Annex III

Product information as approved by the PRAC on 6 July 2017, revised on 9 August 2017, and endorsed by the European Commission.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zinbryta 150 mg solution for injection in pre-filled syringe
Zinbryta 150 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 150 mg of daclizumab in 1 mL solution for injection.

Each pre-filled pen contains a pre-filled syringe, containing 150 mg of daclizumab in 1 mL solution for injection.

Daclizumab is produced in a mammalian cell line (NS0) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Colourless to slightly yellow, clear to slightly opalescent liquid with pH 6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis (RMS) in adult patients:

- with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or,
- with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs.

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the management of multiple sclerosis.

Posology

The recommended dose of Zinbryta is 150 mg injected subcutaneously once a month.

In case a dose is missed and it is within 2 weeks of the missed dose, patients should be instructed to inject without delay their missed dose and then remain on their original monthly dosing schedule.

If a dose is missed and it is more than 2 weeks from the missed dose, patients should skip the missed dose, wait until their next scheduled dose, and then remain on their original monthly dosing schedule.

Only one dose should be administered at a time to make up for a missed dose.

Special populations

Elderly population
There was limited exposure in patients over 55 years of age in clinical studies with daclizumab. It has not been determined whether these patients respond differently compared with younger patients.

Renal impairment
Daclizumab has not been studied in patients with renal impairment. As renal excretion is not a major route of elimination, no dose adjustments are considered necessary (see section 5.2).

Hepatic impairment
Daclizumab has not been studied in patients with hepatic impairment. Zinbryta is contraindicated in patients with pre-existing hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Zinbryta in children and adolescents below 18 years have not been established. No data are available.

Method of administration

Zinbryta is for subcutaneous use.

It is recommended that patients should be trained in the proper technique for self-administering subcutaneous injection using the pre-filled syringe/pre-filled pen. The usual sites for subcutaneous injection include the thigh, abdomen, and back of the upper arm.

Zinbryta is provided with the needle pre-attached. Pre-filled syringes/Pre-filled pens contain a single dose only and should be discarded after use.

Precautions to be taken before handling or administering the medicinal product
Once removed from the refrigerator, Zinbryta should be allowed to warm to room temperature (20°C-30°C) (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm Zinbryta.

This medicinal product should not be used if:
- the syringe/pen is cracked or broken
- the solution is cloudy or you can see particles floating in it
- the solution is any other colour than colourless to slightly yellow
- the pen has been dropped or is visibly damaged.

4.3 Contraindications

Zinbryta is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylaxis or anaphylactoid reactions) to daclizumab or to any of the excipients (see section 6.1).

Pre-existing hepatic disease or hepatic impairment (see section 4.4).

4.4 Special warnings and precautions for use

Hepatic injury
Serious hepatic injury including elevations of serum transaminases and fatal cases of autoimmune hepatitis and fulminant liver failure have occurred in patients treated with Zinbryta (see section 4.8). Cases occurred early after treatment initiation, in patients having received repeated treatment courses and several months after discontinuation.

Prior to treatment initiation with Zinbryta, serum transaminases (ALT and AST) and bilirubin levels should be obtained. Patient serum transaminase levels and bilirubin levels should be monitored at least monthly and more frequently as clinically indicated during treatment and up to 4 months after the last dose of Zinbryta.

Patients with ALT or AST ≥2 times the ULN prior to treatment were not included in clinical studies; treatment initiation is not recommended in patients with ALT or AST ≥2 times the ULN and is contraindicated in patients with pre-existing hepatic impairment. Treatment initiation is not recommended in patients with history of concurrent autoimmune conditions. Monitor all patients for signs and symptoms of hepatic injury. In case of signs or symptoms suggestive of such injury, the patient should be promptly referred to a hepatologist.
Caution should be used when administering medicinal products of known hepatotoxic potential, including non-prescription products and herbal supplements, concomitantly with Zinbryta (see section 4.5).

Consider discontinuing therapy if an adequate response has not been achieved.

A summary of action as a function of the test results during treatment with Zinbryta is presented in table 1 below.

Table 1: Summary of action required as a result of liver function test results

Test result	**Summary of action required**
Confirmed ALT or AST > 5 x ULN *or* Confirmed ALT or AST > 3 x ULN and bilirubin > 2 x ULN	**Treatment discontinuation.***
ALT or AST > 3 x ULN	**Treatment interruption and close monitoring.** Resume when ALT or AST have reached < 2 x ULN.

* Re-initiation of therapy may be considered if other aetiologies are found, values have returned to normal and benefits to the patient of resuming therapy outweigh the risks.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), it is recommended to promptly measure serum transaminases and interrupt or discontinue treatment with Zinbryta, as appropriate.

In patients with prolonged elevations of serum transaminases, it is appropriate to evaluate for other possible causes, such as infection, and referral to a specialist may be required. Autoimmune hepatitis (without the presence of auto-antibodies) has been observed in clinical studies. Treatment with systemic corticosteroids may be appropriate.

Refer to section below, ‘Educational Guidance’, for details of the Physician Guidelines and Patient Card that are recommended for use with this medicine.

Educational guidance
All physicians who intend to prescribe Zinbryta must ensure they are familiar with the Physician Guidelines for this medicinal product.

The physician should discuss the risk of hepatic injury with patients and provide them with a Patient Card. The Card informs patients of the risk of severe hepatic injury, and its possible symptoms, so that they are aware of situations in which they should contact a healthcare professional in a timely manner. In addition, the Card explains the need for monitoring of liver function and educates the patient on the importance of adherence to their monthly blood tests.

Skin reactions
Skin reactions, some serious (e.g. exfoliative rash or dermatitis, toxic skin eruption), have been reported with Zinbryta. Skin reactions generally resolved with standard care, including treatment with topical or systemic steroids. If a patient develops a diffuse or highly inflammatory rash, referral to a dermatologist and discontinuation of Zinbryta may be required (see section 4.8).

Depression
Zinbryta should be administered with caution to patients with previous or current depressive disorders. Patients treated with Zinbryta should be advised to report any symptoms of new or worsening depression, and/or suicidal ideation immediately to the prescribing physician. If a patient develops severe depression, and/or suicidal ideation, discontinuation of Zinbryta should be considered (see section 4.8).

Infections
Infections, some serious (e.g. pneumonia and bronchitis), have been reported with Zinbryta. If serious infection develops, it could be necessary to withhold treatment with Zinbryta until the infection resolves.

Tuberculosis infections have been reported in patients treated with Zinbryta. In patients who have had tuberculosis or who live in endemic areas of the disease, screening for active tuberculosis should be performed before starting treatment, and patients should be monitored during treatment.

In patients with severe active infection, a delay in initiation of Zinbryta therapy should be considered (see section 4.8).

Zinbryta has not been studied in patients with immunodeficiency syndromes.

Autoimmune haemolytic anaemia
Autoimmune haemolytic anaemia has been reported in patients treated with Zinbryta which resolved with standard treatment and discontinuation of Zinbryta.
If a patient develops signs or symptoms of autoimmune haemolytic anaemia (e.g. pallor, fatigue, dark urine, jaundice, shortness of breath), consider referring to a specialist and discontinuing Zinbryta (see section 4.8).

Gastrointestinal disorders
Colitis has been reported with Zinbryta. The colitis improved with discontinuation of Zinbryta and standard treatment. Referring patients who develop symptoms of colitis (e.g. abdominal pain, fever, prolonged diarrhoea) to a specialist is advisable (see section 4.8).

Lymphopenia
When observed during Zinbryta clinical studies, lymphopenia was mostly mild to moderate ($\geq 500/mm^3$). Sustained severe lymphopenia ($< 500/mm^3$), was not observed in clinical studies with Zinbryta. However, as a precaution, monitoring of complete blood count is recommended every 3 months.

The risk of Progressive Multifocal Leukoencephalopathy (PML) associated to the treatment with Zinbryta has not been established.

Excipient related considerations
This medicinal product contains 0.14 mmol sodium per dose. It is essentially 'sodium-free' and can be used by patients on a sodium-restricted diet.

4.5 Interaction with other medicinal products and other forms of interaction

Zinbryta is not expected to undergo metabolism by hepatic enzymes or renal elimination.
There is limited data on concomitant use of Zinbryta with MS symptomatic therapies. Cases of hepatic injury have occurred in patients taking Zinbryta with other hepatotoxic drugs, although the role of these medicinal products is uncertain. Caution is recommended when administering medicinal products of known hepatotoxic potential concomitantly with Zinbryta (see section 4.4).

Immunisations
The safety of immunisation with live viral vaccines during treatment with Zinbryta has not been studied. Vaccination with live vaccines is not advised during treatment and up to 4 months after discontinuation.

In a clinical study, patients (n=90) on long-term treatment with Zinbryta mounted appropriate immune responses to an inactivated trivalent seasonal influenza vaccine. The magnitude of the immune response to the seasonal influenza vaccine, and proportion of patients with seroconversion and seroprotection were consistent with those observed in healthy volunteer populations. Patients on Zinbryta may receive non-live vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of Zinbryta in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reprotoxicity (see section 5.3).

