, each ml contains 250 microgram (8.0 million IU) of recombinant interferon beta-1b.

* produced by genetic engineering from strain of *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder - white to off-white in colour.

Solvent - clear/colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Extavia is indicated for the treatment of:

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).
- Patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years.
- Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

4.2 Posology and method of administration

The treatment with Extavia should be initiated under the supervision of a physician experienced in the treatment of the disease.

Posology

Adults and adolescents from 12-17 years of age

The recommended dose of Extavia is 250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution (see section 6.6), to be injected subcutaneously every other day.

Generally, dose titration is recommended at the start of treatment.

Patients should be started at 62.5 microgram (0.25 ml) subcutaneously every other day, and increased slowly to a dose of 250 microgram (1.0 ml) every other day (see Table A). The titration period may be adjusted, if any significant adverse reaction occurs. In order to obtain adequate efficacy, a dose of 250 microgram (1.0 ml) every other day should be reached.

Table A: Schedule for dose titration*

Treatment day	Dose	Volume
1, 3, 5	62.5 microgram	0.25 ml
7, 9, 11	125 microgram	0.5 ml
13, 15, 17	187.5 microgram	0.75 ml
≥ 19	250 microgram	1.0 ml

* The titration period may be adjusted if any significant adverse reaction occurs.

The optimal dose has not been fully clarified.

At the present time, it is not known for how long the patient should be treated. There are follow-up data under controlled clinical conditions for patients with relapsing-remitting multiple sclerosis for up to 5 years and for patients with secondary progressive multiple sclerosis for up to 3 years. For relapsing-remitting multiple sclerosis, efficacy has been demonstrated for therapy for the first two years. The available data for the additional three years are consistent with sustained treatment efficacy of Extavia over the whole time period.

In patients with a single clinical event suggestive of multiple sclerosis, efficacy has been demonstrated over a period of three years.

Treatment is not recommended in patients with relapsing-remitting multiple sclerosis who have experienced less than 2 relapses in the previous 2 years or in patients with secondary-progressive multiple sclerosis who have had no active disease in the previous 2 years.

If the patient fails to respond, for example a steady progression in Expanded Disability Status Scale (EDSS) for 6 months occurs or treatment with at least 3 courses of adrenocorticotrophic hormone (ACTH) or corticosteroids during a one-year period is required despite Extavia therapy, treatment with Extavia should be stopped.

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 17 years of age receiving Extavia 8.0 million IU subcutaneously every other day is similar to that seen in adults. No data are available on the use of Extavia in children under 12 years of age and therefore Extavia should not be used in this population.

Method of administration

The reconstituted solution is to be injected subcutaneously every other day.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta, human albumin or to any of the excipients listed in section 6.1.
- Initiation of treatment in pregnancy (see section 4.6).
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).
- Patients with decompensated liver disease (see sections 4.4, 4.5 and 4.8).

4.4 Special warnings and precautions for use

Immune system disorders

The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.

Gastrointestinal disorders

Cases of pancreatitis were observed with Extavia use, often associated with hypertriglyceridaemia.

Nervous system disorders

Extavia 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 with increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Extavia 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 Extavia and treated appropriately. Cessation of therapy with Extavia should be considered (see also sections 4.3 and 4.8).

Extavia should be administered with caution to patients with a history of seizures, to patients receiving treatment with anti-epileptics, and in particular to patients with epilepsy who are not adequately controlled with anti-epileptics (see sections 4.5 and 4.8).

This medicinal product contains human albumin and hence carries a potential risk for transmission of viral diseases. A risk for transmission of Creutzfeld-Jacob disease (CJD) cannot be excluded.

Laboratory tests

Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. aspartate aminotransferase serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase serum glutamate pyruvate transaminase (SGPT) and gamma glutamyltransferase), are recommended prior to initiation and at regular intervals following introduction of Extavia therapy, and then periodically thereafter in the absence of clinical symptoms.

Patients with anaemia, thrombocytopenia or leukopenia (alone or in any combination) may require more intensive monitoring of complete blood cell counts, with differential and platelet counts. Patients who develop neutropenia should be monitored closely for the development of fever or infection. There have been reports of thrombocytopenia, with profound decreases in platelet count.

Hepatobiliary disorders

Asymptomatic elevations of serum transaminases, in most cases mild and transient, occurred very commonly in patients treated with Extavia during clinical trials. As for other beta interferons, cases of severe hepatic injury, including hepatic failure, have been reported in patients treated with Extavia. The most serious events often occurred in patients exposed to other medicinal products or substances known to be associated with hepatotoxicity or in the presence of co-morbid medical conditions (e.g. metastasising malignant disease, severe infection and sepsis, alcohol abuse).

Patients should be monitored for signs of hepatic injury. The occurrence of elevations in serum transaminases should lead to close monitoring and investigation. Withdrawal of Extavia should be considered if the levels significantly increase or if they are associated with clinical symptoms such as jaundice. In the absence of clinical evidence for liver damage, and after normalisation of liver enzymes, a reintroduction of therapy could be considered with appropriate follow-up of hepatic functions.

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. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Extavia is recommended.

Renal and urinary disorders

Caution should be used and close monitoring considered when administering interferon beta to patients with severe renal failure.

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function, is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Extavia should be considered.

Cardiac disorders

Extavia should also be used with caution in patients who suffer from pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia, should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Extavia.

While Extavia does not have any known direct-acting cardiac toxicity, symptoms of the flu-like syndrome associated with beta interferons may prove stressful to patients with pre-existing significant cardiac disease. During the post-marketing period very rare reports have been received of temporary worsening of cardiac status at the start of Extavia therapy in patients with pre-existing significant cardiac disease.

Cases of cardiomyopathy have been reported. If this occurs and a relationship to Extavia is suspected, treatment should be discontinued.

General disorders and administration site conditions

Serious hypersensitivity reactions (severe acute reactions such as bronchospasm, anaphylaxis and urticaria) may occur. If reactions are severe, Extavia should be discontinued and appropriate medical intervention instituted.

Injection site necrosis has been reported in patients using Extavia (see section 4.8). It can be extensive and may involve muscle fascia as well as fat and therefore can result in scar formation. Debridement and, less often, skin grafting are occasionally required and healing may take up to 6 months.

If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with his/her physician before continuing injections with Extavia.

If the patient has multiple lesions Extavia should be discontinued until healing has occurred. Patients with single lesions may continue on Extavia provided the necrosis is not too extensive, as some patients have experienced healing of injection site necrosis whilst on Extavia.

To minimise the risk of injection site necrosis patients should be advised to:

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

The incidence of injection site reactions may be reduced by the use of an auto-injector. In the pivotal study of patients with a single clinical event suggestive of multiple sclerosis an auto-injector was used in the majority of patients. Injection site reactions and necroses were observed less frequently in this study than in the other pivotal studies.

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

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In controlled clinical trials serum samples were collected every 3 months for monitoring of development of antibodies to Extavia.

In the different controlled clinical trials, between 23% and 41% of the patients developed serum interferon beta-1b neutralising activity confirmed by at least two consecutive positive titres. Between 43% and 55% of these patients converted to a stable antibody negative status (based on two consecutive negative titres) during the subsequent observational period of the trial concerned.

The development of neutralising activity is associated with a reduction in clinical efficacy only with regard to relapse activity. Some analyses suggest that this effect might be more pronounced in patients with higher titre levels of neutralising activity.

In the study of patients with a single clinical event suggestive of multiple sclerosis, neutralising activity measured every 6 months was observed at least once in 32% (89) of the patients treated immediately with Extavia. 60% (53) of these patients returned to negative status based on the last available assessment within the 5-year period. Within this period, the development of neutralising activity was associated with a significant increase in newly active lesions and T2 lesion volume on magnetic resonance imaging. However, this did not seem to be associated with a reduction in clinical efficacy (with regard to time to clinically definite multiple sclerosis (CDMS), time to confirmed EDSS progression and relapse rate).

New adverse events have not been associated with the development of neutralising activity.

It has been demonstrated *in vitro* that Extavia cross-reacts with natural interferon beta. However, this has not been investigated *in vivo* and its clinical significance is uncertain.

There are sparse and inconclusive data on patients who have developed neutralising activity and have completed Extavia therapy.

The decision to continue or discontinue treatment should be based on clinical disease activity rather than on neutralising activity status.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free'.

Latex-sensitive individuals

The removable tip cap of the Extavia pre-filled syringe contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the cap, the safe use of Extavia pre-filled syringe in latex-sensitive individuals has not been studied and there is therefore a potential risk for hypersensitivity reactions which cannot be completely ruled out.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The effect of alternate-day administration of 250 microgram (8.0 million IU) Extavia on drug metabolism in multiple sclerosis patients is unknown. Corticosteroid or ACTH treatment of relapses for periods of up to 28 days has been well tolerated in patients receiving Extavia.

Due to the lack of clinical experience in multiple sclerosis patients, the use of Extavia together with immunomodulators other than corticosteroids or ACTH is not recommended.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Extavia is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. anti-epileptics. Additional caution should be exercised with any co-medication which has an effect on the haematopoietic system.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential should take appropriate contraceptive measures.

