Clinical perspectives on MAVENCLAD® (cladribine 10mg tablets), for highly active relapsing multiple sclerosis (MS), and real-world experiences from members of the multidisciplinary MS team

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Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS). Consequential pathological changes such as inflammation, demyelination, and variable degrees of axonal loss and gliosis result in a multitude of distressing symptoms for people with MS, and have a significant impact on their quality of life.[1]

Advances in our understanding of the immunopathophysiology of the disease, and the pivotal role of both B lymphocytes and T cells, have led to significant developments in the treatment of MS. [1-4] As the treatment options for relapsing-remitting MS (RRMS) evolve, patients and clinicians alike are now able to make treatment decisions based on modes of administration as well as efficacy and safety.

One such advance is MAVENCLAD®, a synthetic small molecule which selectively targets B and T lymphocytes resulting in their transient reduction.[4]

MAVENCLAD® has been available in Europe for the treatment of adult patients with highly active relapsing MS, as defined by clinical or imaging features, since September 2017.[4] It has been suggested that MAVENCLAD® is classified as immune reconstitution therapy (IRT), because of its impact on key cellular components of the immune system.[1,4,9]

This MS-DIGEST paper summarises the key data from the MAVENCLAD® clinical development programme.[10-12] In a separate commentary, clinical experts from the multidisciplinary MS team share their thoughts on the clinical data and provide insights into real-world experiences of introducing MAVENCLAD® into clinical practice.

MAVENCLAD® clinical development programme

CLARITY is a 96-week, phase III, double-blind, placebo-controlled, multicentre trial, which aimed to investigate the efficacy and safety of MAVENCLAD® as an annual short-course oral therapy, in patients with RRMS (N=1326).[10]

Patients were randomly assigned to receive a cumulative dose of either 3.5mg/kg MAVENCLAD® or an unlicensed dose of 5.25mg/kg cladribine tablets or matched placebo. Each treatment course consisted of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consisted of 4 or 5 days on which the patient received one or two tablets as a single daily dose, depending on body weight [Figure 2].[10,11,12] Primary endpoint for the CLARITY study was rate of relapse over 2 years.[10]

Overall, 1184 patients (89.3%) completed the 96-week CLARITY study. This study demonstrated that MAVENCLAD® delivered consistent clinical and radiologic efficacy across the overall study population.[10]

Clinical efficacy

- A significant reduction in annualised relapse rates (ARR) over 2 years with MAVENCLAD®, versus placebo [0.14 versus 0.33, respectively], p<0.001.[10]
- Time to first relapse was 13.3 months (HR 0.46) in the MAVENCLAD® 3.5mg/kg treatment group, compared with placebo, 4.6 months (p< 0.001).[1]