Zinbryta should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
Available toxicology data in lactating cynomolgus monkeys have shown excretion of daclizumab in milk (for details see section 5.3). It is not known whether Zinbryta is secreted in human milk. Although human IgG is secreted into human milk, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. A risk to newborns/infants cannot be excluded.

If a woman wishes to breast-feed during treatment with Zinbryta, the benefit of breast-feeding to the child and of therapy to the woman should be considered.

Fertility
No impact on male or female fertility as assessed by fertility indices was detected in animal studies (see section 5.3). There are no data on the effects of Zinbryta on human fertility.

4.7 Effects on ability to drive and use machines

Zinbryta has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In the placebo-controlled study (the SELECT study), 417 patients received Zinbryta (150 mg, n=208; 300 mg, n=209; every 4 weeks) for up to 1 year. In the active-controlled study (the DECIDE study), 919 patients received Zinbryta (150 mg, every 4 weeks) and 922 patients received interferon beta-1a intramuscular, (30 microgram weekly) for a minimum of 2 years and up to 3 years.

The most commonly reported adverse reactions leading to discontinuation in patients treated with Zinbryta were hepatic reactions, including elevations of serum transaminases (5%), and cutaneous reactions (4%) (see section 4.4).

The most common adverse reactions reported for Zinbryta were rash, increased alanine aminotransferase (ALT), depression, nasopharyngitis, upper respiratory tract infection, influenza, oropharyngeal pain, and lymphadenopathy.

Tabulated list of adverse reactions

The adverse reactions are presented as MedDRA preferred terms under the MedDRA System Order Class by frequency and incidence. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The incidence of the adverse reactions is expressed according to the following categories:

- Very common (≥ 1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)

Table 2: Adverse reactions reported for Zinbryta 150mg

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Upper respiratory tract infection†	Very Common
	Nasopharyngitis†	Very Common
	Pneumonia	Common
	Respiratory tract infection	Common
	Bronchitis	Common
	Viral infection	Common
	Influenza†	Common
	Laryngitis	Common
	Tonsillitis†	Common
	Pharyngitis	Common
	Folliculitis	Common
	Rhinitis*	Common
Blood and lymphatic system disorders	Lymphadenopathy†	Common
	Lymphadenitis	Common
	Anaemia*	Common
	Autoimmune haemolytic anaemia	Uncommon
Psychiatric disorders	Depression*	Common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain†	Common
Gastrointestinal disorders	Diarrhoea	Common
Skin and subcutaneous tissue disorders	Dermatitis	Common
	Dermatitis allergic	Common
	Eczema†	Common
	Psoriasis	Common
	Seborrhoeic dermatitis†	Common
	Skin exfoliation	Common
	Rash*†	Common
	Rash maculopapular	Common

	Acne†	Common
	Erythema	Common
	Pruritus	Common
	Dry skin	Common
	Exfoliative rash	Uncommon
	Toxic skin eruption	Uncommon
	Eczema nummular	Uncommon
General disorders and administration site conditions	Pyrexia*	Common
Hepatobiliary disorders	Hepatitis	Common
Investigations	ALT increased*	Common
	AST increased*	Common
	Liver function test abnormal	Common
	Hepatic enzyme increased	Common
	Lymphocyte count decreased	Common

*Observed with a ≥2% higher incidence than placebo
†Observed with a ≥2% higher incidence than interferon beta-1a (intramuscular)

Description of selected adverse reactions

Hepatic injury
Serious hepatic injury, including fatal cases of autoimmune hepatitis and fulminant liver failure have occurred in patients treated with Zinbryta. Serious reactions, including autoimmune hepatitis, hepatitis and jaundice, were observed in 1.7% of patients. In a clinical study, a case of fatal autoimmune hepatitis occurred in a patient re-initiating treatment with 300 mg of daclizumab after a planned 6 month treatment interruption period.

In clinical studies, serum transaminase elevations occurred during treatment and up to 4 months after the last dose of Zinbryta. Most patients had elevations that were asymptomatic and resolved spontaneously. An increased incidence of elevations of ALT or AST > 5 times the ULN was reported in Zinbryta-treated patients compared to placebo (4% versus <1%) or interferon beta-1a (intramuscular) (6% versus 3%). The incidence of discontinuation due to medicine related hepatic disorders was 5% in Zinbryta-treated patients and 4% in interferon beta-1a (intramuscular).

Skin reactions
In clinical studies Zinbryta increased the incidence of skin reactions [18% vs 13% (placebo); 37% vs 19% (interferon beta-1a (intramuscular))] and serious skin reactions [<1% vs 0% (placebo); 2% vs <1% (interferon beta-1a (intramuscular))] compared to placebo and interferon beta-1a (intramuscular).

The most common skin reactions were rash, dermatitis, and eczema. The majority of patients had skin reactions that were mild or moderate in severity. Discontinuation due to skin reactions was 4% in Zinbryta-treated patients.

Depression
In clinical studies, Zinbryta increased the incidence of depression [5% vs 1% (placebo); 8% vs 6% (interferon beta-1a (intramuscular))]; the incidence of serious reactions of depression was <1% with Zinbryta.

Infections
In clinical studies, Zinbryta increased the incidence of infections [50% vs 44% (placebo) and 65% vs 57% (interferon beta-1a (intramuscular))] and serious infections [3% vs 0% (placebo); 4% vs 2% (interferon beta-1a (intramuscular))] compared to placebo and interferon beta-1a (intramuscular). The most common types of infections were upper respiratory tract infections and viral infections. The median duration was similar between the treatment groups. The rate of infections and serious

infections did not increase over time. The majority of patients with infections continued on treatment with Zinbryta. Discontinuation of Zinbryta due to infections was <1%.

Autoimmune haemolytic anaemia
Autoimmune haemolytic anaemia was reported in < 1% of patients treated with Zinbryta in clinical studies.

Gastrointestinal disorders
An increased incidence of serious colitis (<1%) was reported in patients treated with Zinbryta in clinical studies.

Lymphadenopathy
In clinical studies, Zinbryta increased the incidence of lymphadenopathy, with onset occurring throughout the treatment period. Discontinuation due to lymphadenopathy was <1% in Zinbryta-treated patients. The majority of patients with lymphadenopathy continued on treatment with Zinbryta, and the majority of cases resolved within 3 months.

Immunogenicity
In the DECIDE study (see section 5.1), patients were tested for anti-drug (daclizumab) antibodies at week 4 and approximately every 3 months thereafter. Treatment-emergent anti-drug antibodies and neutralising antibodies were observed in 19% (175/913) and 8% (71/913) of study patients, respectively. The majority of the treatment-emergent anti-drug antibodies responses were transient (12% [110/913]) and the remaining minority (7% [65/913]) were persistent. Among the evaluable patients, the majority of treatment-emergent neutralising antibody responses were transient (6% [56 of 913]) and 2% of patients (15 of 913) had persistent responses. Treatment-emergent anti-drug antibodies and neutralising antibodies responses predominantly occurred during the first year of treatment and their frequency declined with continued Zinbryta treatment.

In patients with neutralising antibodies, daclizumab clearance was increased on average by 19% (see section 5.2). There was no apparent correlation of anti-drug antibodies or neutralising antibodies development to clinical response, adverse reactions, or pharmacodynamic profile of daclizumab.

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

Reported experience with overdose is limited. The safety of doses above 300 mg administered subcutaneously and 400 mg intravenously have not been evaluated. Doses up to this level were well tolerated with no evidence of acute toxicity. Potential adverse reactions beyond this level are expected to be consistent with the safety profile for daclizumab in MS patients.

Management
In case of overdose, patients may require medical attention and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, interleukin inhibitors, ATC code: L04AC01

Mechanism of action

Daclizumab is a humanised IgG1 monoclonal antibody that binds to CD25 (IL-2Rα), and prevents IL-2 binding to CD25. Daclizumab modulates IL-2 signalling by blocking CD25-dependent, high-affinity IL-2 receptor signalling, resulting in higher levels of IL-2 available for signalling through the intermediate-affinity IL-2 receptor. Key effects of this IL-2 pathway modulation potentially related to the therapeutic effects of daclizumab in MS include selective antagonism of activated T-cell responses, and expansion of immunoregulatory $CD56^{bright}$ natural killer (NK) cells, which have been shown to selectively decrease activated T-cells. Together, these immunomodulatory effects of daclizumab are believed to reduce CNS pathology in MS and thereby reduce the occurrence of relapses and disability progression.

