SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Brabio 20 mg/ml solution for injection, pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 20 mg glatiramer acetate*, equivalent to 18 mg of glatiramer base per pre-filled syringe.

* The average molecular weight of glatiramer acetate is in the range of 5,000-9,000 daltons. Due to its compositional complexity, no specified polypeptide can be fully characterized in terms of amino acid sequence, although the final glatiramer acetate composition is not entirely random.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection, Pre-filled Syringe

Clear, colourless to slightly yellow/brownish solution free from visible particles.
The solution for injection has a pH of 5.5 - 7.0 and an osmolarity of about 265 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glatiramer acetate is indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see Section 5.1 for important information on the population for which efficacy has been established).

Glatiramer acetate is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration

Posology
The recommended dosage in adults is 20 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection once daily.

At the present time, it is not known for how long the patient should be treated.

A decision concerning long term treatment should be made on an individual basis by the treating physician.

Paediatric population
Children and adolescents: No prospective, randomised, controlled clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, some published data suggest that the safety profile in adolescents from 12 to 18 years of age receiving glatiramer acetate subcutaneously every day is similar to that seen in adults.

There is not enough information available on the use of glatiramer acetate in children below 12 years of age to make any recommendation for its use. Therefore, glatiramer acetate should not be used in this population.

Special populations
Elderly patients
Glatiramer acetate has not been specifically studied in the elderly.

Patients with renal impairment
Glatiramer acetate has not been specifically studied in patients with renal impairment (see section 4.4).

Method of administration
Patients should be instructed in self-injection techniques and should be supervised by a health-care professional the first time they self-inject and for 30 minutes after.

A different site for injection should be chosen every day, so this will reduce the chances of any irritation or pain at the site of the injection. Sites for self-injection include the abdomen, arms, hips and thighs.

4.3 Contraindications

Glatiramer acetate is contraindicated under the following conditions:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Glatiramer acetate should only be administered subcutaneously. Glatiramer acetate should not be administered by intravenous or intramuscular routes.

The initiation of glatiramer acetate treatment should be supervised by a neurologist or a physician experienced in the treatment of MS.

The treating physician should explain to the patient that a reaction associated with at least one of the following symptoms may occur within minutes of a glatiramer acetate injection: vasodilatation (flushing), chest pain, dyspnoea, palpitations or tachycardia. The majority of these symptoms is short-lived and resolves spontaneously without any sequelae. Should a severe adverse event occur, the patient must immediately stop glatiramer acetate treatment and contact his/her physician or any emergency doctor. Symptomatic treatment may be instituted at the discretion of the physician.

There is no evidence to suggest that any particular patient groups are at special risk from these reactions. Nevertheless, caution should be exercised when administering glatiramer acetate to patients with pre-existing cardiac disorders. These patients should be followed up regularly during treatment.

Convulsions and/or anaphylactoid or allergic reactions have been reported rarely.

Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis or urticaria) may rarely occur. If reactions are severe, appropriate treatment should be instituted and glatiramer acetate should be discontinued.

Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with glatiramer acetate. Maximal levels were attained after average treatment duration of 3-4 months and, thereafter, declined and stabilised at a level slightly higher than baseline.

There is no evidence to suggest that these glatiramer acetate-reactive antibodies are neutralising or that their formation is likely to affect the clinical efficacy of glatiramer acetate.

In patients with renal impairment, renal function should be monitored while they are treated with glatiramer acetate. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction between glatiramer acetate and other medicinal products have not been formally evaluated.

Observations from existing clinical trials and post-marketing experience do not suggest any significant interactions of glatiramer acetate with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days.

In vitro work suggests that glatiramer acetate in blood is highly bound to plasma proteins but that it is not displaced by, and does not itself displace, phenytoin or carbamazepine. Nevertheless, as glatiramer acetate has, theoretically, the potential to affect the distribution of protein-bound substances, concomitant use of such medicinal products should be monitored carefully.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have not shown reproductive toxicity (see section 5.3). Current data on pregnant women indicate no malformative or feto/neonatal toxicity of glatiramer acetate. To date, no relevant epidemiological data are available. As a precautionary measure, it is preferable to avoid the use of glatiramer acetate during pregnancy unless the benefit to the mother outweighs the risk to the foetus.

Breast feeding
Data regarding excretion of glatiramer acetate, its metabolites or antibodies in human milk are unavailable. Caution should be exercised when glatiramer acetate is administered to a nursing mother. The relative risk and benefit to the mother and child should be taken into consideration.

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.