Pregnancy

There is limited information on the use of Extavia in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3). If a patient becomes pregnant or plans to become pregnant while using Extavia, she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before initiation of treatment, the risk of a severe relapse following discontinuation of Extavia in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Breast-feeding

It is not known whether interferon beta-1b is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants a decision should be made whether to discontinue breast-feeding or Extavia therapy.

Fertility

No investigations on fertility have been performed (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse events related to the central nervous system associated with the use of Extavia might influence the ability to drive and use machines in susceptible patients.

4.8 Undesirable effects

Summary of the safety profile

At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache, or myalgia), which is mainly due to the pharmacological effects of the medicinal product, and injection site reactions. Injection site reactions occurred frequently after administration of Extavia. Redness, swelling, discolouration, inflammation, pain, hypersensitivity, necrosis and non-specific reactions were significantly associated with 250 microgram (8.0 million IU) Extavia treatment.

Generally, dose titration is recommended at the start of treatment in order to increase tolerability to Extavia (see section 4.2). Flu-like symptoms may also be reduced by administration of non-steroidal anti-inflammatory medicinal products. The incidence of injection site reactions may be reduced by the use of an auto-injector.

Tabulated list of adverse reactions

In the following tables, the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The following adverse event listings are based on reports from clinical trials (*Table 1, adverse events and laboratory abnormalities*) and from post-marketing surveillance (*Table 2, frequencies - where known - based on pooled clinical trials (very common $\geq 1/10$, common $\geq 1/100$ to $< 1/10$, uncommon $\geq 1/1,000$ to $< 1/100$, rare $\geq 1/10,000$ to $< 1/1,000$, very rare $< 1/10,000$)) of Extavia use. Experience with Extavia in patients with multiple sclerosis (MS) is limited, consequently those adverse events which occur very rarely may not yet have been observed.*

Table 1 Adverse events and laboratory abnormalities with incidence rates $\geq 10\%$ and the respective percentages under placebo; significantly associated side effects $< 10\%$ based on reports from clinical trials

System Organ Class Adverse Event and Laboratory Abnormalities	Single Event suggestive of Multiple Sclerosis (BENEFIT)	Secondary Progressive Multiple Sclerosis (European Study)	Secondary Progressive Multiple Sclerosis (North American Study)	Relapsing- Remitting Multiple Sclerosis
	Extavia 250 microgram (Placebo) n=292 (n=176)	Extavia 250 microgram (Placebo) n=360 (n=358)	Extavia 250 microgram (Placebo) n=317 (n=308)	Extavia 250 microgram (Placebo) n=124 (n=123)
Infections and infestations				
Infection	6% (3%)	13% (11%)	11% (10%)	14% (13%)
Abscess	0% (1%)	4% (2%)	4% (5%)	1% (6%)
Blood and lymphatic system disorders				
Lymphocyte count decreased ($< 1500/\text{mm}^3$) [×] [△] ○	79% (45%)	53% (28%)	88% (68%)	82% (67%)
Absolute neutrophil count decreased ($< 1500/\text{mm}^3$) [×] [△] * ○	11% (2%)	18% (5%)	4% (10%)	18% (5%)
White blood cell count decreased ($< 3000/\text{mm}^3$) [×] [△] * ○	11% (2%)	13% (4%)	13% (4%)	16% (4%)
Lymphadenopathy	1% (1%)	3% (1%)	11% (5%)	14% (11%)

Metabolism and nutrition disorders				
Blood glucose decreased (<55 mg/dl) ^x	3% (5%)	27% (27%)	5% (3%)	15% (13%)
Psychiatric disorders				
Depression	10% (11%)	24% (31%)	44% (41%)	25% (24%)
Anxiety	3% (5%)	6% (5%)	10% (11%)	15% (13%)
Nervous system disorders				
Headache [^]	27% (17%)	47% (41%)	55% (46%)	84% (77%)
Dizziness	3% (4%)	14% (14%)	28% (26%)	35% (28%)
Insomnia	8% (4%)	12% (8%)	26% (25%)	31% (33%)
Migraine	2% (2%)	4% (3%)	5% (4%)	12% (7%)
Paraesthesia	16% (17%)	35% (39%)	40% (43%)	19% (21%)
Eye disorders				
Conjunctivitis	1% (1%)	2% (3%)	6% (6%)	12% (10%)
Abnormal vision [^]	3% (1%)	11% (15%)	11% (11%)	7% (4%)
Ear and labyrinth disorders				
Ear pain	0% (1%)	<1% (1%)	6% (8%)	16% (15%)
Cardiac disorders				
Palpitation [*]	1% (1%)	2% (3%)	5% (2%)	8% (2%)
Vascular disorders				
Vasodilatation	0% (0%)	6% (4%)	13% (8%)	18% (17%)
Hypertension ^o	2% (0%)	4% (2%)	9% (8%)	7% (2%)
Respiratory, thoracic and mediastinal disorders				
Upper respiratory infection	18% (19%)	3% (2%)		
Sinusitis	4% (6%)	6% (6%)	16% (18%)	36% (26%)
Cough increased	2% (2%)	5% (10%)	11% (15%)	31% (23%)
Dyspnoea [*]	0% (0%)	3% (2%)	8% (6%)	8% (2%)
Gastrointestinal disorders				
Diarrhoea	4% (2%)	7% (10%)	21% (19%)	35% (29%)
Constipation	1% (1%)	12% (12%)	22% (24%)	24% (18%)
Nausea	3% (4%)	13% (13%)	32% (30%)	48% (49%)
Vomiting [^]	5% (1%)	4% (6%)	10% (12%)	21% (19%)
Abdominal pain ^o	5% (3%)	11% (6%)	18% (16%)	32% (24%)
Hepatobiliary disorders				
Alanine aminotransferase increased (SGPT >5 times baseline) ^{x ^ * o}	18% (5%)	14% (5%)	4% (2%)	19% (6%)
Aspartate aminotransferase increased (SGOT >5 times baseline) ^{x ^ * o}	6% (1%)	4% (1%)	2% (1%)	4% (0%)
Skin and subcutaneous tissue disorders				
Skin disorder	1% (0%)	4% (4%)	19% (17%)	6% (8%)
Rash ^{^ o}	11% (3%)	20% (12%)	26% (20%)	27% (32%)
Musculoskeletal and connective tissue disorders				
Hypertonia ^o	2% (1%)	41% (31%)	57% (57%)	26% (24%)
Myalgia ^{* o}	8% (8%)	23% (9%)	19% (29%)	44% (28%)
Myasthenia	2% (2%)	39% (40%)	57% (60%)	13% (10%)
Back pain	10% (7%)	26% (24%)	31% (32%)	36% (37%)
Pain in extremity	6% (3%)	14% (12%)		0% (0%)

Renal and urinary disorders				
Urinary retention	1% (1%)	4% (6%)	15% (13%)	
Urinary protein positive (>1+) ^x	25% (26%)	14% (11%)	5% (5%)	5% (3%)
Urinary frequency	1% (1%)	6% (5%)	12% (11%)	3% (5%)
Urinary incontinence	1% (1%)	8% (15%)	20% (19%)	2% (1%)
Urinary urgency	1% (1%)	8% (7%)	21% (17%)	4% (2%)
Reproductive system and breast disorders				
Dysmenorrhoea	2% (0%)	<1% (<1%)	6% (5%)	18% (11%)
Menstrual disorder *	1% (2%)	9% (13%)	10% (8%)	17% (8%)
Metrorrhagia	2% (0%)	12% (6%)	10% (10%)	15% (8%)
Impotence	1% (0%)	7% (4%)	10% (11%)	2% (1%)
General disorders and administration site conditions				
Injection site reaction (various kinds) ^{^ * ° §}	52% (11%)	78% (20%)	89% (37%)	85% (37%)
Injection site necrosis ^{* °}	1% (0%)	5% (0%)	6% (0%)	5% (0%)
Flu-like symptoms ^{& ^ * °}	44% (18%)	61% (40%)	43% (33%)	52% (48%)
Fever ^{^ * °}	13% (5%)	40% (13%)	29% (24%)	59% (41%)
Pain	4% (4%)	31% (25%)	59% (59%)	52% (48%)
Chest pain [°]	1% (0%)	5% (4%)	15% (8%)	15% (15%)
Peripheral oedema	0% (0%)	7% (7%)	21% (18%)	7% (8%)
Asthenia *	22% (17%)	63% (58%)	64% (58%)	49% (35%)
Chills ^{^ * °}	5% (1%)	23% (7%)	22% (12%)	46% (19%)
Sweating *	2% (1%)	6% (6%)	10% (10%)	23% (11%)
Malaise *	0% (1%)	8% (5%)	6% (2%)	15% (3%)
The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.				
^x Laboratory abnormality [^] Significantly associated with Extavia treatment for patients with first event suggestive of MS, p <0.05 * Significantly associated with Extavia treatment for RRMS, p <0.05 [°] Significantly associated with Extavia treatment for SPMS, p <0.05 [§] Injection site reaction (various kinds) comprises all adverse events occurring at the injection site, i.e. the following terms: injection site haemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site necrosis, injection site pain, injection site reaction, injection site oedema, and injection site atrophy & “Flu-like symptom complex” denotes flu syndrome and/or a combination of at least two adverse events from fever, chills, myalgia, malaise, sweating.				