Pharmacodynamic effects

In clinical studies, the pharmacodynamic effects of Zinbryta 150 mg administered subcutaneously every 4 weeks were consistent with modulation of IL-2 signalling as evidenced by the rapid and sustained saturation of the target CD25 receptors on circulating T-cells and a sustained approximately 2-fold increase in serum IL-2 concentration. In addition, an increase in $CD56^{bright}$ NK cells and a decrease in regulatory T-cells (defined as $CD4^{+}CD127^{low}FoxP3^{+}$ T-cells) was observed within 2 weeks after the first dose, with a sustained 5-fold increase in $CD56^{bright}$ NK cells above baseline and an approximately 60% decrease in regulatory T-cells in the treatment phase, with a return to baseline levels approximately 20-24 weeks after the last dose. During Zinbryta treatment, mean cell counts for the major immune subsets (T, B, and NK cells) remained within normal ranges; total lymphocyte, T and B cell counts decreased on average ≤10% from baseline during the first year of treatment. Total lymphocyte counts returned to baseline levels approximately 8-12 weeks after the last dose of Zinbryta (150mg). Total lymphocyte counts $<0.8x10^{9}$ cells/L ([Common Terminology Criteria for Adverse Events – CTCAE] Grade 2; at least one measurement) occurred in 4% of placebo-treated and 5% of Zinbryta-treated patients in the SELECT study, and 9% of the interferon beta-1a (intramuscular)-treated and 8% of Zinbryta-treated patients in the DECIDE study. Total NK cell counts increased approximately 1.5-fold as a result of the change in $CD56^{bright}$ NK cells.

Clinical efficacy and safety

The efficacy of Zinbryta was demonstrated in two studies (SELECT and DECIDE) in patients with RMS. The SELECT study was double-blind, randomised, placebo-controlled, with either Zinbryta 150 mg (n=208), or 300 mg (n=209) versus placebo (n=204) every 4 weeks for 52 weeks. The DECIDE study was double-blind, randomised, parallel-group, active-controlled with Zinbryta 150 mg every 4 weeks (n=919) versus interferon beta-1a (intramuscular) 30 micrograms weekly (n=922), for a minimum of 2 to a maximum of 3 years (96 to 144 weeks). The study designs and baseline characteristics are presented in Table 3.

Table 3: Study design and baseline characteristics for SELECT study and DECIDE study

Study name	**SELECT**	**DECIDE**
Study design		
Treatment	52 weeks	96 to 144 weeks
Disease history	Patients with RMS, at least 1 relapse (clinical and/or MRI) during the year prior to randomisation, and had an EDSS score between 0 to 5.0. For DECIDE, at least 2 relapses (one of which was a clinical relapse) within the prior 3 years was also required	
Baseline characteristics		
Mean age (years)	35.7	36.3
Mean disease duration (years)	4.1	4.2

Mean number of relapses within 12 months prior to study	1.4	1.6
Median EDSS score	2.5	2.0
Percent with EDSS ≥ 3.5	36%	30%
Percent with ≥ 1 Gd enhancing lesion (mean)	44% (1.8)	46% (2.1)
Percent ≥ 2 relapses in the year prior to study	31%	46%
Percent prior DMT use (**%**)	20%	41%

Results for the SELECT study are shown in Table 4. Treatment with Zinbryta 150 mg every 4 weeks versus placebo significantly reduced the annualised relapse rate (ARR) and risk of relapse compared to placebo. In addition, there was a statistically significant effect on 24 week confirmed disability progression in Zinbryta treated patients with a hazard ratio 0.24 [95% CI: 0.09, 0.63]. The 300 mg dose did not provide additional benefit over the 150 mg dose.

Table 4: SELECT study clinical and MRI results (at 52 weeks)

	Placebo	**Zinbryta 150 mg**	**p-value**
Clinical endpoints			
Number of patients	196	201	
Annualised relapse rate Rate ratio [95% CI]	0.458	0.211 0.461 [0.318, 0.668]	 p<0.0001
Percentage of patients relapse-free Hazard ratio* [95% CI]	64%	81% 0.45 [0.30, 0.67]	 p<0.0001
Percentage with 24 weeks confirmed disability progression Hazard ratio [95% CI]	11%	2.6% 0.24 [0.09, 0.63]	 p=0.0037
Percentage with 12 weeks confirmed disability progression Hazard ratio [95% CI]	13%	6% 0.43 [0.21, 0.88]	 p=0.0211
Mean change in MSIS-29 physical score	3.0 point worsening	1.0 point improvement	p=0.0008
MRI endpoints[#]			
Mean number of new or newly enlarging T2 hyperintense lesions Lesion mean ratio [95% CI]	8.13	2.4 0.30 [0.22, 0.40]	 p<0.0001
Mean number of new T1 Gd-enhancing lesions between 8 and 24 weeks (on monthly MRI scans) Lesion mean ratio [95% CI]	4.79	1.46 0.31 [0.20, 0.48]	 p<0.0001

*Hazard ratio for the risk of relapse

[#]MRI analyses used evaluable dataset for each endpoint; T1 Gd-enhancing: MRI intensive population

Table 5 and Figures 1-2 show the results for the DECIDE study. Zinbryta significantly reduced the ARR and the risk of relapse, compared to interferon beta-1a (intramuscular)-treated patients. In addition, there was a statistically significant effect on 24 week confirmed disability progression in Zinbryta treated patients with a hazard ratio 0.73 [95% CI: 0.55, 0.98]. At week 96, Zinbryta demonstrated a statistically significant reduction in the number of new or newly enlarging T2 hyperintense lesions, the number of new T1 Gd-enhancing lesions and the mean number of new T1 hypointense lesions. In addition, Zinbryta reduced clinically meaningful worsening in the patient-reported physical impact of MS (≥7.5 point worsening from baseline to week 96 in the MSIS-29 physical score) compared to interferon beta-1a (intramuscular).

Table 5: DECIDE study clinical and MRI results (96 to 144 weeks) *(Values refer to results at 96 weeks, unless otherwise indicated.*)

	Interferon beta-1a (intramuscular) 30 micrograms	**Zinbryta 150 mg**	**p-value**
Clinical endpoints			
Number of patients	922	919	
Annualised relapse rate* Rate ratio* [95% CI]	0.393	0.216 0.550 [0.469, 0.645]	 p<0.0001
Percentage of patients relapse-free Hazard ratio# * [95% CI]	59%	73% 0.59 [0.50, 0.69]	 p<0.0001
Percentage with 24 weeks confirmed disability progression Hazard ratio* [95% CI]	12%	9% 0.73 [0.55, 0.98]	 p=0.03
Percentage with 12 weeks confirmed disability progression Hazard ratio* [95% CI]	14%	12% 0.84 [0.66, 1.07]	 p=0.16
Percentage of patients with clinically meaningful worsening in MSIS-29 physical score (≥7.5 point) Odds ratio [95% CI]	23%	19% 0.76 [0.60, 0.95]	 p=0.018
MRI endpoints†			
Mean number of new or newly enlarging T2 hyperintense lesions Lesion mean ratio [95% CI]	9.44	4.31 0.46 [0.39, 0.53]	 p<0.0001
Mean number of new T1 Gd-enhancing lesions Odds ratio [95% CI]	1.0	0.4 0.25 [0.20, 0.32]	 p<0.0001
Mean number of new T1 hypointense lesions Lesion mean ratio [95% CI]	4.43	2.13 0.48 [0.42, 0.55]	 p<0.0001

* Rates and risk reductions/endpoints are calculated over the treatment period up to 144 weeks.
# Hazard ratio for the risk of relapse.
† MRI analyses used evaluable dataset for each MRI endpoint.

Subgroup analyses of the SELECT and DECIDE studies demonstrated a consistent effect of Zinbryta compared to placebo and interferon beta-1a (intramuscular) across subgroups defined by demographic and MS disease characteristics. In the DECIDE study subgroup analysis, there was a statistically significant reduction observed compared to interferon beta-1a (intramuscular) on ARR and the number of new or newly enlarging T2 hyperintense lesions across subgroups (gender, age, prior MS DMT therapy, and disease activity levels).

Although the effect on disability progression was mainly seen in patients with baseline EDSS < 3.5, evidence of efficacy was shown in patients with relapsing secondary progressive MS (SPMS) as defined by baseline EDSS ≥ 3.5 and at least one of the three: confirmed 24 week worsening of EDSS, or ≥ 20% decline on Timed 25-foot Walk (T25FW), or, ≥ 20% decline on 9-Hole Peg Test (9-HPT).

Efficacy in patients with highly active disease

Highly active disease was defined as follows:

- Patients with 2 or more relapses in 1 year, and with 1 or more Gd-enhancing lesions on brain MRI, or
- Patients who had failed to respond to a full and adequate course (at least 1 year) of prior DMT treatment, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2 hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years.

Clinical trial data from the DECIDE study demonstrated consistent treatment effects in the highly active disease subgroup. Compared with interferon beta-1a intramuscular (n=440), Zinbryta (n=404) led to reductions on ARR (rate ratio 0.52 [95% CI: 0.42, 0.64], p<0.0001), number of new or newly enlarging T2 hyperintense lesions (lesion mean ratio 0.46 [95% CI: 0.37, 0.57], p<0.0001), and 24 weeks confirmed disability progression (hazard ratio 0.60 [95% CI: 0.40, 0.89], p=0.012).