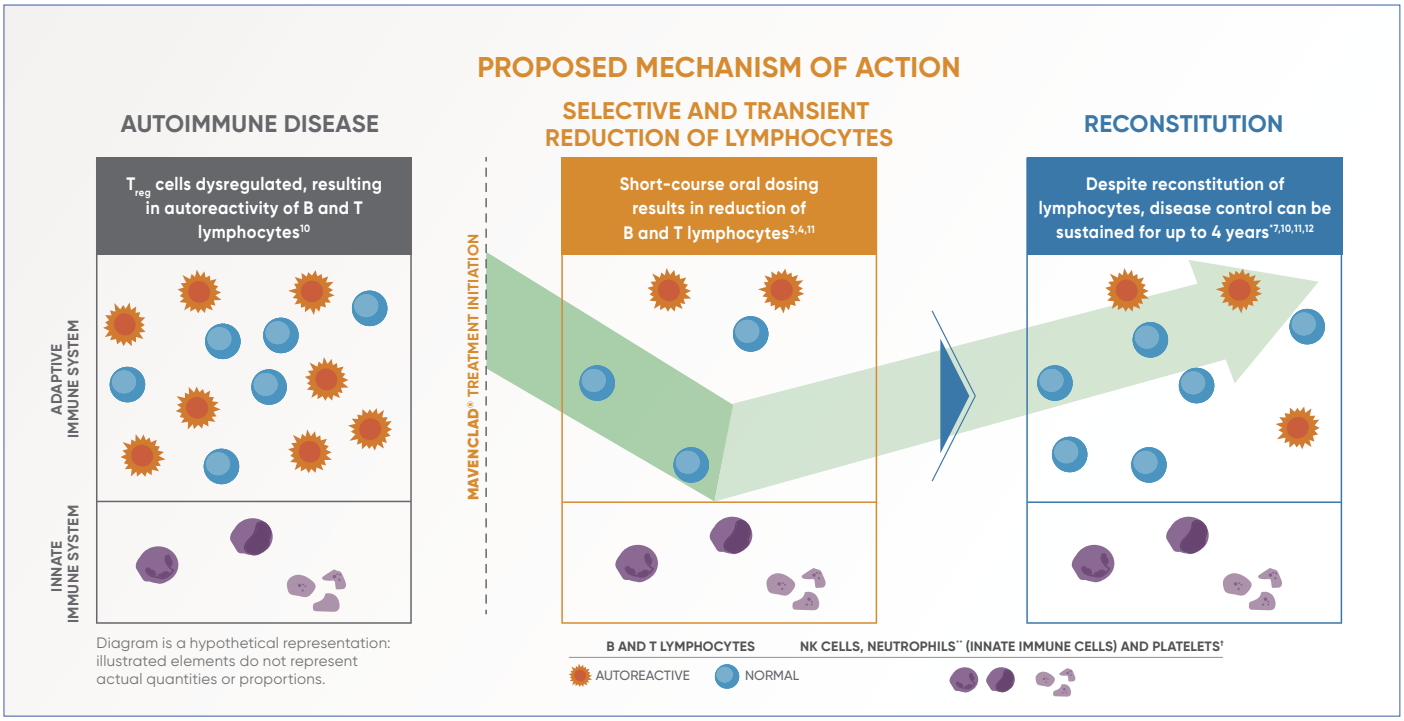


Figure 1. Schematic hypothetical representation of the mechanism of action by which MAVENCLAD® exerts its therapeutic effect in MS: illustrated elements do not represent actual quantities or proportions. [Adapted from 1,2,4–11]