Table 2 Adverse drug reactions (ADRs) identified during post-marketing surveillance (frequencies - where known - calculated based on pooled clinical trial data N = 1,093)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome [#]	
Immune system disorders				Anaphylactic reactions	Capillary leak syndrome in pre-existing monoclonal gammopathy*
Endocrine disorders		Hypothyroidism		Hyperthyroidism, Thyroid disorders	
Metabolism and nutrition disorders		Weight increased, Weight decreased	Blood triglycerides increased	Anorexia*	
Psychiatric disorders		Confusional state	Suicide attempt (see also section 4.4), Emotional lability		
Nervous system disorders			Convulsion		
Cardiac disorders		Tachycardia		Cardiomyopathy*	
Respiratory, thoracic and mediastinal disorders				Bronchospasm*	Pulmonary arterial hypertension**
Gastrointestinal disorders				Pancreatitis	
Hepatobiliary disorders		Blood bilirubin increased	Gamma-glutamyl-transferase increased, Hepatitis	Hepatic injury (including hepatitis), Hepatic failure*	
Skin and subcutaneous tissue disorders		Urticaria, Pruritus, Alopecia	Skin discolouration		
Musculoskeletal and connective tissue disorders	Arthralgia				Drug-induced lupus erythematosus
Renal and urinary disorders			Nephrotic syndrome, glomerulosclerosis (see section 4.4)*, #		
Reproductive system and breast disorders		Menorrhagia			

* ADRs derived only during post-marketing.

Class label for interferon beta products (see section 4.4).

** Class label for interferon products, see below “Pulmonary arterial hypertension”.

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Interferon beta-1b has been given to adult cancer patients at individual doses as high as 5,500 microgram (176 million IU) intravenously three times a week without serious adverse events compromising vital functions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC Code: L03AB08

Interferons belong to the family of cytokines, which are naturally occurring proteins. Interferons have molecular weights ranging from 15,000 to 21,000 Daltons. Three major classes of interferons have been identified: alpha, beta, and gamma. Interferon alpha, interferon beta, and interferon gamma have overlapping yet distinct biological activities. The activities of interferon beta-1b are species-restricted and therefore, the most pertinent pharmacological information on interferon beta-1b is derived from studies of human cells in culture or human *in vivo* studies.

Mechanism of action

Interferon beta-1b has been shown to possess both antiviral and immunoregulatory activity. The mechanisms by which interferon beta-1b exerts its actions in multiple sclerosis are not clearly understood. However, it is known that the biological response-modifying properties of interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of interferon beta-1b to these receptors induces the expression of a number of gene products that are believed to be the mediators of the biological actions of interferon beta-1b. A number of these products have been measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1b. Interferon beta-1b both decreases the binding affinity and enhances the internalisation and degradation of the interferon-gamma receptor. Interferon beta-1b also enhances the suppressor activity of peripheral blood mononuclear cells.

Clinical efficacy and safety

No separate investigations were performed regarding the influence of Extavia on the cardiovascular system, respiratory system and the function of endocrine organs.

Relapsing-remitting multiple sclerosis (RR-MS)

One controlled clinical trial was performed with Extavia in patients with relapsing-remitting multiple sclerosis and able to walk unaided (baseline EDSS 0 to 5.5). In patients receiving Extavia there was a reduction in the frequency (30%) and severity of clinical relapses and in the number of hospitalisations due to disease. Furthermore, there was a prolongation of the relapse-free interval. There is no evidence of an effect of Extavia on the duration of relapses or on symptoms in between relapses, and no significant effect was seen on the progression of the disease in relapsing-remitting multiple sclerosis.

Secondary progressive multiple sclerosis (SP-MS)

Two controlled clinical trials were performed with Extavia involving a total of 1,657 patients with secondary progressive multiple sclerosis (baseline EDSS 3 to 6.5, i.e. patients were able to walk). Patients with mild disease and those unable to walk were not studied. The two studies showed inconsistent results for the primary endpoint time to confirmed progression, representing delay of disability progression:

One of the two studies demonstrated a statistically significant delay in the time to disability progression (Hazard Ratio = 0.69, 95% confidence interval (0.55, 0.86), $p=0.0010$, corresponding to a 31% risk reduction due to Extavia) and in the time to becoming wheelchair-bound (Hazard Ratio = 0.61, 95% confidence interval (0.44, 0.85), $p=0.0036$, corresponding to a 39% risk reduction due to Extavia) in patients who received Extavia. This effect continued over the observation period of up to 33 months. The treatment effect occurred in patients at all levels of disability investigated and independent of relapse activity.

In the second trial of Extavia in secondary progressive multiple sclerosis, no delay in the time to disability progression was observed. There is evidence that the patients included in this study had overall less active disease than in the other study in secondary progressive multiple sclerosis.

In retrospective meta-analyses including the data of both studies, a statistically significant overall treatment effect was found ($p=0.0076$; 8.0 million IU Extavia versus all placebo patients).

Retrospective analyses in subgroups showed that a treatment effect on disability progression is most likely in patients with active disease before treatment commences (Hazard Ratio 0.72, 95% confidence interval (0.59, 0.88), $p=0.0011$, corresponding to a 28% risk reduction due to Extavia in patients with relapses or pronounced EDSS progression, 8.0 million IU Extavia versus all placebo patients). From these retrospective subgroup analyses there was evidence to suggest that relapses as well as pronounced EDSS progression (EDSS >1 point or >0.5 point for EDSS ≥ 6 in the previous two years) can help to identify patients with active disease.

In both trials there was a reduction (30%) in frequency of clinical relapses in patients with secondary progressive multiple sclerosis patients receiving Extavia. There is no evidence of Extavia having an effect on the duration of relapses.

Single clinical event suggestive of multiple sclerosis

One controlled clinical trial with Extavia was performed in patients with a single clinical event and Magnetic Resonance Imaging (MRI) features suggestive of multiple sclerosis (at least two clinically silent lesions on the T2-weighted MRI). Patients with monofocal or multifocal onset of the disease were included (i.e. patients with clinical evidence of a single or at least two lesions, respectively, of the central nervous system). Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded. This study consisted of two phases, a placebo-controlled phase followed by a pre-planned follow-up phase. The placebo-controlled phase lasted for 2 years or until the patient developed clinically definite multiple sclerosis (CDMS), whichever came first. After the placebo-controlled phase, patients entered a pre-planned follow-up phase with Extavia to evaluate the effects of immediate versus delayed start of Extavia treatment, comparing patients initially randomised to Extavia (“immediate treatment group”) or to placebo (“delayed treatment group”). Patients and investigators remained blinded to the initial treatment allocation.

In the placebo-controlled phase, Extavia delayed the progression from the first clinical event to clinically definite multiple sclerosis (CDMS) in a statistically significant and clinically meaningful manner, corresponding to a risk reduction of 47% (Hazard Ratio = 0.53, 95% confidence interval (0.39, 0.73), $p < 0.0001$). Within the study period of two years, CDMS occurred in 45% of the placebo group compared to 28% of the Extavia group (Kaplan-Meier estimates). Extavia prolonged the time to CDMS by 363 days, from 255 days in the placebo group to 618 days in the Extavia group (based on the 25th percentiles). This treatment effect was still evident after the additional year of follow-up at which stage the risk reduction was 41% (Hazard Ratio = 0.59, 95% confidence interval (0.42, 0.83), $p = 0.0011$). Within the study period of three years, CDMS occurred in 51% of the delayed treatment group compared to 37% of the immediate treatment group (Kaplan-Meier estimates). The persistence of the treatment effect was observed although the majority of patients from the placebo-group was treated with Extavia in the third year of the study.

The robustness of the treatment effect was also shown by the delay of progression to multiple sclerosis according to the McDonald criteria. In two years, the risk was 85% in the placebo group and 69% in the Extavia group (Hazard Ratio = 0.57, 95% confidence interval (0.46, 0.71), $p < 0.00001$).

After 3 years, a pre-planned interim analysis showed EDSS progression (confirmed increase in EDSS of greater than or equal to 1.0 compared to baseline) occurred in 24% of the patients in the delayed treatment group compared to 16% in the immediate treatment group [Hazard Ratio = 0.6, 95% confidence interval (0.39, 0.92), $p = 0.022$]. There is no evidence for benefit in terms of confirmed disability progression in the majority of patients receiving “immediate” treatment. Follow-up of patients is continuing in order to provide additional data. No benefit, attributable to Extavia, in quality of life (as measured by FAMS – Functional Assessment of MS: Treatment Outcomes Index) was seen.

Subgroup analyses according to baseline factors demonstrated evidence of efficacy in all subgroups evaluated. Significant effects were also obtained in patients with less disseminated and less active disease at the time of the first event. The risk for progression to CDMS within two years in patients with monofocal onset was 47% for placebo and 24% for Extavia, without gadolinium (Gd-) enhancement 41% and 20%, with less than 9 T2 lesions 39% and 18%. Further subgroup analyses indicated a high risk for progression to CDMS within 2 years in monofocal patients with at least 9 T2-lesions (55% risk for placebo, 26% for Extavia) or Gd-enhancement (63% versus 33%). In multifocal patients, the risk for CDMS was independent from MRI findings at baseline, indicating a high risk for CDMS because of the dissemination of the disease based on clinical findings. However, the long-term impact of early treatment with Extavia is unknown even in these high risk subgroups as this study was mainly designed to assess the time to CDMS rather than the long-term evolution of the disease. Furthermore, for the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

Therapy with Extavia was well accepted in the study of patients with a single clinical event as indicated by a high rate of trial completion (92.8% in the Extavia group). To increase tolerability of Extavia in the study of patients with a first clinical event, a dose titration was applied and non-steroidal anti-inflammatory medicinal products were administered at start of therapy. Moreover, an autoinjector was used by the majority of patients throughout the study.