Figure 1: Percentage of patients relapse-free (DECIDE study)

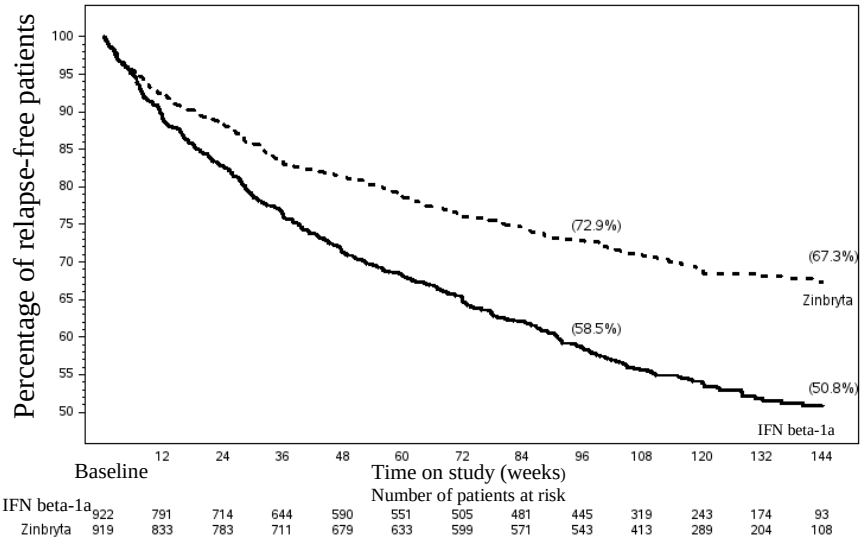
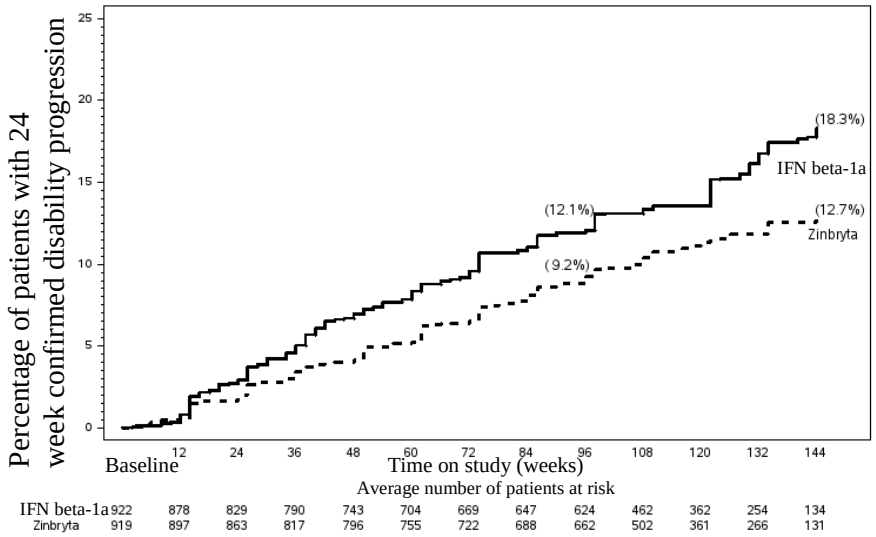


Figure 2: Proportion of patients with 24 week confirmed disability (DECIDE study)



Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zinbryta in one or more subsets of the paediatric population in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Daclizumab pharmacokinetics are well described by a two-compartment model with first-order absorption and elimination.

Absorption
Following subcutaneous administration of daclizumab, the median time to reach maximum serum concentrations (T_{max}) ranged from 5 to 7 days. The absolute bioavailability of daclizumab 150 mg subcutaneously administered was approximately 90% based on a cross-study population pharmacokinetic analysis of subcutaneous and intravenous dosing.

Distribution
Following subcutaneous administration of daclizumab 150 mg every 4 weeks, steady-state serum daclizumab concentrations were achieved by the 4th dose and daclizumab accumulated to a level approximately 2.5-fold compared to a single dose. At steady state, daclizumab mean maximum serum concentration (C_{max}), minimum serum concentration (C_{min}) and area under the serum concentration-time curve over the dosing interval (AUC_{tau}) values were approximately 30 micrograms/mL, 15 micrograms/mL and 640 day*micrograms/mL, respectively, with inter-patient variability (% CV) of approximately 40%.

Based on the cross-study population pharmacokinetic analysis, the steady-state volume of distribution of daclizumab is 6.34 L in a patient with a body weight of 68 kg (approximate median of evaluated patients). This small volume of distribution indicates that daclizumab is primarily confined to the vascular and interstitial spaces.

Biotransformation
The exact metabolic pathway for daclizumab has not been characterised. As an IgG1 monoclonal antibody, daclizumab is expected to undergo catabolism to peptides and amino acids in the same manner as endogenous IgG. Daclizumab is not expected to undergo metabolism by hepatic enzymes such as CYP isoenzymes (see section 4.5).

Elimination
As an IgG1 monoclonal antibody, daclizumab is not expected to undergo renal elimination.

Based on the cross-study population pharmacokinetic analysis, the clearance of daclizumab is 0.212 L/day with a terminal half-life value of approximately 21 days. Daclizumab clearance in patients who developed neutralising antibodies was, on average, 19% higher (see section 4.8 Immunogenicity).

Linearity/non-linearity
Consistent with results from individual studies, a cross-study population pharmacokinetic analysis indicated that daclizumab exposure is more than dose-proportional in the 50 mg to 100 mg subcutaneous dose range and is dose proportional in the 100 mg to 300 mg subcutaneous dose range.

Pharmacokinetic/pharmacodynamic relationship(s)
Within the studied regimens of daclizumab 150 mg and 300 mg administered subcutaneous every 4 weeks in MS patients, there was no clear relationship between daclizumab exposure and clinical efficacy endpoints (ARR, T2 lesions and Gd-enhancing lesions) or safety endpoints of interest (serious infection status, moderate or severe cutaneous adverse reaction, and AST/ALT > 5 times the ULN).

Special populations

Renal or hepatic impairment
No studies were conducted to evaluate daclizumab pharmacokinetics in patients with renal or hepatic impairment. Daclizumab is not expected to undergo renal elimination or metabolism by hepatic enzymes (see section 4.2).

Weight
Based on the cross-study population pharmacokinetic analysis, body weight accounted for less than 40% of the inter-patient variability in daclizumab clearance. No meaningful differences in clinical efficacy or safety were observed among the subgroups of MS patients by weight quartile in the DECIDE study.

Age and gender
Based on the cross-study population pharmacokinetic analysis, daclizumab pharmacokinetics were not influenced by age (range: 18 to 66 years; n=1670) or gender (n = 567 males and 1103 females).

Race
No pharmacokinetic differences were observed between Japanese and Caucasian healthy volunteers.

5.3 Preclinical safety data

Preclinical safety studies were conducted in cynomolgus monkeys due to species specificity of daclizumab binding only to human or primate CD25.

Carcinogenesis
Carcinogenicity studies with daclizumab have not been conducted. In two 9 month studies in monkeys there were no pre-neoplastic or neoplastic tissue observed.

Mutagenesis
Genotoxicity studies have not been conducted.

Reproductive toxicity
Daclizumab did not affect reproductive capacity in female and male cynomolgus monkeys (AUC in females and males up to 85 and 100 times higher than the exposure at the clinical dose respectively). There was no effect on foetal development and no evidence of teratogenicity. Daclizumab had no effect on peri- and post-natal development from birth to up to 6 months in the offspring. Exposures (AUC) in these studies ranged from 55 to 140 times that observed with the clinical dose. Daclizumab was detected in the milk of 11/14 lactating monkeys at levels that were <0.122% of the maternal serum levels, with no adverse reactions observed in the off-spring.

Toxicology
In two 9 month studies conducted in cynomolgus monkeys daclizumab was subcutaneously administered at bi-weekly doses of 10-200 mg/kg.
Chronic administration of daclizumab at all doses increased the incidence of skin findings (compared to those observed in control animals). These findings (dry, red raised patchy areas of the skin, as compared to controls, that correlated microscopically with acanthosis/hyperkeratosis and sub-acute to chronic inflammation) were characterised predominantly as mild to moderate, with one case assessed as severe.

A dose dependent increase in incidence of microglial aggregates above background was observed in the brain and spinal cord of monkeys treated with ≥35 mg/kg, (AUC 27 times higher than the clinical dose). Following a recovery period of up to 12 weeks, there was evidence of reversibility. Microglial aggregates in monkeys did not increase in incidence or severity with increased duration of dosing and were not associated with neuronal damage or neurobehavioral effects. A small subset of microglial aggregates were associated with microhaemorrhage but with no evident functional sequelae in monkeys.