4.8 Undesirable effects

In all clinical trials, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving glatiramer acetate. In controlled studies, the proportion of patients reporting these reactions, at least once, was higher following treatment with glatiramer acetate (70%) than placebo injections (37%). The most commonly reported injection-site reactions, in clinical trials and in post-marketing experience, were erythema, pain, mass, pruritus, oedema, inflammation and hypersensitivity and rare occurrences of lipoatrophy and skin necrosis.

A reaction, associated with at least one or more of the following symptoms, has been described as the Immediate Post-Injection Reaction: vasodilatation (flushing), chest pain, dyspnoea, palpitation or tachycardia. This reaction may occur within minutes of a glatiramer acetate injection. At least one component of this

Immediate Post-Injection Reaction was reported at least once by 31% of patients receiving glatiramer acetate compared to 13% of patients receiving placebo.

All adverse reactions, which were more frequently reported in glatiramer acetate vs. placebo-treated patients, are presented in the table below. This data was derived from four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with glatiramer acetate and 509 patients treated with placebo for up to 36 months. Three trials in relapsing-remitting MS (RRMS) included a total of 269 patients treated with glatiramer acetate and 271 patients treated with placebo for up to 35 months. The fourth trial in patients who have experienced a first clinical episode and were determined to be at high risk of developing clinically definite MS included 243 patients treated with glatiramer acetate and 238 patients treated with placebo for up to 36 months.

System Organ Class (SOC)	**Very Common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Infections And Infestations	Infection, Influenza	Bronchitis, Gastroenteritis, Herpes Simplex, Otitis Media, Rhinitis, Tooth Abscess, Vaginal Candidiasis*	Abscess, Cellulitis, Furuncle, Herpes Zoster, Pyelonephritis
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)		Benign Neoplasm Of Skin, Neoplasm	Skin Cancer
Blood And Lymphatic System Disorders		Lymphadenopathy*	Leukocytosis, Leukopenia, Splenomegaly, Thrombocytopenia, Lymphocyte Morphology Abnormal
Immune System Disorders		Hypersensitivity	
Endocrine Disorders			Goitre, Hyperthyroidism
Metabolism And Nutrition Disorders		Anorexia, Weight Increased*	Alcohol Intolerance, Gout, Hyperlipidaemia, Blood Sodium Increased, Serum Ferritin Decreased
Psychiatric Disorders	Anxiety*, Depression	Nervousness	Abnormal Dreams, Confusional State, Euphoric Mood, Hallucination, Hostility, Mania, Personality Disorder, Suicide Attempt
Nervous System Disorders	Headache	Dysgeusia, Hypertonia, Migraine, Speech Disorder, Syncope, Tremor*	Carpal Tunnel Syndrome, Cognitive Disorder, Convulsion, Dysgraphia, Dyslexia, Dystonia, Motor Dysfunction, Myoclonus,

			Neuritis, Neuromuscular Blockade, Nystagmus, Paralysis, Peroneal Nerve Palsy, Stupor, Visual Field Defect
Eye Disorders		Diplopia, Eye Disorder*	Cataract, Corneal Lesion, Dry Eye, Eye Haemorrhage, Eyelid Ptosis, Mydriasis, Optic Atrophy
Ear And Labyrinth Disorders		Ear Disorder	
Cardiac Disorders		Palpitations*, Tachycardia*	Extrasystoles, Sinus Bradycardia, Tachycardia Paroxysmal
Vascular Disorders	Vasodilatation*		Varicose Vein
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea*	Cough, Rhinitis Seasonal	Apnoea, Epistaxis, Hyperventilation, Laryngospasm, Lung Disorder, Choking Sensation
Gastrointestinal Disorders	Nausea*	Anorectal Disorder, Constipation, Dental Caries, Dyspepsia, Dysphagia, Faecal Incontinence, Vomiting*	Colitis, Colonic Polyp, Enterocolitis, Eructation, Oesophageal Ulcer, Periodontitis, Rectal Haemorrhage, Salivary Gland Enlargement
Hepatobiliary Disorders		Liver Function Test Abnormal	Cholelithiasis, Hepatomegaly
Skin And Subcutaneous Tissue Disorders	Rash*	Ecchymosis, Hyperhidrosis, Pruritus, Skin Disorder*, Urticaria	Angioedema, Dermatitis Contact, Erythema Nodosum, Skin Nodule
Musculoskeletal And Connective Tissue Disorders	Arthralgia, Back Pain*	Neck Pain	Arthritis, Bursitis, Flank Pain, Muscle Atrophy, Osteoarthritis
Renal And Urinary Disorders		Micturition Urgency, Pollakiuria, Urinary Retention	Haematuria, Nephrolithiasis, Urinary Tract Disorder, Urine Abnormality
Pregnancy, Puerperium And Perinatal Conditions			Abortion
Reproductive System And Breast Disorders			Breast Engorgement, Erectile Dysfunction, Pelvic Prolapse, Priapism, Prostatic Disorder, Smear Cervix Abnormal,

			Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder
General Disorders And Administration Site Conditions	Asthenia, Chest Pain*, Injection Site Reactions*§, Pain*	Chills*, Face Oedema*, Injection Site Atrophy♣, Local Reaction*, Oedema Peripheral, Oedema, Pyrexia	Cyst, Hangover, Hypothermia, Immediate Post-Injection Reaction, Inflammation, Injection Site Necrosis, Mucous Membrane Disorder
Injury, Poisoning And Procedural Complications			Post Vaccination Syndrome

* More than 2% (> 2/100) higher incidence in the glatiramer acetate treatment group than in the placebo group. Adverse reaction without the * symbol represents a difference of less than or equal to 2%.

§ The term 'Injection site reactions' (various kinds) comprises all adverse events occurring at the injection site excluding injection site atrophy and injection site necrosis, which are presented separately within the table.

♣ Includes terms which relate to localised lipoatrophy at the injection sites**.**

In the fourth trial noted above, an open-label treatment phase followed the placebo-controlled period (see section 5.1). No change in the known risk profile of glatiramer acetate was observed during the open-label follow-up period of up to 5 years.

The following adverse reaction reports were collected from MS patients treated with glatiramer acetate in uncontrolled clinical trials and from post-marketing experience with glatiramer acetate: hypersensitivity reactions (including rare occurrence of anaphylaxis, > 1/10000, < 1/1000.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

A few cases of overdose with glatiramer acetate (up to 300 mg glatiramer acetate) have been reported. These cases were not associated with any adverse reactions other than those mentioned in section 4.8.

In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunostimulants

ATC code: L03AX13

Mechanism of action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunisation against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in MS patients suggest that upon its administration, glatiramer acetate-specific suppressor T cells are induced and activated in the periphery.

Clinical efficacy and safety

RRMS:

A total of 269 patients have been treated with glatiramer acetate in three controlled trials. The first was a two-year study involving 50 patients (glatiramer acetate n=25, placebo n=25) who were diagnosed with relapsing-remitting MS by the then-applicable standard criteria, and who had at least two attacks of neurological dysfunction (exacerbations) during the preceding two years. The second study applied the same inclusion criteria and included 251 patients treated for up to 35 months (glatiramer acetate n=125, placebo n=126). The third study was a nine-month study involving 239 patients (glatiramer acetate n=119, placebo n=120) where inclusion criteria were similar to those in the first and second studies with the additional criterion that patients had to have at least one gadolinium-enhancing lesion on the screening MRI.

In clinical trials in MS patients receiving glatiramer acetate, a significant reduction in the number of relapses, compared with placebo, was seen.

In the largest controlled study, the relapse rate was reduced by 32% from 1.98 under placebo to 1.34 under glatiramer acetate.

Exposure data are available for up to twelve years in 103 patients treated with glatiramer acetate.

Glatiramer acetate has also demonstrated beneficial effects over placebo on MRI parameters relevant to relapsing-remitting MS.

Glatiramer acetate had, however, no beneficial effect on progression of disability in relapsing-remitting MS patients.

There is no evidence that glatiramer acetate treatment has an effect on relapse duration or severity.

There is currently no evidence for the use of glatiramer acetate in patients with primary or secondary progressive disease.

Single Clinical Event Suggestive of MS:

One placebo-controlled study involving 481 patients (glatiramer acetate n=243, placebo n=238) was performed in patients with a well-defined, single, unifocal neurological manifestation and MRI features highly suggestive of MS (at least two cerebral lesions on the T2-weighted MRI above 6 mm diameter). Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.
The placebo-controlled period was followed by an open label treatment: Patients who either presented with MS symptoms or were asymptomatic for three years, whichever came first, were assigned to active drug treatment in an open-label phase for an additional period of two years, not exceeding a maximal total treatment duration of 5 years. Of the 243 patients initially randomized to glatiramer acetate, 198 continued glatiramer acetate treatment in the open-label phase. Of the 238 patients initially randomized to placebo, 211 switched to glatiramer acetate treatment in the open-label phase.