RR-MS, SP-MS and single clinical event suggestive of MS

In all multiple sclerosis studies Extavia was effective in reducing disease activity (acute inflammation in the central nervous system and permanent tissue alterations) as measured by magnetic resonance imaging (MRI). The relation of multiple sclerosis disease activity as measured by MRI and clinical outcome is currently not fully understood.

5.2 Pharmacokinetic properties

Extavia serum levels were followed in patients and volunteers by means of a bioassay that was not completely specific. Maximum serum levels of about 40 IU/ml were found 1-8 hours after subcutaneous injection of 500 microgram (16.0 million IU) interferon beta-1b. From various studies mean clearance rates and half-lives of disposition phases from serum were estimated to be at most $30 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ and 5 hours, respectively.

Administration of Extavia injections every other day does not lead to serum level increase, and the pharmacokinetics do not seem to change during therapy.

The absolute bioavailability of subcutaneously administered interferon beta-1b was approximately 50%.

5.3 Preclinical safety data

No acute toxicity studies have been performed. As rodents do not react to human interferon beta, repeated dose studies were carried out with rhesus monkeys. Transitory hyperthermia was observed, as well as a significant rise in lymphocytes and a significant decrease in thrombocytes and segmented neutrophils.

No long-term studies have been conducted. Reproduction studies with rhesus monkeys revealed maternal toxicity and an increased rate of abortion, resulting in prenatal mortality. No malformations have been observed in the surviving animals.

No investigations on fertility have been conducted. No influence on the monkey oestrous cycle has been observed. Experience with other interferons suggest a potential for impairment of male and female fertility.

In one single genotoxicity study (Ames test), no mutagenic effect has been observed. Carcinogenicity studies have not been performed. An *in vitro* cell transformation test gave no indication of tumorigenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Human albumin
Mannitol (E421)

Solvent

Sodium chloride
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for the supplied solvent mentioned in section 6.6.

6.3 Shelf life

2 years.

After reconstitution immediate use is recommended. However, in-use stability has been demonstrated for 3 hours at $2^{\circ}\text{C} - 8^{\circ}\text{C}$.

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder

3 ml vial (clear type I glass) with a butyl rubber stopper (type I) and aluminium overseas containing 300 microgram (9.6 million IU) of (recombinant interferon beta-1b) powder.

Solvent

2.25 ml graduated (with dose marks of: 0.25 ml, 0.5 ml, 0.75 ml, 1.0 ml) pre-filled syringe (type I glass) with 1.2 ml solvent.

Pack sizes

- Pack containing 5 vials with powder and 5 pre-filled syringes with solvent
- Pack containing 14 vials with powder and 14 pre-filled syringes with solvent
- Pack containing 15 vials with powder and 15 pre-filled syringes with solvent
- Pack containing 14 vials with powder and 15 pre-filled syringes with solvent

- 3-month multipack containing 42 (3x14) vials with powder and 42 (3x14) pre-filled syringes with solvent
- 3-month multipack containing 45 (3x15) vials with powder and 45 (3x15) pre-filled syringes with solvent
- 3-month multipack containing 42 (3x14) vials with powder and 45 (3x15) pre-filled syringes with solvent

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex, which should not be handled by persons sensitive to this substance.

Reconstitution

To reconstitute the powder, the pre-filled syringe with solvent should be used with a needle or a vial adapter to inject the 1.2 ml of the solvent (sodium chloride 5.4 mg/ml (0.54%) solution for injection) into the Extavia vial. The powder should dissolve completely without shaking. After reconstitution, 1.0 ml of the solution should be drawn from the vial into the syringe for the administration of 250 microgram Extavia.

Inspection prior to use

The reconstituted product should be inspected visually before use. The reconstituted product is colourless to light yellow and slightly opalescent to opalescent.

The medicinal product should be discarded before use if it contains particulate matter or is discoloured.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/08/454/008-014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2008

Date of latest renewal: 20 May 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND
USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim RCV GmbH & Co KG
Dr.-Boehringer-Gasse 5-11
A-1121 Vienna
Austria

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. The PSUR cycle of Extavia is aligned with the cross-referred product, Betaferon, until otherwise specified.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Extavia 250 microgram/ml powder and solvent for solution for injection
interferon beta-1b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 300 microgram (9.6 million IU) interferon beta-1b.
1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients:
Powder: Human albumin, mannitol.
Solvent: Sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

5 vials with powder and 5 pre-filled syringes with 1.2 ml solvent.
14 vials with powder and 14 pre-filled syringes with 1.2 ml solvent.
15 vials with powder and 15 pre-filled syringes with 1.2 ml solvent.
14 vials with powder and 15 pre-filled syringes with 1.2 ml solvent.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous use after reconstitution with 1.2 ml of solvent.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution immediate use is recommended. In-use stability demonstrated for 3 hours at 2°C - 8°C.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/08/454/008	15 vials with powder and 15 pre-filled syringes with solvent
EU/1/08/454/010	5 vials with powder and 5 pre-filled syringes with solvent
EU/1/08/454/011	14 vials with powder and 14 pre-filled syringes with solvent
EU/1/08/454/013	14 vials with powder and 15 pre-filled syringes with solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Extavia

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Extavia 250 microgram/ml powder and solvent for solution for injection
interferon beta-1b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 300 microgram (9.6 million IU) interferon beta-1b.
1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients:
Powder: Human albumin, mannitol.
Solvent: Sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

3-month multipack: 42 (3 packs of 14) vials with powder and 42 (3 packs of 14) pre-filled syringes with 1.2 ml solvent.

3-month multipack: 45 (3 packs of 15) vials with powder and 45 (3 packs of 15) pre-filled syringes with 1.2 ml solvent.

3-month multipack: 42 (3 packs of 14) vials with powder and 45 (3 packs of 15) pre-filled syringes with 1.2 ml solvent.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous use after reconstitution with 1.2 ml of solvent.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution immediate use is recommended. In-use stability demonstrated for 3 hours at 2°C - 8°C.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/08/454/009	3-month multipack comprising 45 vials with powder and 45 pre-filled syringes with solvent
EU/1/08/454/012	3-month multipack comprising 42 vials with powder and 42 pre-filled syringes with solvent
EU/1/08/454/014	3-month multipack comprising 42 vials with powder and 45 pre-filled syringes with solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Extavia

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Extavia 250 microgram/ml powder and solvent for solution for injection
interferon beta-1b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 300 microgram (9.6 million IU) interferon beta-1b.
1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients:
Powder: Human albumin, mannitol.
Solvent: Sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

14 vials with powder and 14 pre-filled syringes with 1.2 ml solvent. Component of a 3-month multipack. Not to be sold separately.

15 vials with powder and 15 pre-filled syringes with 1.2 ml solvent. Component of a 3-month multipack. Not to be sold separately.

14 vials with powder and 15 pre-filled syringes with 1.2 ml solvent. Component of a 3-month multipack. Not to be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous use after reconstitution with 1.2 ml of solvent.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution immediate use is recommended. In-use stability demonstrated for 3 hours at 2°C - 8°C.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/08/454/009	3-month multipack comprising 45 vials with powder and 45 pre-filled syringes with solvent
EU/1/08/454/012	3-month multipack comprising 42 vials with powder and 42 pre-filled syringes with solvent
EU/1/08/454/014	3-month multipack comprising 42 vials with powder and 45 pre-filled syringes with solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Extavia

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Extavia 250 microgram/ml powder for solution for injection
interferon beta-1b
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

After reconstitution immediate use recommended. In-use stability demonstrated for 3 hours at 2°C - 8°C.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 microgram (8.0 million IU) per ml after reconstitution.

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Solvent for reconstitution of Extavia
1.2 ml sodium chloride solution 5.4 mg/ml

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Read the package leaflet before use.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
LABEL OF PRE-FILLED SYRINGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for Extavia
For subcutaneous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.2 ml sodium chloride solution 5.4 mg/ml

6. OTHER

0.25 / 0.5 / 0.75 / 1.0

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Extavia 250 microgram/ml powder and solvent for solution for injection interferon beta-1b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Extavia is and what it is used for
2. What you need to know before you use Extavia
3. How to use Extavia
4. Possible side effects
5. How to store Extavia
6. Contents of the pack and other information
Annex – self-injection procedure

1. What Extavia is and what it is used for

What Extavia is

Extavia is a type of medicine known as interferon used to treat multiple sclerosis. Interferons are proteins produced by the body that help it fight against attacks on the immune system such as viral infections.

How Extavia works

Multiple sclerosis (MS) is a long-term condition that affects the central nervous system (CNS), particularly the functioning of the brain and spinal cord. In MS, inflammation destroys the protective sheath (called myelin) around the nerves of the CNS and stops the nerves from working properly. This is called demyelination.