In vitro investigative studies suggest that microglial aggregates are not due to a direct effect of daclizumab on microglial cells but are likely to be attributable to an increase in local IL-2 bioavailability.

The clinical relevance of microglial aggregates is unknown, however no deleterious neurologic effects attributed to the microscopic change have been observed in monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium succinate
Succinic acid
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

Zinbryta can be stored at room temperature (up to 30^{o}C) in the original pack for 30 days.
Do not place Zinbryta back into the refrigerator after warming to room temperature.
If Zinbryta has been outside of the refrigerator for more than a total of 30 days or if you are not sure how long Zinbryta has been at room temperature, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2^{o}C-8^{o}C).
Do not freeze.
Store in the original package in order to protect from light.

For additional information on storage at room temperature, see section 6.3.

6.5 Nature and contents of container

Pre-filled syringe made of glass (Type 1) with a rubber stopper and thermoplastic rigid needle shield containing 1 mL of solution. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe.

Pack sizes:
- Pack containing one 150 mg pre-filled syringe.
- 3 month multipack containing three 150 mg pre-filled syringes (3 boxes containing 1 syringe each).

A pre-filled syringe of Zinbryta is contained within a spring-powered pen injector called Zinbryta Pen. The syringe inside the pen is a pre-filled syringe made of glass (Type 1) with a rubber stopper and thermoplastic rigid needle shield, containing 1 mL of solution. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe.

Pack sizes:
- Pack containing one 150 mg pre-filled pen.
- 3 month multipack containing three 150 mg pre-filled pens (3 boxes containing 1 pen each).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

BIOGEN IDEC Limited
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1107/001
EU/1/16/1107/002
EU/1/16/1107/003
EU/1/16/1107/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 July 2016

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:

Biogen Inc
5000 Davis Drive
Research Triangle Park
North Carolina
27709
UNITED STATES

Name and address of the manufacturer responsible for batch release

Biogen (Denmark) Manufacturing ApS
Biogen Allé 1
Hillerød
DK-3400
Denmark

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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

- **Additional risk minimisation measures**

Hepatic Risk Management Guide, Patient Card

Prior to launch of Zinbryta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

Objective and rationale:

To educate patients and physicians about the risk of severe hepatic injury and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

Proposed action:

The Hepatic Risk Management Guide will contain information for the physician on the risk of elevations in liver enzyme levels and severe liver injury in patients treated with Zinbryta, as well guide the physician/patient discussion around hepatic risk and the measures to manage this risk. The physician should discuss the risk of hepatic injury with the patient and provide them with a Patient Card.

The Patient Card informs patients of the risk of severe hepatic injury, and the possible symptoms, so that they are aware of situations in which they should contact a physician in a timely manner. In addition, the Patient Card explains the need for monitoring of liver function and educates the patient on the importance of adherence to their monthly blood tests

The Patient Card is designed to enable the physician to present patient-friendly information about Zinbryta to a patient at the time Zinbryta is prescribed. It will focus on the potential for severe hepatic injury with Zinbryta, and will also include information about symptoms of liver injury and instructions about monthly liver function monitoring.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zinbryta 150 mg solution for injection in pre-filled syringe
Zinbryta 150 mg solution for injection in pre-filled pen
daclizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 150 mg of daclizumab in 1 mL
Each pre-filled pen contains 150 mg of daclizumab in 1 mL

3. LIST OF EXCIPIENTS

Sodium succinate, succinic acid, sodium chloride, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.

Open here
Tear here

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

Can be stored at room temperature (up to 30°C) for a single period of up to 30 days. Must not be returned to refrigerator after storage at room temperature.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

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

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1107/001
EU/1/16/1107/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zinbryta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK OUTER CARTON (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zinbryta 150 mg solution for injection in pre-filled syringe
Zinbryta 150 mg solution for injection in pre-filled pen
daclizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 150 mg of daclizumab in 1 mL
Each pre-filled pen contains 150 mg of daclizumab in 1 mL

3. LIST OF EXCIPIENTS

Sodium succinate, succinic acid, sodium chloride, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 3 (3 packs of 1) pre-filled syringes.

Multipack: 3 (3 packs of 1) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.

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

Can be stored at room temperature (up to 30°C) for a single period up of to 30 days. Must not be returned to refrigerator after storage at room temperature.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

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

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1107/002
EU/1/16/1107/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zinbryta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK INNER CARTON (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zinbryta 150 mg solution for injection in pre-filled syringe
Zinbryta 150 mg solution for injection in pre-filled pen
daclizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 150 mg of daclizumab in 1 mL
Each pre-filled pen contains 150 mg of daclizumab in 1 mL

3. LIST OF EXCIPIENTS

Sodium succinate, succinic acid, sodium chloride, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe. Component of a multipack, cannot be sold separately.
1 pre-filled pen. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.

Open here
Tear here

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

Can be stored at room temperature (up to 30°C) for a single period of up to 30 days. Must not be returned to refrigerator after storage at room temperature.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

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

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1107/002
EU/1/16/1107/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zinbryta

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-Filled Syringe Label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zinbryta 150 mg injection
daclizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-Filled Pen Label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zinbryta 150 mg injection
daclizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zinbryta 150 mg solution for injection in pre-filled syringe
Zinbryta 150 mg solution for injection in pre-filled pen
daclizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

In addition to this leaflet you will be given a Patient Card by your doctor. This has important safety information that you need to know before and during treatment with Zinbryta.

- Keep this leaflet and the Patient Card. You may need to read them again. Keep the leaflet and Card with you during treatment and for 4 months after the last dose of Zinbryta, since side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zinbryta is and what it is used for

The active substance in Zinbryta is daclizumab. This is a type of medicine called a monoclonal antibody.

What Zinbryta is used for
Zinbryta is used to treat relapsing forms of multiple sclerosis (RMS) in adult patients, more specifically in:

- Patients with highly active disease who have failed to respond despite treatment with at least one MS treatment. or,
- with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other MS treatments.

In MS, the body's immune system causes inflammation which damages the protective sheath (called myelin) around the nerves in the central nervous system (including the brain and spinal cord). This loss of myelin is called demyelination. This stops nerves from working properly.

People with relapsing MS have repeated attacks (relapses) of symptoms caused by their nerves not working properly. These symptoms vary from patient to patient but usually involve problems such as difficulty with walking, vision and balance.

Symptoms may disappear completely after the relapse is over but, over time, some problems may remain between relapses and interfere with daily activities.

How Zinbryta works
Zinbryta works by stopping the body's immune system from damaging your brain and spinal cord. This can help to reduce the number of relapses that you have and slow down the disabling effects of MS. Treatment with Zinbryta can help to prevent you from getting worse, although it will not cure MS. Your doctor will decide whether Zinbryta is the right medicine for you.

2. What you need to know before you use Zinbryta

Do not use Zinbryta
- if you have previously had a serious allergic reaction to daclizumab, or any of the other ingredients of this medicine listed in section 6.
- if you have had any liver problems.

Warnings and precautions
Talk to your doctor before using Zinbryta:
- if you have any other autoimmune disorders in addition to MS
- if you are taking, have recently taken or might take any other medicines, vitamins and herbal supplements. Your doctor will evaluate if any medicines you are taking have liver side effects and whether you should continue these medicines while taking Zinbryta
- if your MS does not respond to Zinbryta, your doctor may decide to discontinue treatment.
- if you have **depression** or have had it in the past.
- if you have **a serious infection**, such as pneumonia.
- if you have ever had **tuberculosis** (also called TB) or live in a region where TB infections are common, you may be at greater risk of TB. You may be tested for TB before starting Zinbryta and monitored during treatment.

Possible liver problems

Zinbryta may cause serious liver problems that may be life-threatening or result in death. Serious liver problems can occur both early after starting treatment with Zinbryta, any time during treatment and several months after discontinuing treatment. Even if you have had no previous liver problems, your doctor will carry out blood tests to test your liver function. You will need:
- **a blood test before starting** treatment. If your blood test shows that you have some liver problems, your doctor will decide whether to start Zinbryta
- at least **monthly blood tests during** treatment and more often if your doctor decides this is necessary
- tests for **up to 4 months after stopping** treatment. Side effects may occur even after stopping treatment (see serious side effects in section 4)

It is very important that you have these regular blood tests.

You will be given a Patient Card with further information about the things to watch out for while taking Zinbryta. Keep this Card with you during treatment and for 4 months afterwards. When you have any medical treatment, even if it is not for your MS, show the Patient Card to the doctor, pharmacist or nurse.

If you experience any of the following, contact your doctor immediately:

- unexplained nausea (feeling sick)
- vomiting (being sick)

- stomach pain
- increased tiredness
- loss of appetite
- your skin or the whites of your eyes turn yellow
- dark (tea-coloured) urine

These symptoms may suggest problems with your liver. If you do develop liver problems your MS doctor may interrupt your treatment with Zinbryta and refer you to a liver specialist (see section 4, Possible side effects).

