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 adrenocorticotropic 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.
- 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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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) and haemolytic anaemia (HA)

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. 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. Additionally, cases of HA not associated with TMA, including immune HA, have been reported with interferon beta products. Life-threatening and fatal cases have been reported. Cases of TMA and/or HA have been reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. If TMA and/or HA is diagnosed, and a relationship to Extavia is suspected, prompt treatment is required (in case of TMA 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.g

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

Hypersensitivity reactions

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 reactions

Injection site reactions, including injection site infection and injection site necrosis have been reported in patients using Extavia (see section 4.8). Injection site necrosis 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 infection and 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 haematopoetic system.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data (more than 1000 pregnancy outcomes) from interferon beta registries, national registries and post-marketing experience indicates no increased risk of major congenital anomalies, after pre-conception exposure or exposure during the first trimester of pregnancy.

However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment was likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimesters is very limited.

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated by means of the currently available data, but the data suggest no increased risk so far.

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

Breast-feeding

Limited information available on the transfer of interferon beta-1b into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1b excreted in human milk are negligible. No harmful effects on the breast-fed newborn/infant are anticipated.

Extavia can be used during breast-feeding.

Fertility

No investigations on fertility have been conducted (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, infection, necrosis and non-specific reactions were significantly associated with 250 microgram (8.0 million IU) Extavia treatment.

The most serious adverse reactions reported include thrombotic microangiopathy (TMA) and haemolytic anaemia (HA).

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

The following adverse event listings are based on reports from clinical trials and from post-marketing surveillance *(very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥1/1000 to <1/100, rare ≥1/10000 to <1/1000, very rare <1/10000)* of Extavia use. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Table 1 Adverse drug reactions (ADRs) based on reports from clinical trials and identified during post-marketing surveillance (frequencies - where known - calculated based on pooled clinical trial data)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)	Frequency not known
Blood and lymphatic system disorders	Lymphocyte count decreased (<1 500/mm^3)[e], White blood cell count decreased (<3 000/mm^3)[e], Absolute neutrophil count decreased (<1 500/mm^3)[e]	Lymphadenopathy, Anaemia	Thrombocytopenia	Thrombotic microangiopathy[d] including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome[b]	Haemolytic anaemia[d]
Immune system disorders				Anaphylactic reactions	Capillary leak syndrome in pre-existing monoclonal gammopathy[a]
Endocrine disorders		Hypothyroidism		Hyperthyroidism, Thyroid disorders	
Metabolism and nutrition disorders		Weight increased, Weight decreased	Blood triglycerides increased	Anorexia[a]	
Psychiatric disorders		Confusional state	Suicide attempt (see also section 4.4), Emotional lability		Depression, Anxiety
Nervous system disorders	Headache, Insomnia		Convulsion		Dizziness
Cardiac disorders		Tachycardia		Cardiomyopathy[a]	Palpitation
Vascular disorders		Hypertension			Vasodilatation
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm[a]	Pulmonary arterial hypertension[c]
Gastrointestinal disorders	Abdominal pain			Pancreatitis	Nausea, Vomiting, Diarrhoea
Hepatobiliary disorders	Alanine aminotransferase increased (ALAT >5 times baseline)[e]	Aspartate aminotransferase increased (ASAT >5 times baseline)[e], Blood bilirubin increased	Gamma-glutamyl-transferase increased, Hepatitis	Hepatic injury, Hepatic failure[a]	
Skin and subcutaneous tissue disorders	Rash, Skin disorder	Urticaria, Pruritus, Alopecia	Skin discolouration		
Musculoskeletal and connective tissue disorders	Myalgia, Hypertonia, Arthralgia				Drug-induced lupus erythematosus

Renal and urinary disorders	Urinary urgency		Nephrotic syndrome, Glomerulosclerosis (see section 4.4)[a., b]		
Reproductive system and breast disorders		Menorrhagia, Impotence, Metrorrhagia			Menstrual disorder
General disorders and administration site conditions	Injection site reaction (various kinds[f]), Flu-like symptoms (complex[g]), Pain, Fever, Chills, Peripheral oedema, Asthenia	Injection site necrosis, Chest pain, Malaise			Sweating

[a] ADRs derived only during post-marketing.
[b] Class label for interferon beta products (see section 4.4).
[c] Class label for interferon products, see below "Pulmonary arterial hypertension".
[d] Life-threatening and/or fatal cases have been reported.
[e] Laboratory abnormality
[f] 'Injection site reaction (various kinds)' comprises all adverse events occurring at the injection site (except injection site necrosis), e.g. the following terms: injection site atrophy, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site infection, injection site inflammation, injection site mass, injection site pain and injection site reaction.
[g] 'Flu-like symptom complex' denotes flu syndrome and/or a combination of at least two adverse events from fever, chills, myalgia, malaise, sweating.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 scleroiss (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 $ml \cdot min^{-1} \cdot kg^{-1}$ 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°C - 8°C.

6.4 Special precautions for storage

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

For storage conditions after reconstitution of the 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 overseal 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

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 Pharmaceuticals UK Limited
2nd Floor, The WestWorks Building, White City Place
195 Wood Lane
London
W12 7FQ

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00101/1072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

24/08/2023