The exact cause of MS is unknown. An abnormal response by the body's immune system is thought to play an important part in the process which damages the CNS.

The damage to the CNS can occur within an MS attack (relapse). It can cause temporary disability, such as difficulty walking. Symptoms may disappear completely or partly.

Interferon beta-1b has been shown to change the response of the immune system and to help to reduce disease activity.

How Extavia helps fight your disease

Single clinical event indicating a high risk of developing multiple sclerosis: Extavia has been shown to delay progression to definite multiple sclerosis.

Relapsing-remitting multiple sclerosis: People with relapsing-remitting MS have occasional attacks or relapses during which symptoms become noticeably worse. Extavia has been shown to cut down the number of attacks and make them less severe. It reduces the number of hospital stays due to the disease and prolongs the time without relapses.

Secondary progressive multiple sclerosis: In some cases people with relapsing-remitting MS find that their symptoms increase and they progress to another form of MS called secondary progressive MS. With this, people find themselves becoming increasingly impaired, whether or not they have relapses. Extavia can reduce the number and severity of the attacks, and slow the progression of disability.

What Extavia is used for

Extavia is for use in patients

- ▶ **who have experienced for the first time symptoms which indicate a high risk of developing multiple sclerosis.** Your doctor will rule out any other reasons which could explain these symptoms before you are treated.
- ▶ **who suffer from relapsing-remitting multiple sclerosis, with at least two relapses within the last two years.**
- ▶ **who suffer from secondary progressive multiple sclerosis with active disease shown by relapses.**

2. What you need to know before you use Extavia

Do not use Extavia

- **if you are allergic** to natural or recombinant interferon beta, human albumin or any of the other ingredients of this medicine (listed in section 6).
 - **if you are pregnant.** You should not start treatment with Extavia (see “Pregnancy” section below).
 - **if you become or plan to become pregnant.** You should stop your treatment with Extavia and tell your doctor (see “Pregnancy” section below).
 - **if you currently suffer from severe depression and/or suicidal thoughts** (see “Warnings and precautions” and section 4, “Possible side effects”).
 - **if you have a severe liver disease** (see “Warnings and precautions”, “Other medicines and Extavia” and section 4, “Possible side effects”).
- ▶ **Tell your doctor**, if any of the above applies to you.

Warnings and precautions

Talk to your doctor before using Extavia:

- **If you have monoclonal gammopathy.** This is a **disorder of the immune system where an abnormal protein is found in the blood.** Problems with your small blood vessels (capillaries) may develop (systemic capillary leak syndrome) when using medicines like Extavia. This can lead to shock (collapse) and even be fatal.
- **If you have had depression or are depressed or previously had thoughts of suicide.** Your doctor will closely monitor you during treatment. If your depression and/or suicidal thoughts are severe, you will not be prescribed Extavia (see also “Do not use Extavia”).
- **If you have ever had seizures or if you are taking medicines to treat epilepsy** (anti-epileptics), your doctor will monitor your treatment carefully (see also “Other medicines and Extavia” and section 4, “Possible side effects”).
- **If you have severe kidney problems**, your doctor may monitor your kidney function during treatment.
- **If you have ever had an allergic reaction to latex.** The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex.

Your doctor also needs to know the following **whilst you are using Extavia**:

- **If you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.** These may be symptoms of a serious allergic reaction, which may become life threatening.
- **If you feel noticeably more sad or hopeless than before the treatment with Extavia, or if you develop thoughts of suicide.** If you become depressed while you are on Extavia, you may need special treatment and your doctor will closely monitor you and may also consider stopping your treatment. If you suffer from severe depression and/or suicidal thoughts, you will not be treated with Extavia (see also “Do not use Extavia”).
- **If you notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections.** These may be symptoms of a fall in your blood cell count or in the number of platelets in your blood (cells, which help the blood to clot). You may need extra monitoring by your doctor.
- **If you experience loss of appetite, tiredness, feeling sick (nausea), repeated vomiting, and especially if you notice widespread itching, yellowing of the skin or of the whites of the eyes, or easy bruising.** These symptoms may suggest problems with your liver. Changes to liver function values occurred in patients treated with Extavia during clinical studies. As for other beta interferons, severe liver damage, including cases of liver failure, have been reported rarely in patients taking Extavia. The most serious were reported in patients taking other medicines or who were suffering from diseases that can affect the liver (e.g. alcohol abuse, severe infection).
- **If you experience symptoms such as irregular heart beat, swelling such as of the ankles or legs, or shortness of breath.** This may suggest a disease of the heart muscle (cardiomyopathy) which has been reported in patients using Extavia.
- **If you notice pain in your belly which is radiating to your back, and/or you feel sick or have a fever.** This may suggest an inflammation of the pancreas (pancreatitis), which has been reported with Extavia use. This is often associated with an increase in certain blood fats (triglycerides).
 - ▶ **Stop using Extavia and tell your doctor immediately** if any of these happens to you.

Other things to consider when using Extavia:

- **You will need blood tests** to determine your blood cell count, blood chemistry and your liver enzymes. These will be performed **before you start using Extavia, regularly after treatment with Extavia has been initiated and then periodically during treatment**, even if you have no particular symptoms. These blood tests will be in addition to the tests which are normally done to monitor your MS.
- **If you have a heart disease, the flu-like symptoms which often occur at the start of treatment may prove stressful to you.** Extavia must be used with caution, and your doctor will monitor you for worsening of your heart condition, particularly at the start of treatment. Extavia itself does not affect the heart directly.
- **The functioning of your thyroid gland will be checked** regularly or whenever thought necessary by your doctor for other reasons.
- **Extavia contains human albumin and therefore carries a potential risk for transmission of viral diseases.** A risk of transmission of Creutzfeld-Jacob disease (CJD) cannot be ruled out.

- **During treatment with Extavia your body may produce substances called neutralising antibodies**, which may react with Extavia. It is not yet clear whether these neutralising antibodies reduce the effectiveness of the treatment. Neutralising antibodies are not produced in all patients. Currently it is not possible to predict which patients belong to this group.
- **During treatment with Extavia, kidney problems that may reduce your kidney function, including scarring (glomerulosclerosis), may occur.** Your doctor may perform tests to check your kidney function.
- **Blood clots in the small blood vessels may occur during your treatment.** These blood clots could affect your kidneys. This might happen several weeks to several years after starting Extavia. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidneys.

Injection site reactions

During Extavia treatment you are likely to experience injection site reactions. Symptoms include redness, swelling, change in skin colour, inflammation, pain, and hypersensitivity. Skin breakdown and tissue damage (necrosis) around the injection site are reported less frequently. Injection site reactions usually become less frequent over time.

Injection site skin and tissue breakdown can result in scars forming. If this is severe a doctor may have to remove foreign matter and dead tissue (debridement) and, less often, skin grafting is required and healing may take up to 6 months.

To reduce the risk of getting injection site reaction you must:

- use a sterile (aseptic) injection technique,
- rotate the injection sites with each injection (see Annex Self-Injection procedure).

Injection site reactions may occur less frequently if you use an auto-injector device. Your doctor or nurse can tell you more about this.

If you experience any break in the skin, associated with swelling or fluid leaking out from the injection site:

- ▶ **Stop injecting Extavia** and talk to your doctor.
- ▶ **If you have only one sore injection site (lesion) and the tissue damage (necrosis) is not too extensive you may continue using Extavia.**
- ▶ **If you have more than one sore injection sites (multiple lesions) you must stop using Extavia until your skin has healed.**

Your doctor will regularly check the way you inject yourself, particularly if you have experienced injection site reactions.

Children and adolescents

There have been no formal clinical trials undertaken in children or adolescents.

However, there are some data available in adolescents aged from 12 to 17 years which suggest that the safety of Extavia in this group is the same as in adults. Extavia should not be used in children under 12 years of age as there is no information available for this age group.

Other medicines and Extavia

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

No formal interaction studies have been carried out to find out whether Extavia affects other medicines or is affected by them.

Using Extavia with other medicines that modify the immune system response is not recommended, except anti-inflammatory medicines called corticosteroids or the adrenocorticotrophic hormone (ACTH).

Extavia should be used with caution with:

- **medicines which need a certain liver enzyme system** (known as cytochrome P450 system) for their removal from the body, for example medicines used to treat epilepsy (such as phenytoin).
- **medicines which affect the production of blood cells.**

Extavia with food and drink

Extavia is injected under the skin so any food or drink you consume is not thought to have any effect on Extavia.

Pregnancy

Women who could become pregnant should use appropriate contraception during treatment with Extavia.

- ▶ **If you are pregnant or you think you may be pregnant**, tell your doctor. Extavia therapy should not be started if you are pregnant (see also “Do not use Extavia”).
- ▶ **If you wish to become pregnant**, discuss this with your doctor before starting Extavia therapy.
- ▶ **If you become pregnant while using Extavia**, stop your treatment and contact your doctor immediately. You and your doctor will decide together whether to continue your Extavia treatment.

Ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding

It is not known whether interferon beta-1b passes into human breast milk. However, it is theoretically possible that a breast-fed baby could experience serious side effects to Extavia.

- ▶ **Discuss with your doctor before starting Extavia therapy** to decide whether to stop breast-feeding so that you can use Extavia.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Extavia may cause side effects in the central nervous system (see section 4 “Possible side effects”). If you are especially sensitive, this might influence your ability to drive or use machines.