Children and adolescents
Zinbryta is **not to be used** in children and adolescents younger than 18 years old. The safety and effectiveness of Zinbryta in this age group are not known.

Elderly
Zinbryta has had very little testing in people older than 55 years old. If you are over 55 your doctor may still prescribe Zinbryta.

Other medicines and Zinbryta
Tell your doctor if you are taking, have recently taken or might take any other medicines, vitamins and herbal supplements.

Vaccinations
If you need a vaccination, ask your doctor first because Zinbryta may affect how well vaccines work. Seasonal flu vaccines (inactive vaccine) have been shown to be effective when given to patients taking Zinbryta. However, Zinbryta's effect on other vaccines (live vaccines) is not known.

Pregnancy and breast-feeding
As data on use of Zinbryta during pregnancy are limited, the risk to the baby and benefit to the mother should be taken into consideration. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

It is not known whether Zinbryta passes into breast milk. Your doctor will help you decide whether you should stop breast-feeding, or stop using Zinbryta.

Driving and using machines
Zinbryta is not expected to affect your ability to drive and use machines. Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely.

Zinbryta contains a small amount of sodium
Each dose of Zinbryta contains 0.14 mmol sodium. It is essentially 'sodium-free' and can be used by people on a sodium-restricted diet.

3. How to use Zinbryta

Zinbryta will be prescribed to you by a doctor experienced in the treatment of MS.

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

Recommended dose
The dose of Zinbryta is 150 mg every month.
Try to do your injection on the same day each month, to help you remember it. For example, inject on the first day of each month.

You will also have a blood test every month to check your liver. It is very important that you do not miss this blood test. Try to keep to a set day for it each month. Contact your doctor if you think you may have missed a blood test.

Injecting yourself
Zinbryta is injected under the skin (subcutaneously) into your thigh, stomach or back of your upper arm. Detailed instructions for injecting Zinbryta are given in section 7, Instructions for injecting Zinbryta.

Your doctor or nurse should train you to give yourself the injections. Read and follow the advice given in section 7.

If you have trouble handling the syringe/pen, tell your doctor or nurse who may be able to help.

How long to use Zinbryta
Your doctor will tell you how long you need to keep using Zinbryta. Do not make changes unless your doctor tells you to.

If your doctor has told you to stop using your medicine, do not restart until your doctor tells you to.

If you use more Zinbryta than you should
If you have injected more than your usual dose, and you notice any side effects, or are concerned, speak with your doctor or nurse. Patients have received double the recommended dose of Zinbryta with no serious extra side effects.

If you forget to take Zinbryta
Zinbryta is injected monthly. Try to keep to a particular day of the month to help remember your injection.

- If you do forget a dose, and it is within 2 weeks of your missed dose, inject as soon as you can. Then carry on as normal, sticking to your usual injection day.
- However, if it is more than 2 weeks from your missed dose, skip the missed dose and take your next dose on your usual day.

In either case, do not use two injections to make up for a missed dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. **Do not try to treat any side effects yourself**, but contact your doctor or nurse. Some side effects may require your doctor to interrupt your treatment and refer you to a specialist.

Serious side effects:

Liver problems:

(Common - may affect up to 1 in 10 people)

- unexplained nausea (feeling sick)

- vomiting (being sick)

- stomach pain
- increased tiredness
- loss of appetite (anorexia)
- your skin or the whites of your eyes turn yellow
- dark (tea-coloured) urine

Contact your doctor immediately. These may be signs of a serious liver problem. Your Patient Card has more information about these side effects.

Skin reactions:
(Common - may affect up to 1 in 10 people)
- severe wide-spread rash.

Depression:
(Uncommon – may affect up to 1 in 100 people)
- feeling unusually sad, hopeless or bad about yourself
- irritability, getting upset easily
- nervousness, anxiety
- thoughts of hurting yourself or suicide

Lung infections:

(Common - may affect up to 1 in 10 people)
- lung infection (e.g. pneumonia, bronchitis)

Low red blood cell counts (autoimmune haemolytic anaemia):
(Uncommon – may affect up to 1 in 100 people)
- paleness
- increased tiredness
- dark urine
- shortness of breath
- your skin or the whites of the eyes turn yellow

Increased tiredness, dark urine and skin or whites of the eyes turning yellow also may be symptoms of liver problems, see section above on liver problems.

Inflammation of the bowel (colitis):
(Uncommon – may affect up to 1 in 100 people)
- diarrhoea that does not go away
- stomach pain
- fever
- blood in your stools

Stomach pain may also be a symptom of liver problems, see section above on liver problems.

Low level of a type of white blood cells (called lymphocytes):
Zinbryta could reduce your level of these white blood cells so you will have a blood test every 3 months.

Contact your doctor immediately if you get any serious side effects.

Other side effects:

Very common side effects
(These may affect more than 1 in 10 people)

- infections of the airways, such as coughs and colds (nasopharyngitis, upper respiratory tract infection)

Common side effects
(These may affect up to 1 in 10 people)
- inflammation (swelling) of the liver
- flu (influenza)
- sore throat, tonsillitis (pharyngitis, laryngitis)
- runny nose (rhinitis)
- skin rashes, including inflamed, irritated, itchy, dry or peeling skin (dermatitis, eczema, psoriasis)
- skin infection (folliculitis, acne)
- decreases in the amount of white blood cells (these will show up in blood tests)
- increases in body temperature (fever)
- increases in liver enzymes in the blood (these will show up in blood tests)
- inflamed or enlarged lymph nodes (lymphadenopathy, lymphadenitis)
- diarrhoea
- changes in your blood (anaemia) which may make you feel weak

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. Do not try to treat any side effects yourself. 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 Zinbryta

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 carton and the label after 'EXP'. The expiry date refers to the last day of that month.

- Keep the Zinbryta pre-filled syringe/pen in its original package to protect from light. Keep the pack closed until you need to use a new syringe/pen.
- Store in a refrigerator (2°C to 8°C).
  - Do not freeze. Throw away any Zinbryta that is accidentally frozen.
- If a refrigerator is not available, Zinbryta syringes/pens can be stored at room temperature (up to 30°C) in the original pack for up to 30 days.
  - Make sure Zinbryta is out of the refrigerator for no longer than 30 days.
  - If Zinbryta has been outside of the refrigerator for more than a total of 30 days or if you are not sure how long Zinbryta has been at room temperature, throw the syringe/pen away (see section 7, Instructions for injecting Zinbryta).
- Do not place Zinbryta back into the refrigerator after warming to room temperature.

Additional information
Do not use this medicine if you notice that:
- the syringe/pen is cracked or broken.
- the solution is cloudy or you can see particles floating in it.
- the solution is any other colour than colourless to slightly yellow.
- the pen has been dropped or is visibly damaged.

Disposal
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 Zinbryta contains

The active substance is daclizumab.

Each pre-filled syringe contains 150 mg of daclizumab in 1 mL solution for injection.
Each pre-filled pen contains 150 mg of daclizumab in 1 mL solution for injection.

The other ingredients are sodium succinate, succinic acid, sodium chloride, polysorbate 80, water for injections (see section 2 ‘Zinbryta contains a small amount of sodium’).

What Zinbryta looks like and contents of the pack
Zinbryta is a colourless to slightly yellow, clear to opalescent liquid contained within a syringe/pen.

Pack sizes: Each pack contains one pre-filled glass syringe/pre-filled pen with an attached needle, ready to inject. A multipack of three packs of one syringe/pen is also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

Manufacturer
Biogen (Denmark) Manufacturing ApS
Biogen Allé 1
Hillerød
DK-3400
Denmark

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Biogen Belgium N.V./S.A.
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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.

Instructions overleaf ➲

7. Instructions for injecting Zinbryta

How to inject Zinbryta
Read the instructions before you start using Zinbryta and each time you get a refill of your prescription. There may be new information. This information does not take the place of talking to your doctor or nurse about your medical condition or your treatment.

Note:
- **Before you use the Zinbryta pre-filled syringe for the first time,** your doctor or nurse should show you or your carer how to prepare and inject the Zinbryta pre-filled syringe.
- ⚠ **Do not** use more than one pre-filled syringe per month.
- Zinbryta pre-filled syringe is for injecting the medicine under the skin only (subcutaneous).
- **Each Zinbryta pre-filled syringe can be used once only. Do not** share Zinbryta pre-filled syringe with anyone else.

Supplies needed for your Zinbryta injection

- Zinbryta pre-filled syringe

150 mg Prefilled Syringe

Figure A

Additional supplies which are not included in the pack (See Figure B):
- alcohol wipe
- gauze pad
- adhesive bandage or plaster

Ask your doctor, pharmacist, or nurse for instructions on throwing away used syringes.