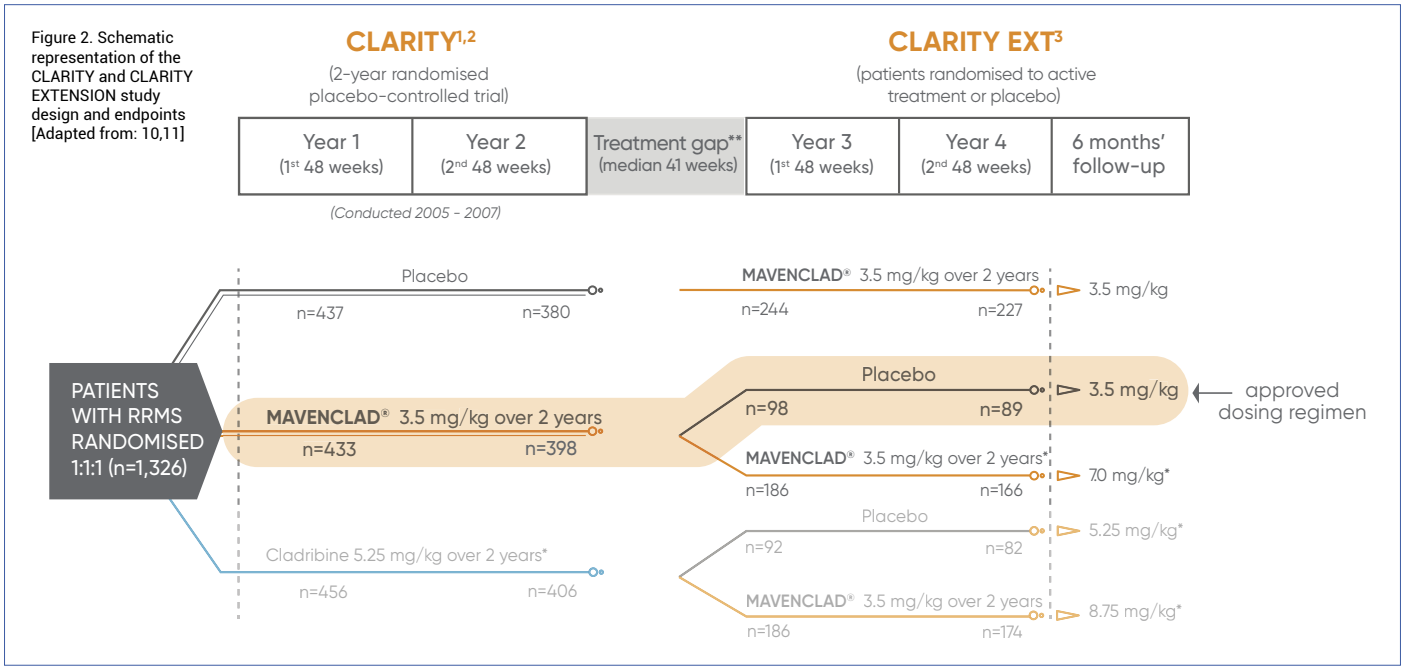


Figure 2. Schematic representation of the CLARITY and CLARITY EXTENSION study design and endpoints [Adapted from: 10,11]

- More patients were relapse-free for 2 years with MAVENCLAD®, versus placebo [79.7% versus 60.9%, respectively p<0.001].[10]
- MAVENCLAD® treated patients had a 47% risk reduction of 6-month-confirmed Expanded Disability Status Scale (EDSS) compared to placebo, p=0.0016, MAVENCLAD® [n=433] vs. placebo [n=437]. Time to 6-month EDSS progression: HR 0.53 (0.36 - 0.79)
- [post hoc analysis].[13]
- MAVENCLAD® treatment showed a significant relative reduction of 86% in T1 Gd-enhancing lesions (0.12), versus placebo (0.91) and a relative reduction of 73% in active T2 lesions on with Mavenclad (0.38), versus placebo (1.43) (P<0.001 for all comparisons).[1,4,10]

These data show that MAVENCLAD® treatment significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks, compared to placebo. The extension study (CLARITY EXTENSION)[11] which assessed safety over a further two-year period (without active treatment) [Figure 2], also demonstrated that the effect of MAVENCLAD® treatment may persist for up to four years.[11] 75% of patients (n=98) in CLARITY Ext receiving placebo (who originally received a cumulative dose of 3.5 mg/kg over 2 years in the CLARITY study) were relapse free in years 3 and 4 despite no further treatment after the first two treatment years.[11]

A post-hoc analysis of the CLARITY study assessed the treatment effects of MAVENCLAD® in the high disease activity (HDA) patient population, compared with the overall study population.[12] Results showed that MAVENCLAD® demonstrated an even greater effect in HDA patients versus non HDA patients.[12] Patients with highly active relapsing MS who received MAVENCLAD showed an 82% relative reduction in 6-month confirmed EDSS progression at 2 years [Hazard Ratio versus placebo for HDA population =0.18 (p<0.0001)], and a 67% relative reduction in annualised relapse rate (ARR) versus placebo [Relative Risk versus placebo for HDA population =0.33, (p<0.0001), MAVENCLAD® (n=140): 0.16 vs. placebo (n=149): 0.47].[12]

Safety

In the pivotal, phase III CLARITY study, incidences of the most commonly reported adverse events for MAVENCLAD® were comparable to placebo (8.4% for MAVENCLAD® versus 6.4% for placebo), with the exception of lymphopenia.[10] Due to its mechanism of action, transitory, mostly mild-to-moderate lymphopenia has been observed following active MAVENCLAD® treatment; 20%-25% of patients receiving MAVENCLAD® over 2 years developed transient Grade 3 or 4 lymphopenia.[4] However, most patients can be expected to recover to either normal lymphocyte counts or Grade 1 lymphopenia within 9 months.[4]