Extavia contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free'.

3. How to use Extavia

Treatment with Extavia should be started under the supervision of a doctor who is experienced in the treatment of multiple sclerosis.

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is every other day (once every two days), 1.0 ml of the prepared Extavia solution (see Annex “Self-injection procedure” in the second part of this leaflet) injected under the skin (subcutaneously). This equals 250 microgram (8.0 million IU) interferon beta-1b.

In general, treatment should be started at a low dose of 0.25 ml (62.5 microgram). Your doses will then be increased gradually to the full dose of 1.0 ml (250 microgram).

The dose should be increased at every fourth injection in four steps (0.25 ml, 0.5 ml, 0.75 ml, 1.0 ml). Your doctor may decide together with you to change the time intervals for dose increase depending on side effects you may experience at the start of treatment.

Preparing the injection

Before injection, the Extavia solution has to be prepared from a vial of Extavia powder and 1.2 ml of liquid from the pre-filled solvent syringe. This will either be done by your doctor or nurse or by yourself after you have been carefully trained.

Detailed instructions for self-injection of Extavia under the skin are provided in the Annex at the back of this leaflet. These instructions also tell you how to prepare the Extavia solution for injection.

The injection site must be changed regularly. See section 2 “Warnings and precautions” and follow the instructions under “Rotating injection sites” in the Annex at the back of this leaflet.

Duration of treatment

At present it is not known how long treatment with Extavia should last. **The length of treatment will be decided by your doctor together with you.**

If you use more Extavia than you should

Giving many times the dose of Extavia recommended for the treatment of multiple sclerosis has not led to life-threatening situations.

- ▶ **Talk to your doctor** if you inject too much Extavia or injected too often.

If you forget to use Extavia

If you have forgotten to give yourself an injection at the right time do it as soon as you remember and then follow on with the next one 48 hours later.

Do not inject a double dose to make up for a forgotten individual dose.

If you stop using Extavia

Talk to your doctor if you stop or wish to stop treatment. Stopping Extavia is not known to cause acute withdrawal symptoms.

- ▶ If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Extavia may cause serious side effects. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, pharmacist or nurse.

► **Tell your doctor immediately and stop using Extavia:**

- if you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.
- if you feel noticeably more sad or hopeless than before the treatment with Extavia, or if you develop thoughts of suicide.
- if you notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections.
- if you experience loss of appetite, tiredness, feeling sick (nausea), repeated vomiting, especially if you notice widespread itching, yellowing of the skin, or of the whites of the eyes or easy bruising.
- if you experience symptoms like irregular heart beat, swelling such as of the ankles or legs, or shortness of breath.
- if you notice pain in your belly which is radiating to your back , and/or you feel sick or have a fever.

► **Tell your doctor immediately:**

- if you get some or all of these symptoms: foamy urine, fatigue, swelling, particularly and the ankles and eyelids, and weight gain, as they may be signs of a possible kidney problem.

At the beginning of treatment side effects are common but in general they decrease with further treatment.

The most common side effects are:

- **Flu-like symptoms** such as fever, chills, painful joints, malaise, sweating, headache, or muscular pain. These symptoms may be reduced by taking paracetamol or non-steroidal anti-inflammatory medicines such as ibuprofen.
- **Injection site reactions.** Symptoms can be redness, swelling, discolouration, inflammation, pain, hypersensitivity, tissue damage (necrosis). See “Warnings and precautions” in section 2 for more information and what to do if you experience an injection site reaction. These may be reduced by the use of an auto-injector device. Talk to your doctor, pharmacist or nurse for further information.

To reduce the risk of side effects at the start of treatment, your doctor should start you on a low dose of Extavia and increase it gradually (see section 3, “How to use Extavia”).

The following side effects listing is based on reports from clinical trials with Extavia (List 1) and from side effects reported on the marketed product (List 2).

List 1: Very common side effects which have occurred in clinical trials with Extavia (may affect more than 1 in 10 people) and at a higher percentage than those observed with placebo. The list also includes side effects which occurred commonly (may affect up to 1 in 10 people) but were significantly associated with the treatment:

- infection, abscess
- reduced number of white blood cells, swollen lymph glands (lymphadenopathy)
- decrease in the amount of sugar in the blood (hypoglycaemia)
- depression, anxiety
- headache, dizziness, sleeplessness, migraine, numbness or tingling feeling (paraesthesia)
- eye inflammation (conjunctivitis), abnormal vision
- ear pain
- irregular, rapid beating or pulsation of the heart (palpitation)
- redness and/or facial flushing due to widening of blood vessels (vasodilation), increased blood pressure (hypertension)
- runny nose, cough, hoarseness due to infection of the upper respiratory tract, sinusitis, cough increased, shortness of breath (dyspnoea)
- diarrhoea, constipation, nausea, vomiting, abdominal pain
- rises in the blood levels of liver enzymes (will show up in blood tests)
- skin disorder, rash
- muscle stiffness (hypertonia), painful muscles (myalgia), muscular debility (myasthenia), back pain, pain in extremities such as fingers and toes
- holding urine (urinary retention), protein in the urine (will show up in urine tests), urinary frequency, inability to hold back urination (urinary incontinence), urinary urgency
- painful periods (dysmenorrhoea), menstrual disorder, heavy uterine bleeding (metrorrhagia) especially between menstrual periods, impotence
- injection site reaction (including redness, swelling, discolouration, inflammation, pain, allergic reaction, see section 2 “Warnings and precautions”), skin breakdown and tissue damage (necrosis) at injection site (see section 2 “Warnings and precautions”)
- flu-like symptoms, fever, pain, chest pain, accumulation of fluid in arm, leg or face (peripheral oedema), lack/loss of strength (asthenia), chills, sweating, general feeling of being unwell.

In addition, the following side effects have been identified during post-marketing experience.

List 2: Side effects reported on the marketed product (frequencies - where known - based on clinical trials):

► **Very common (may affect more than 1 in 10 people):**

- painful joints (arthralgia).

► **Common (may affect up to 1 in 10 people):**

- the number of red cells in the blood may fall (anaemia),
- the thyroid gland does not work properly (too little hormone is produced) (hypothyroidism),
- weight increase or decrease,
- confusion,
- abnormally rapid heartbeat (tachycardia),
- a reddish yellow pigment (bilirubin), which is produced by your liver, may rise (this will show up in blood tests),

- swollen and usually itchy patches of skin or mucous membranes (urticaria),
- itching (pruritus),
- loss of scalp hair (alopecia),
- menstrual disorders (menorrhagia).

► **Uncommon (may affect up to 1 in 100 people):**

- the number of platelets (which help the blood to clot) may fall (thrombocytopenia),
- a certain type of blood fats (triglycerides) may increase (will show up in blood tests), see section 2 “Warnings and precautions”,
- suicide attempts,
- mood swings,
- convulsion,
- a specific liver enzyme (gamma GT) which is produced by your liver, may rise (this will show up in blood tests),
- inflammation of the liver (hepatitis),
- skin discolouration.

► **Rare (may affect up to 1 in 1,000 people):**

- serious allergic (anaphylactic) reactions,
- the thyroid gland does not work properly (thyroid disorders), too much hormone is produced (hyperthyroidism),
- inflammation of the pancreas (pancreatitis), see section 2 “Warnings and precautions”,
- blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

Side effects derived only during post marketing:

- kidney problems including scarring (glomerulosclerosis) that may reduce your kidney function, (uncommon).
- severe loss of appetite leading to weight loss (anorexia), (rare).
- disease of the heart muscle (cardiomyopathy), (rare).
- sudden shortness of breath (bronchospasm), (rare).
- the liver does not work properly (hepatic injury [including hepatitis], hepatic failure), (rare).
- problems with your small blood vessels (capillaries) may develop when using medicines like Extavia (systemic capillary leak syndrome), (frequency unknown).
- rash, redness of the skin in the face, joint pain, fever, weakness and others caused by the medicine (drug-induced lupus erythematosus), frequency unknown.
- severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs (*pulmonary arterial hypertension*), (frequency unknown). Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Extavia.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Extavia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

Do not store above 25°C. Do not freeze.

After preparing the solution you should use it immediately. However, if you are not able to do so, it will remain usable for a period of 3 hours, if kept in a refrigerator (2°C - 8°C).

Do not use this medicine if you notice it contains particles or is discoloured.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Extavia contains

- **The active substance is** interferon beta-1b. Each vial contains 300 microgram (9.6 million IU) interferon beta-1b per vial. After reconstitution, each millilitre contains 250 microgram (8.0 million IU) interferon beta-1b.
- **The other ingredients are**
 - in the powder: mannitol and human albumin.
 - in the solvent: sodium chloride, water for injection.

The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex.

What Extavia looks like and contents of the pack

Extavia is a powder and solvent for solution for injection.

The powder is white to off-white in colour.

The Extavia powder is provided in a 3-millilitre vial.

The solvent is a clear/colourless solution.

The solvent for Extavia is provided in a 2.25 ml pre-filled syringe and contains 1.2 ml sodium chloride 5.4 mg/ml (0.54% w/v) solution for injection.