Alcohol Wipe | Gauze Pad | Adhesive Bandage

Figure B

Parts of the Zinbryta pre-filled syringe (See Figure C)

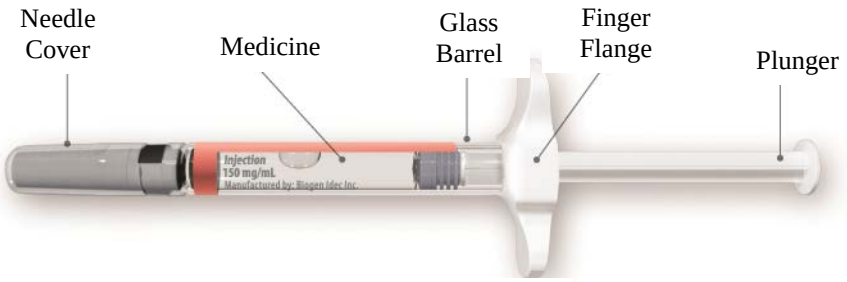


Figure C

Preparing for your injection

Note:

- **Before you prepare your injection, take the syringe out of the fridge and let it warm to room temperature. This takes around 30 minutes.**
  - ⚠ **Do not** use external heat sources such as hot water to warm Zinbryta pre-filled syringe.
- The Finger Flange will allow you to better grip the syringe and should remain attached.

Step 1: Collect your supplies and wash your hands

- Use a well-lit, clean, flat surface to work on, like a table. Collect all the supplies you will need to give yourself or to receive an injection.
- Wash your hands with soap and water.

Step 2: Check The Zinbryta Pre-filled Syringe

- Check the expiry date on the Zinbryta pre-filled syringe (See Figure D).
  - ⚠ **Do not** use the Zinbryta pre-filled syringe past the expiry date.
- Check that the Zinbryta medicine is colourless or slightly yellow (See Figure E).
  - ⚠ **Do not** use the Zinbryta pre-filled syringe if the liquid is cloudy, or has floating particles in it.
  - o You might see air bubbles in the Zinbryta medicine. This is normal and the bubbles do not need to be expelled before your injection.

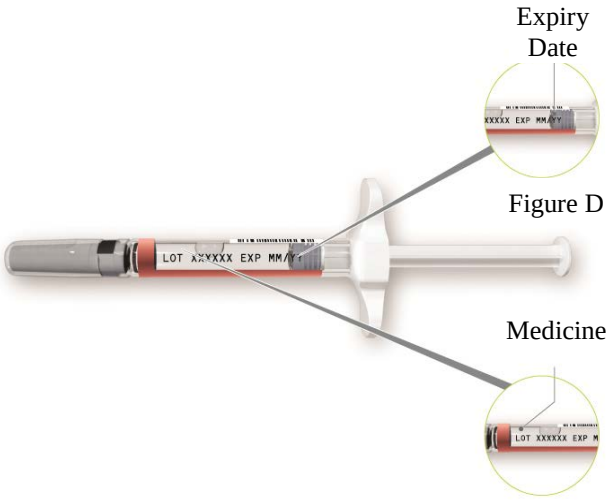


Figure D

Figure E

Giving the Injection

Step 3: Choose and clean your injection site

- Zinbryta pre-filled syringe is for subcutaneous injection (injection into skin).
- Zinbryta pre-filled syringe should be injected into the abdomen, thigh, or the back of the upper arm (see Figure F).
  - ⚠ **Do not** inject directly into your belly button.
  - ⚠ **Do not** inject into an area of the body where the skin is irritated, tender, red, bruised, tattooed, infected or scarred.
- Choose an injection site and wipe the skin with an alcohol wipe.
- Let the injection site dry on its own before injecting the dose.

⚠ **Do not** touch or blow on this area again before giving your injection.

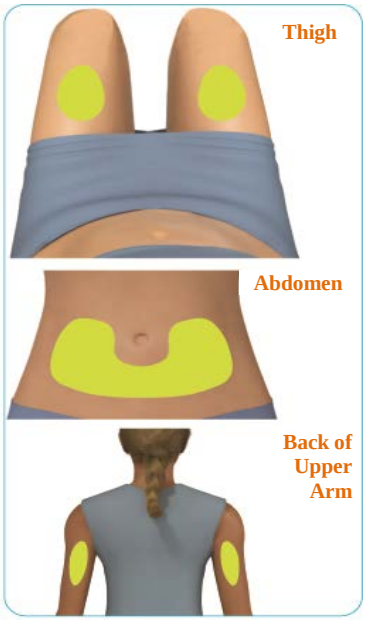


Figure F

Step 4: Firmly remove the needle cover

- Using one hand, hold the syringe by the glass barrel. Be sure that this hand is not pushing on the Finger Flange. With your other hand, firmly grasp the needle cover and pull it straight off the needle (See Figure G).

⚠ **Use caution** when removing the needle cover to avoid getting a needle injury.

⚠ **Do not** touch the needle.

⚠ **Caution - do not** recap the Zinbryta pre-filled syringe. You could get a needle injury.

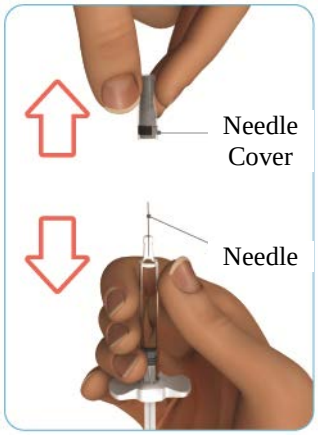


Figure G

Step 5: Gently pinch your injection site

- Gently pinch the skin around the cleaned injection site using thumb and forefinger to create a slight bulge. (See Figure H.)

Figure H

Step 6: Inject Medicine

- Hold the Zinbryta pre-filled syringe at a 45°-90° angle to the injection site (see Figure I). Quickly insert the needle straight into the skin fold until the needle is fully under the skin. (See Figure I.)
- After the needle is in, let go of your skin
- ⚠ **Do not** pull back on the plunger.

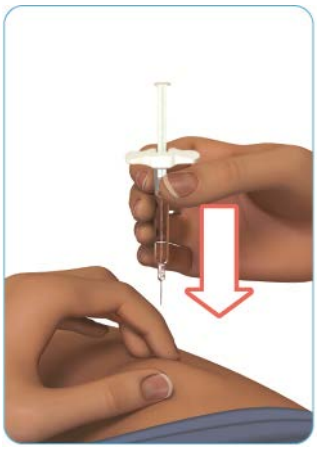


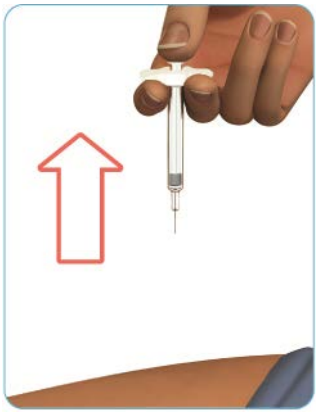
Figure I

- Slowly push the plunger all the way down until the syringe is empty. (See Figure J.)
- ⚠ **Do not** take the Zinbryta pre-filled syringe out of the injection site until you have pushed the plunger all the way down.

Figure J

<table>
<tr><td colspan="2">Step 7: Remove the pre-filled syringe from your injection site</td></tr>
<tr><td>• Pull the needle straight out. (See Figure K.)

⚠ Caution - do not recap the Zinbryta pre-filled syringe. You could get a needle injury.

⚠ Do not reuse the Zinbryta pre-filled syringe.</td><td> 
Figure K</td></tr>
<tr><td colspan="2">After your injection</td></tr>
<tr><td colspan="2">Step 8: Disposing of the used Zinbryta Pre-filled Syringe</td></tr>
<tr><td colspan="2">• Check with your doctor, pharmacist or nurse about the right way to throw away the used syringe.</td></tr>
<tr><td colspan="2">Step 9: Care for your injection site</td></tr>
<tr><td colspan="2">• If needed, apply the gauze pad, adhesive bandage or plaster to the injection site.</td></tr>
</table>

General Warnings

⚠ **Do not** reuse Zinbryta pre-filled syringe.
⚠ **Do not** share Zinbryta pre-filled syringe.
• **Keep Zinbryta pre-filled syringe and all medicines out of reach and sight of children.**

Storage

• Recommended storage is controlled refrigeration 2°C to 8°C in the closed original carton to protect from light.
• If needed, Zinbryta may be stored in the closed original carton without refrigeration up to 30°C for up to 30 days.
⚠ **Do not** place Zinbryta pre-filled syringe back into the refrigerator after warming to room temperature.
⚠ **Do not** freeze or expose to high temperatures.

7. Instructions for injecting Zinbryta

⚠ **Caution! Do not** remove the cap until you are ready to inject.

Read the instructions before you start using Zinbryta and each time you get a refill of your prescription. There may be new information. This information does not take the place of talking to your doctor or nurse about your medical condition or your treatment.

Note:

- **Before you use the pen for the first time,** your doctor or nurse should show you or your carer how to prepare and inject the pen.
- The pen is for use under the skin only (subcutaneous).
- Each pen can be used once only.
- ⚠ **Do not share** the pen with anyone else to avoid giving an infection to them or getting an infection from them.
- ⚠ **Do not use more than 1** pen per month.
- ⚠ **Do not use** the pen if it has been **dropped or is visibly damaged**.