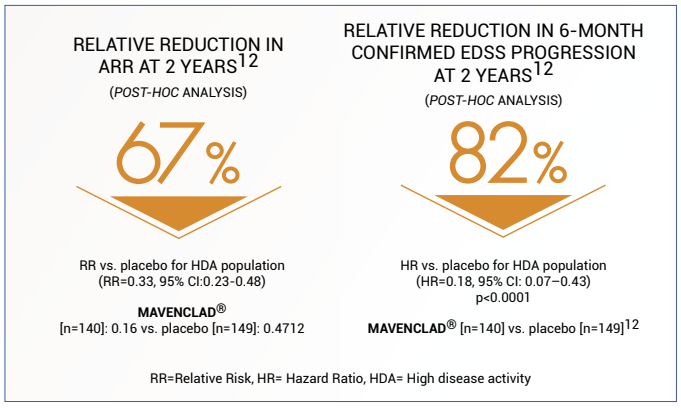
The most clinically relevant infection reported in MS patients who received MAVENCLAD® at the recommended cumulative dose of 3.5 mg/kg over 2 years in clinical studies was herpes zoster.[4] All cases of herpes zoster were dermatomal, and no case was disseminated. If such signs and symptoms occur, anti-infective treatment should be initiated as clinically indicated. Interruption or delay of MAVENCLAD® may be considered until proper resolution of the infection. There was no increased risk of opportunistic infections compared to placebo.[16]

To date, there have been no cases of secondary autoimmunity reported by cladribine treated patients in the PREMIERE registry.[17]

Events of malignancies were observed more frequently in cladribine-treated patients compared to patients who received placebo in the CLARITY trial.[4]

MAVENCLAD® is contraindicated in MS patients with active malignancies. An individual benefit-risk evaluation should be performed before initiating MAVENCLAD® in patients with prior malignancy.[4] Overall, there was no obvious pattern or cluster of specific tumour types or locations for either cladribine or placebo.[14]

A review of the malignancy risk for DMT treatments for MS by an academic group based in the UK compared published data from 2-year clinical studies and found that the malignancy rate of cladribine-treated subjects in the CLARITY study (0.34%) was not significantly different from all other active treatment groups (0.67%, p=0.3669) for other disease modifying therapies.[15]



The long-term safety of MAVENCLAD® continues to be monitored in clinical registries, which currently have up to 10 years' of safety follow-up.[17] Knowledge around the adverse events associated with MAVENCLAD® has helped to inform risk mitigation strategies prior to treatment initiation.[4,14] Overall, MAVENCLAD® is generally well tolerated with only 3.5% of MAVENCLAD® treated patients discontinuing treatment due to adverse events in the CLARITY study.[10]

MAVENCLAD® clinical data: The Consultant Neurologist's perspective – Dr Adrian Pace

Initial indications gathered from personal experience prescribing MAVENCLAD® to patients with MS in the first six months post-UK availability have been positive, confirming its reassuring tolerability regardless of patients' MS profile, and past experiences with other disease modifying therapies. From my initial cohort of patients we have not experienced any early recrudescence of their MS Symptoms.

Overall, available results from clinical studies position MAVENCLAD® confidently within the MS treatment algorithm for the management of patients with highly active relapsing MS.[12] In turn, eligible members of the MS community may now access a therapeutic option which marries high efficacy*, with a reassuring safety profile and the potential for reducing their disease progression over the four-year period.[12,18-20]

* High-efficacy, defined by the ABN as "[Disease-Modifying Therapies] with an average relapse reduction substantially more than 50%"[20]

MAVENCLAD® clinical data: The Consultant Neurologist's perspective – Dr Peter Brex

From the clinical practice perspective, MAVENCLAD® is a welcome addition to our arsenal of treatments available for people with RRMS. Patients treated with MAVENCLAD® initially attend an out-patient assessment with one of our MS nurses or MS pharmacist, where the benefits and potential risks are explained, active malignancy, active, chronic and latent infections are excluded, in women of childbearing potential, pregnancy must be excluded and a full blood count is taken to ensure the lymphocyte count is normal before the first course.[4] Vaccination is arranged for patients who are found not to have antibodies to varicella-zoster virus.

The supporting clinical data, as outlined above, show that the clinical benefits of the MAVENCLAD® treatment regimen can last for up to four years.[11] In addition, it is generally well-tolerated and there are no mandatory MRI monitoring requirements, except at pre-initiation, but we perform a baseline MRI and routine annual brain MRI subsequently to assess disease activity.[4]

I feel that MAVENCLAD® will be of particular benefit as first-line use for people with MS who present with high disease activity, or for those people who relapse on platform therapies.