Extavia is available in pack sizes of:

- 5 vials of interferon beta-1b and 5 pre-filled syringes containing solvent.
- 14 vials of interferon beta-1b and 14 pre-filled syringes containing solvent.
- 15 vials of interferon beta-1b and 15 pre-filled syringes containing solvent.
- 14 vials of interferon beta-1b and 15 pre-filled syringes containing solvent.

- 3-month multipack containing 42 (3x14) vials of interferon beta-1b and 42 (3x14) pre-filled syringes containing solvent.
- 3-month multipack containing 45 (3x15) vials of interferon beta-1b and 45 (3x15) pre-filled syringes containing solvent.
- 3-month multipack containing 42 (3x14) vials of interferon beta-1b and 45 (3x15) pre-filled syringes containing solvent.

Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

Annex: SELF-INJECTION PROCEDURE

The following instructions and pictures explain how to prepare Extavia for injection and how to inject Extavia yourself. Please read the instructions carefully and follow them step by step. Your doctor or nurse will help you to learn the process of self-administration. Do not attempt to inject yourself until you are sure that you understand how to prepare the injection solution and give the injection to yourself.

PART I: STEP BY STEP INSTRUCTIONS

The instructions include the following main steps:

- A) General advice**
- B) Getting ready to inject**
- C) Reconstituting and drawing up the solution for injection, step by step**
- D) Making the injection manually (to make an injection with the ExtaviPro 30G auto-injector, refer to the instructions for use provided with the auto-injector)**

A) General advice

- **Getting off to a good start!**

You will find that within a few weeks your treatment will become a natural part of your routine. As you get started, you may find the following tips helpful:

- Set up a permanent storage area in a convenient location out of the sight and reach of children so that your Extavia and other supplies are always easy to find.
For details on storage conditions see section 5 of the leaflet, “How to store Extavia”.
- Try to give yourself the injection at the same time each day. This makes it easier to remember and easier to plan a block of time when you will not be interrupted.
Please refer to section 3 of the leaflet, “How to use Extavia”, for further details on how to use Extavia.
- Prepare each dose only when you are ready for an injection. After mixing Extavia, you should administer the injection immediately (if this medicine is not used immediately, see section 5 of the leaflet, “How to store Extavia”).

- **Important tips to keep in mind**

- Be consistent - use this medicine as described in section 3 of the leaflet, “How to use Extavia”. Always double-check your dosage.
- Keep your syringes and syringe disposal unit out of the sight and reach of children; lock the supplies away if possible.
- Never re-use syringes or needles.
- Always use a sterile (aseptic) technique as described in here.
- Always place the used syringes in the proper disposal unit.

B) Getting ready to inject

- **Choosing an injection site**

Before preparing your injection, decide where you are going to inject. You should inject this medicine into the fatty layer between the skin and muscle (that is, subcutaneously, about 8 mm to 12 mm under the skin). The best places for injections are where the skin is loose and soft, and away from joints, nerves and bones, for example the abdomen, arm, thigh or buttocks.

Important:

The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex. If you are allergic to latex, talk to your doctor before using Extavia.

Do not use any area where you can feel lumps, bumps, firm knots, pain or an area that is discoloured, indented, scabbed, or where the skin is broken. Talk to your doctor or nurse about these or any other unusual conditions you may find.

You should rotate the injection site at every injection. If some areas are too difficult for you to reach, you may need a family member or friend to help you with these injections. Follow the sequence described in the schedule at the end of the Annex (see Part II “Rotating injection sites”) and you will come back to your first injection site area after 8 injections (16 days). This will give each injection site a chance to fully recover before receiving another injection.

Please refer to the rotation schedule at the end of this Annex to learn how to choose an injection site. An example of a medication record is also included (see Annex Part III). This should give you an idea of how you can keep track of your injection sites and dates.

• **Medicine**

You will need the medicine:

- 1 Extavia vial (with powder for solution for injection)
- 1 pre-filled syringe of solvent for Extavia (sodium chloride solution)

To reconstitute and inject your medicine you will need to use an ExtaviPro 30G application kit (supplied separately to your medicine), which contains the following components and instructions on how to use them:

- Vial adapters for use when reconstituting your medicine
- 30-gauge needles for injecting your medicine
- Alcohol swabs

You will also need a disposal unit for used syringes and needles.

The 30-gauge needles provided with the application kit for the administration of this medicine can be used either for manual injection **OR** with an ExtaviPro 30G auto-injector.

For skin disinfection use an appropriate disinfectant recommended by your pharmacist.

C) Reconstituting and drawing up the solution for injection, step by step



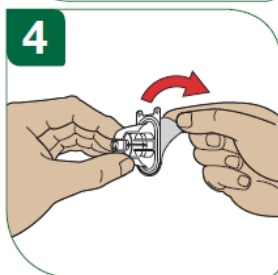
1 - Wash your hands thoroughly with soap and water before beginning this process.



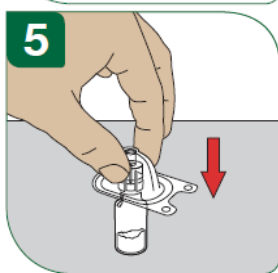
2 - Remove the flip off cap from the Extavia vial. It is best to use your thumb rather than your nail, as your nail could break. Put the vial on the table.



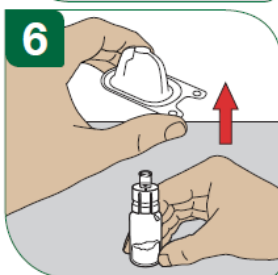
3 - Clean the top of the vial with an alcohol swab, moving the swab in one direction only. Leave the swab on top of the vial.



4 - Peel back and remove the cover from the vial adapter packaging. **Do not remove the vial adapter from its packaging.**



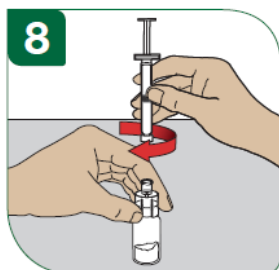
5 - Remove the swab from the top of the vial. Use the packaging to handle the vial adapter. Attach it to the vial by pushing down until the vial adapter penetrates and locks around the top of the vial.



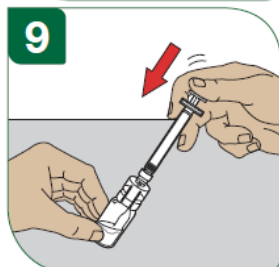
6 - Holding the edges securely, remove and discard the packaging **ensuring the vial adapter remains on the vial.**



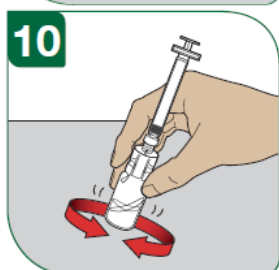
7 - Take out the pre-filled solvent syringe from its package. Snap off and discard the tip of the syringe. **Note:** Be careful not to touch the exposed end of the syringe. Do not push the plunger.



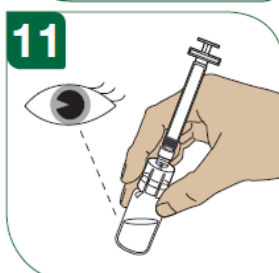
8 - Holding the vial and adapter securely, screw the syringe fully onto the vial adapter.
This forms the syringe-vial assembly.



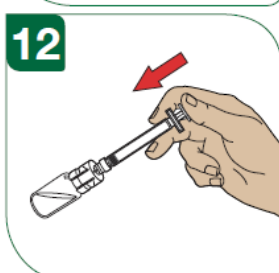
9 - Hold the syringe-vial assembly at a slight angle. Push the plunger down slowly so that the liquid runs down the inside of the vial.
Transfer **all** the solvent to the vial.
Note: Do not shake the vial as this may cause excessive foaming.



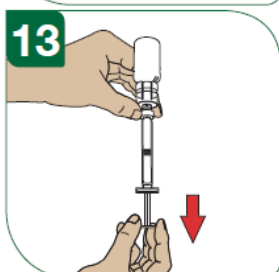
10 - Hold the vial between your thumb and fingers. Swirl the syringe-vial assembly gently until the powder is completely dissolved.
Note: Do not shake the vial.



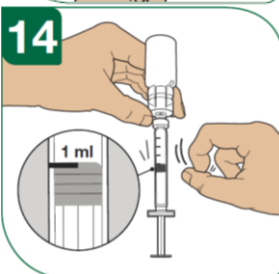
11 - Examine the solution carefully. It should be clear and contain no particles.
Note: If the solution is discoloured or contains particles, discard it and start again with a new syringe and vial from your package.
If excessive foaming is present – which can happen if the vial is shaken or swirled too vigorously – let the vial sit undisturbed until the foam settles.



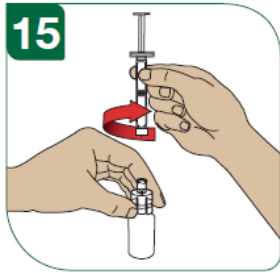
12 - Ensure the plunger stays fully pushed in before proceeding to the next step, as it may have moved.



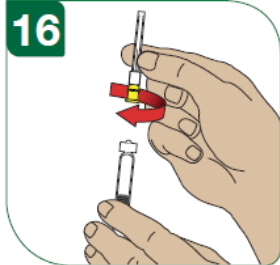
13 - Turn the syringe-vial-assembly so that the vial is at the top. Slowly pull the plunger back to draw all of the solution into the syringe.