During the placebo-controlled period of up to three years, glatiramer acetate delayed the progression from the first clinical event to clinically definite multiple sclerosis (CDMS) according to Poser criteria in a statistically

significant and clinically meaningful manner, corresponding to a risk reduction of 45% (Hazard Ratio = 0.55; 95% CI [0.40; 0.77], p-value=0.0005). The proportion of patients who converted to CDMS was 43% for the placebo group and 25% in the glatiramer acetate group.

The favourable effect of treatment with glatiramer acetate over placebo was also demonstrated in two secondary MRI endpoints, i.e. number of new T2 lesions and T2 lesion volume.

Post-hoc subgroup analyses were performed in patients with various baseline characteristics to identify a population at high risk to develop the second attack. For subjects with baseline MRI with at least one T1 Gd-enhancing lesion and 9 or more T2 lesions, conversion to CDMS was evident for 50% of the placebo subjects vs. 28% of the glatiramer acetate subjects in 2.4 years. For subjects with 9 or more T2 lesions at baseline, conversion to CDMS was evident for 45% of the placebo subjects vs. 26% on glatiramer acetate in 2.4 years. However, the impact of early treatment with glatiramer acetate on the long term evolution of the disease is unknown even in these high-risk subgroups as the study was mainly designed to assess the time to the second event. In any case, treatment should only be considered for patients classified at high risk.

The effect shown in the placebo-controlled phase was sustained in the long-term follow-up period of up to 5 years. The time progression from the first clinical event to CDMS was prolonged with earlier glatiramer acetate treatment as compared to delayed treatment, reflecting a 41% risk reduction with earlier versus later treatment (Hazard Ratio = 0.59; 95% CI [0.44; 0.80], p-value=0.0005). The proportion of subjects in the Delayed Start group who progressed was higher (49.6%) compared to those in the Early Start group (32.9%).

A consistent effect in favour of early treatment over delayed treatment across time was shown for the annualized number of lesions over the entire study period in new T1 Gd-enhancing lesions (reduced by 54%; $p<0.0001$), new T2 lesions (reduced by 42%; $p<0.0001$) and new T1 hypointense lesions (reduced by 52%; $p<0.0001$). An effect in reductions in favor of early versus delayed treatment was observed for the total number of new T1 Gd-enhancing lesions (reduced by 46%; $p=0.001$), T1 Gd-enhancing lesions volume (a mean difference of -0.06 ml; $p<0.001$), as well as the total number of new T1 hypointense lesions (reduced by 46%; $p<0.001$) measured over the entire study period.

No appreciable differences between the Early Start and Delayed Start cohorts were observed for either hypointense T1 lesions volume or brain atrophy over 5 years. However, analysis of brain atrophy at last observed value (adjusted to treatment exposure) showed a reduction in favour of early treatment with glatiramer acetate (the mean difference of percent change in brain volume was 0.28%; $p=0.0209$).

Brabio is a hybrid medicinal product. Detailed information is available on the MRI product index; http://mri.medagencies.org/Human/.

5.2 Pharmacokinetic properties

Pharmacokinetic studies in patients have not been performed. *In vitro* data and limited data from healthy volunteers indicate that with subcutaneous administration of glatiramer acetate, the active substance is readily absorbed and that a large part of the dose is rapidly degraded to smaller fragments already in subcutaneous tissue.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity or carcinogenicity, beyond the information included in other sections of the SmPC.
Due to the lack of pharmacokinetic data in humans, margins of exposure between humans and animals cannot be established.

Immune complex deposition in the glomeruli of the kidney was reported in a small number of rats and monkeys treated for at least 6 months. In a 2 years rat study, no indication of immune complex deposition in the glomeruli of the kidney was seen.

Anaphylaxis after administration to sensitised animals (guinea pigs or mice) was reported. The relevance of these data for humans is unknown.

Toxicity at the injection site was a common finding after repeated administration in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Store in a refrigerator (2°C to 8°C).
Do not freeze.

If the pre-filled syringes cannot be stored in a refrigerator, they can be stored between 15°C and 25°C, once, for up to one month.
After this one month period, if the glatiramer acetate pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2°C to 8°C).

6.5 Nature and contents of container

The container closure system consists of a single use glass syringe barrel with an integrated needle. A rubber stopper (bromobutyl, type 1) is fitted in the barrel for closure and acts as a piston during injection. A driving rod is screwed in the rubber stopper. The needle is covered with a needle shield.

The volume of solution in the syringe is 1.0 ml.

7 pre-filled syringes
28 pre-filled syringes
30 pre-filled syringes
90 (3x30) pre-filled syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd. T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PA0577/211/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th November 2016

10 DATE OF REVISION OF THE TEXT

February 2019