MAVENCLAD® dosing regimen, treatment adherence and tolerability: The Neuroscience Pharmacist perspective – Joela Mathews

The oral dosing of MAVENCLAD® occurs at weeks one and five, administered in years one and two, as outlined in the CLARITY study. The exact number of tablets taken within each week uses a dose-banding principle based on weight and a cumulative dose of 3.5mg/kg over 2 years. The distribution of the total dose over the two years of treatment can be found in the Summary of Product Characteristics and in Table 1 below.[4]

Efficacy results from the CLARITY extension trial show that MAVENCLAD® can sustain up to four years of disease control, without the need for further treatment in years three or four.[11]

MAVENCLAD® is generally well tolerated, with good medication adherence over the short courses of treatment seen at our practice to date, which results in less pharmaceutical wastage.

Good compliance also helps to ensure that patients receive the maximum benefit possible from their treatment.

For some patients it is the reduced burden compared to other approved high-efficacy Disease-Modifying Therapies in a 4-year horizon, in terms of days on active treatment and monitoring, which may be of benefit to them. MAVENCLAD® offers a treatment option which allows patients to take treatment for up to 20 days over two years at home. MAVENCLAD® could also ease the burden on family members, who may have found their lives restricted in the past due to hospital transportation and giving injections.

Table 1. Dose of MAVENCLAD® per treatment week by patient weight in each treatment year.[4]

Weight Range	Dose in mg (number of 10mg tablets) per treatment week	
kg	Treatment week 1	Treatment week 2
40 to <50	40mg (4 tablets)	40mg (4 tablets)
50 to <60	50mg (5 tablets)	50mg (5 tablets)
60 to <70	60mg (6 tablets)	60mg (6 tablets)
70 to <80	70mg (7 tablets)	70mg (7 tablets)
80 to <90	80mg (8 tablets)	70mg (7 tablets)
90 to <100	90mg (9 tablets)	80mg (8 tablets)
100 to <110	100mg (10 tablets)	90mg (9 tablets)
110 and above	100mg (10 tablets)	100mg (10 tablets)

MAVENCLAD® benefits to patients: The Clinical Nurse Specialist in MS perspective – Samantha Colhoun

MAVENCLAD® is an alternative treatment option for patients with highly active MS, offering a number of benefits along with the added reassurance from long-term safety data[14,17]. In addition to the clinical benefits already outlined above, MAVENCLAD® offers people with MS:

- A medication schedule that offers an opportunity for planning of pregnancy for women 6 months after the last dose in year 2 (note: MAVENCLAD® is contraindicated in pregnancy, please see full prescribing information for MAVENCLAD® fertility, pregnancy and lactation recommendations)[4]
- A short course oral treatment with low monitoring requirements
- A self-dosing regimen that can be taken at home at a time convenient to the patient, without the need to take time off from work

Alongside the benefits to patients, MAVENCLAD® has the potential to reduce demands on the NHS and current MS services. A reduction in the need for frequent monitoring or the need for infusions, could reduce the demands on infusion services, potentially resulting in long-term cost savings to the NHS.

Summary

MAVENCLAD® is the only oral immune reconstitution therapy that selectively reduces B and T lymphocytes with minimal impact on innate immune function.[1-4] Supported by robust clinical data, the annual therapy taken for up to 20 days over two years can provide disease control in patients with highly active relapsing MS, for up to four years, and is generally well-tolerated.[4,12]

An increased knowledge around the pathophysiology of MS is driving an era of effective treatment options for patients with the disease. Favourable developments in methods of administration allow for simple dosing regimens and low monitoring, helping to lessen the burden of the disease for people with MS.

Ease of administration and low monitoring burden, along with the efficacy and long-term safety data from clinical trials, means the benefits of MAVENCLAD® are now being seen by patients and members of the multidisciplinary MS team in 'real-world' practice.

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Cladribine tablets (MAVENCLAD®) funding and reimbursement

MAVENCLAD® has been approved for use by all relevant funding bodies in the UK and Ireland, which include Scottish Medicines consortium, NICE, AWMSG and HSE.