14 - Remove any excess air bubbles by gently tapping the syringe. Push the plunger to the **1 ml** mark (or to the volume prescribed by your doctor).
Note: It may be necessary to adjust the plunger position back and forth a few times to ensure the excess air bubbles are gone and there is 1 ml of solution in the syringe.



15 - Unscrew the syringe, leaving the vial adapter on the vial. Dispose of the vial and the remaining unused portion of the solution into the disposal unit.



16 - Take the needle out of its wrapping and screw it firmly onto the top of the syringe.



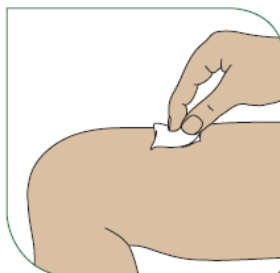
17 - Leave the needle cap on. You are now ready to manually inject yourself or to use the ExtaviPro 30G auto-injector for the administration of Extavia.

Storage after reconstitution

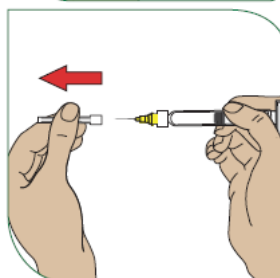
If, for some reason, you are not able to inject Extavia immediately, you can refrigerate the reconstituted solution for up to 3 hours before using it. Do not freeze the solution, and do not wait longer than 3 hours to inject it. **If more than 3 hours pass, discard the medicine and prepare a new injection.** When you use the solution, warm it up by holding the syringe or vial in your hands before injecting to avoid pain.

D) Making the injection manually (to make an injection with the ExtaviPro 30G auto-injector, refer to the instructions for use provided with the auto-injector)

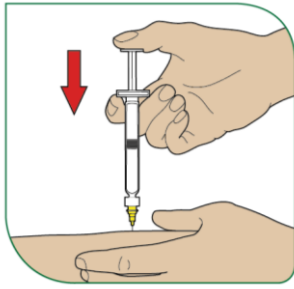
1 - Choose a site for the injection (refer to the section “Choosing an injection site” and the diagrams at the end of this leaflet) and make a note of it in your medication record.



2 - Use an alcohol swab to clean the skin at the injection site. Let the skin air-dry. Throw the swab away.



3 - Remove the cap from the needle by pulling and not twisting it.



4 - Where possible gently pinch the skin together around the disinfected injection site (to raise it up a little).

5 - Holding the syringe like a pencil or a dart, push the needle straight into the skin at a 90° angle with a quick, firm motion.

6 - Inject the medicine (by pushing the plunger slowly and steadily all the way in until the syringe is empty).

7 - Discard the syringe in the disposal unit.

PART II: ROTATING INJECTION SITES

You need to choose a new site for each injection to allow the area time to recover and help prevent infection. Advice on which areas to choose is given in the first part of this Annex. It is a good idea to know where you plan to inject before you prepare your syringe. The schedule shown in the diagram below will help you to vary the sites appropriately. For example, give the first injection into the right side of the abdomen, choose the left side for the second injection, then move to the right thigh for the third, and so on through the diagram until all suitable areas of the body have been used. Keep a record of where and when you last gave yourself an injection. One way to do that is to note the injection site on the enclosed medication record card.

By following this schedule, you will come back to your first area (e.g. the right side of the abdomen) after 8 injections (16 days). This is called a Rotation Cycle. On our example schedule each area is split again into 6 injection sites (which adds up to 48 injection sites altogether), left and right: upper, middle and lower part of each area. If you come back to an area after one Rotation Cycle choose the most distant injection site within this area. If an area becomes sore, talk to your doctor or nurse about choosing other injection sites.

Rotation schedule

To help you rotate the injection sites appropriately, we recommend that you keep a record of the date and location of your injection. You can use the following rotation schedule.

Work through each rotation cycle in turn. Each cycle will be 8 injections (16 days), given in area 1 through to area 8 in turn. By following this sequence, you will give each area a chance to recover before receiving another injection.

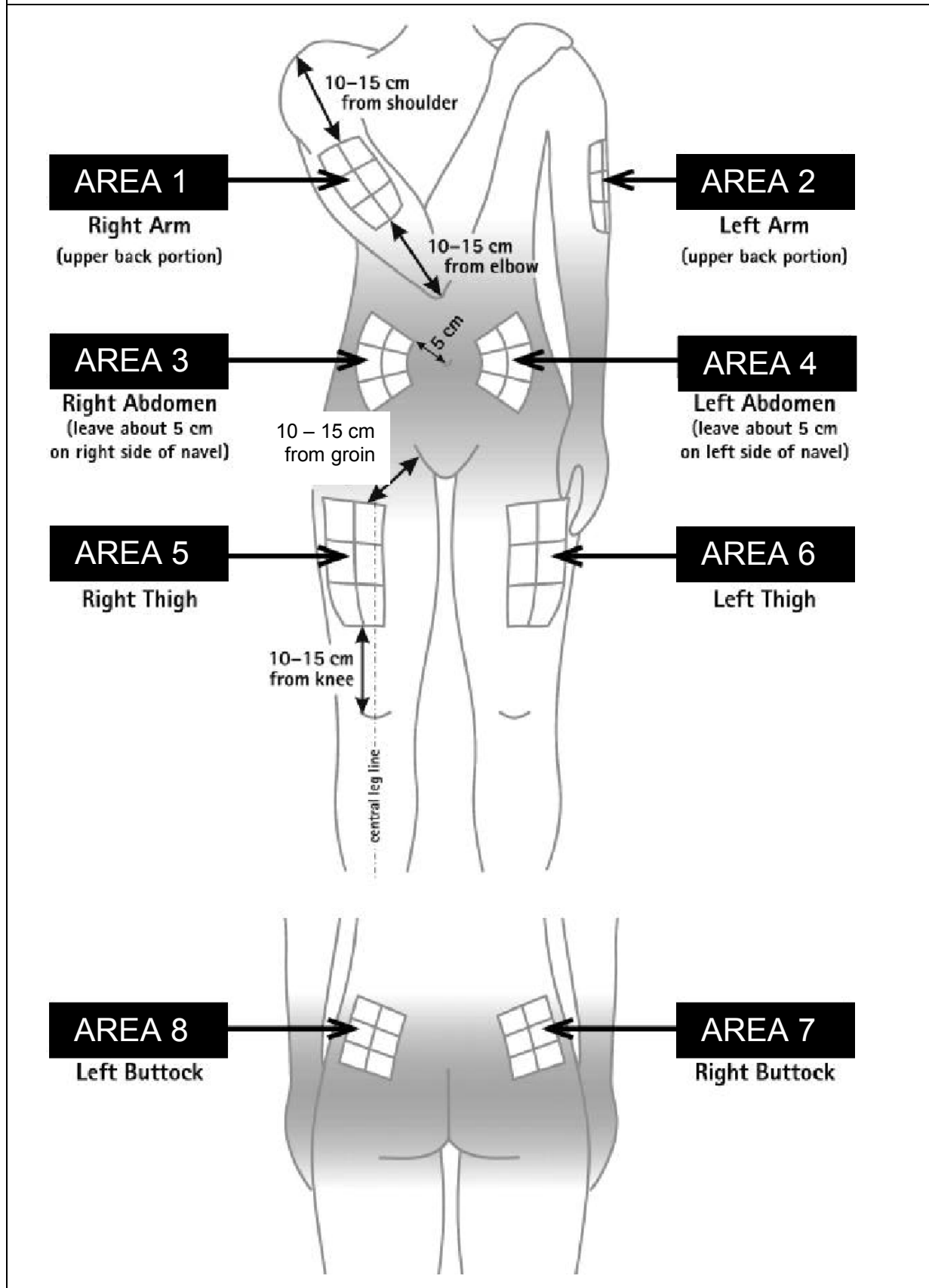
- Rotation Cycle 1:** Upper left section of each area
- Rotation Cycle 2:** Lower right section of each area
- Rotation Cycle 3:** Middle left section of each area
- Rotation Cycle 4:** Upper right section of each area
- Rotation Cycle 5:** Lower left section of each area
- Rotation Cycle 6:** Middle right section of each area

PART III: EXTAVIA Medication record

Instructions for keeping track of your injection sites and dates

- Start with your first injection (or your last injection if you are not a new Extavia user).
- Select an injection site. If you have already been using Extavia start with the area that has not been used during the last rotation cycle (i.e. the past 16 days).
- After your injection, fill in the used injection site and date in the table in your injection record (see the example: Keeping track of your injection sites and dates).

ROTATION SCHEDULE:



EXAMPLE OF A MEDICATION RECORD:

Keeping track of your injection sites and dates

Right Arm

04/12	
	20/12

Right Abdomen

08/12	

Right Thigh

12/12	

Left Arm

06/12	

Left Abdomen

10/12	

Left Thigh

14/12	

Left Buttock

18/12	

Right Buttock

16/12	

Measurement guidelines shown in the diagram:

- 10-15 cm from shoulder
- 10-15 cm from elbow
- 5 cm
- 10-15 cm from groin
- 10-15 cm from knee
- central leg line