MAVENCLAD® cladribine tablets prescribing information (Please refer to the full Summary of Product Characteristics before prescribing). **PRESENTATION:** Cartons of 1, 4 or 6 tablets. Each tablet contains 10mg of cladribine. **INDICATIONS:** Treatment of adults with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. **DOSAGE AND ADMINISTRATION:** Must be initiated and supervised by a physician experienced in MS treatment. Recommended cumulative dose: 3.5mg/kg body weight over 2 years, administered as one treatment course of 1.75mg/kg per year. Each course comprises 2 treatment weeks, one at the start of the first month and one at the start of the second month of each year. Each treatment week comprises 4 or 5 days on which the patient receives 10mg or 20mg as a single daily dose, depending on body weight. For details, see dosage tables in the SPC. No further cladribine treatment is required in years 3 and 4. **CONTRAINDICATIONS:** Hypersensitivity to cladribine or to the excipients; HIV infection; active chronic infection (tuberculosis or hepatitis); initiation in immunocompromised patients including those receiving immunosuppressive or myelosuppressive therapy; active malignancy; moderate or severe renal impairment (creatinine clearance <60mL/min); pregnancy and breast-feeding. **PRECAUTIONS:** Not recommended in moderate or severe hepatic impairment. Exercise caution in elderly patients. Determine lymphocyte counts before initiation in years 1 and 2, 2 and 6 months after treatment start in each treatment year. Count should be normal pre-treatment in year 1. If count below 500 cells/mm^3 at 2 or 6 months, actively monitor until values increase. If count below 800 cells/mm^3 pre-treatment in year 2, delay treatment. Stop treatment if recovery takes more than 6 months. Screen for latent infections prior to initiation in years 1 and 2. Delay initiation in latent or acute infection until treated. Varicella zoster vaccination is recommended in antibody-negative patients prior to treatment initiation. Delay initiation for 4-6 weeks following vaccination. Consider anti-herpes prophylaxis during grade 4 lymphopenia. If lymphocyte count falls below 500 cells/mm^3, actively monitor for symptoms suggestive of infection and initiate anti-infective treatment accordingly. Interrupt or delay MAVENCLAD® until infection has resolved. Perform baseline MRI before initiating MAVENCLAD® (usually within 3-months). Evaluate benefit-risk prior to initiation in patients with previous malignancy. Advise patients to follow standard cancer screening guidelines. Exclude pregnancy before initiation in years 1 and 2. Before initiation in year 1 and 2, counsel male and female patients on potential for risk to the foetus and need for effective contraception. Contraception should be used by both male and female patients during treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraception should add barrier method during treatment and for at least 4 weeks after last dose in each treatment year. In patients previously treated with immunomodulatory or immunosuppressive products, consider their mode of action and duration of effect before initiation of MAVENCLAD®. Consider an additive effect on the immune system when such products are used after treatment with MAVENCLAD®. When switching from another MS agent, perform a baseline MRI. In patients requiring blood transfusion, irradiation of cellular blood components is recommended prior to administration. Not to be taken by patients with hereditary fructose intolerance. Separate administration of any other oral medicinal product by at least three hours from MAVENCLAD® administration. Concomitant treatment with other disease-modifying treatments for MS not recommended. Monitor haematological parameters when taken with other substances that affect the haematological profile. Do not initiate treatment within 4-6 weeks of live or attenuated live vaccines. Avoid vaccines during and after treatment while white blood cells not within normal limits. Avoid co-administration of ENT1, CNT3 or BCRP inhibitors during the 4-5 day treatment period. Consider possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered. **SIDE EFFECTS: Very common:** Lymphopenia **Common:** Oral herpes, dermatomal herpes zoster, decreased neutrophils, rash, alopecia **Other side effects:** Tuberculosis. In clinical studies and long-term follow-up, malignancies were observed more frequently in cladribine-treated patients compared to placebo. Prescribers should consult the Summary of Product Characteristics in relation to other side effects.

LEGAL CATEGORY: POM.

PRICE:
Pack of 1 tablet: £2,047.24
Pack of 4 tablets: £8,188.97
Pack of 6 tablets: £12,283.46
For prices in Ireland, consult distributor Allphar Services Ltd. Marketing Authorisation Holder and Numbers: Merck Europe B.V., Gustav Mahlerplein 102,1082 MA Amsterdam, The Netherlands;
EU/1/17/1212/001, 002 & 004

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