Supplies needed for Zinbryta Pen injection:

- 1 Zinbryta 150 mg Pen (see Figure A)

Before Use – Parts of Zinbryta Pen (See Figure A):

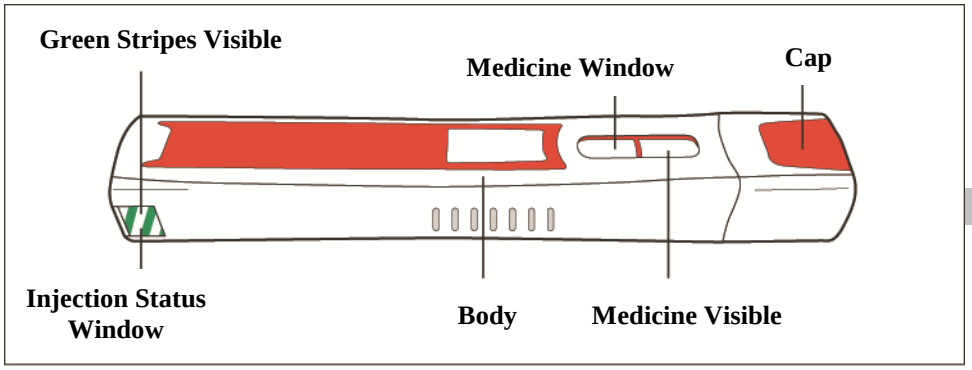


Figure A

⚠ **Caution! Do not remove the cap** until you are ready to inject. If you remove the cap, do not re-cap the pen. Re-capping could cause the pen to lock.

Additional supplies which are not included in the pack (See Figure B):

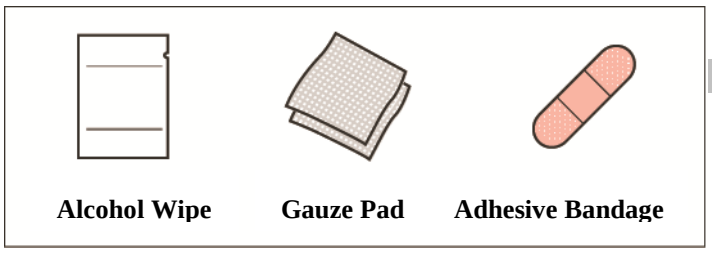


Figure B

Preparing for your injection

Step 1: Remove the pen from the fridge

a. Remove the pen from the carton in the fridge 30 minutes before giving your injection to allow it to warm to room temperature.

⚠ **Do not** use external heat sources, such as hot water, to warm the pen.

Step 2: Collect your supplies and wash your hands

a. Find a well-lit area and a clean, flat surface, like a table, and collect all the supplies you will need to give yourself, or to receive, an injection.

b. Wash your hands with soap and water.

Step 3: Check the Zinbryta Pen (Figure C)

a. Check the injection status window. You should see green stripes.

b. Check the expiry date.

c. Check the medicine window and make sure the Zinbryta medicine is colourless to slightly yellow.

⚠ **Do not** use the pen if:

- **You do not see the green stripes** in the injection status window.
- **It is expired**.
- **The liquid is cloudy or contains floating particles**.

Note: You might see air bubbles in the medicine window. This is normal and will not affect your dose.

⚠ **Do not use** the pen if it has been **dropped or is visibly damaged**.

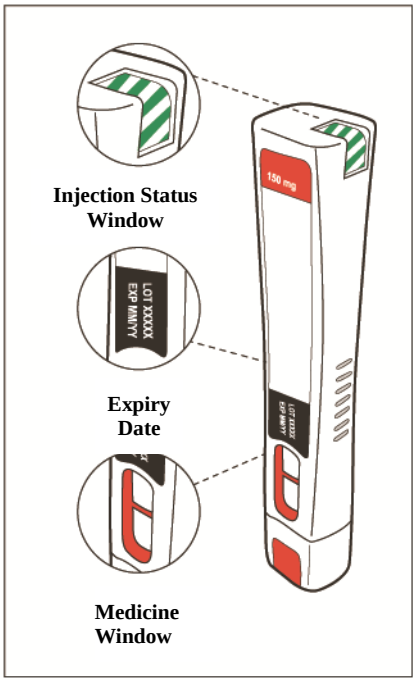


Figure C

Step 4: Choose and clean your injection site

a. Choose an injection site in your thigh, abdomen, or the back of your upper arm (See highlighted areas in Figure D).

- If some areas are too difficult for you to reach, ask a carer who has been trained to help you.

⚠ **Do not** inject into an area of your body where **the skin is irritated, red, bruised, tattooed, infected, or scarred**.

⚠ **Do not** inject directly **into your belly button**.

b. Wipe your skin with an alcohol wipe.

⚠ **Note: Do not touch or blow** on this area before giving your injection.

c. Let your injection site dry on its own before injecting your dose.

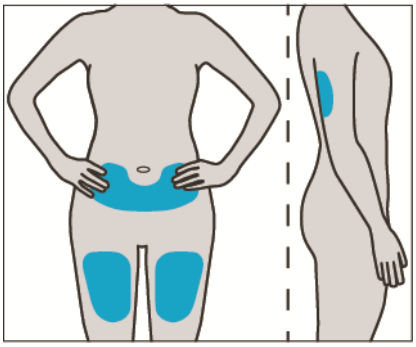


Figure D

Giving your injection

Step 5: Remove the Zinbryta Pen cap

a. Pull the pen cap straight off and set it aside (See Figure E). Your pen is now ready to inject.

⚠ **Warning! Do not** touch, clean or manipulate the needle cover. You could get a needle injury or the pen may lock.

⚠ **Do not re-cap the pen**. This could lock the pen.

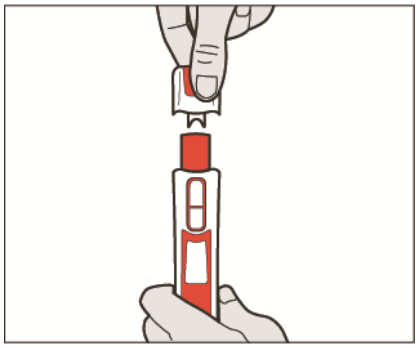


Figure E

Step 6: Give the injection

a. Hold the pen over your injection site. Make sure you can see the green stripes in the injection status window (see Figure F).

- You should hold the pen over your injection site at a 90° angle.

Note: Do not rest the pen on the injection site until you are ready to inject. This may cause the pen to accidentally lock.

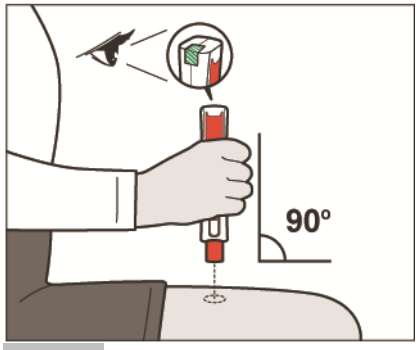


Figure F

b. Firmly press and hold down the pen on your injection site. You will hear the clicking sounds start.
This tells you that the injection is happening (see Figure G).

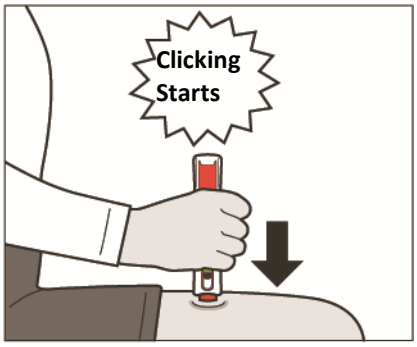


Figure G

c. Continue to hold the pen firmly down on your injection site until the clicking sounds have stopped (see Figure H).

⚠ **Do not lift** your pen off your injection site until the clicking sounds stop and you see green ticks in the injection status window.

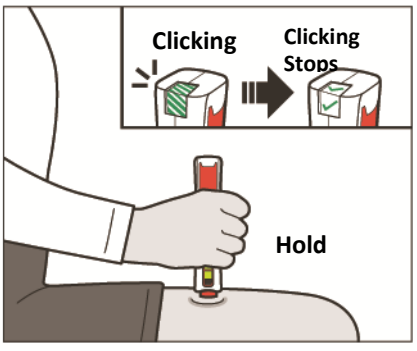


Figure H

Warning! If you do not hear clicking sounds or you do not see green ticks in the injection status window after attempting to inject, the pen may have locked and you may not have received your injection. You should then **contact your doctor, nurse or pharmacist.**

Step 7: Remove the Zinbryta Pen from your injection site

a. After the clicking sound has stopped, lift the pen from your injection site. The needle cover will extend to cover the needle and will lock (See Figure I).

• If you see blood at your injection site, wipe it off with the gauze pad and apply an adhesive bandage or plaster.

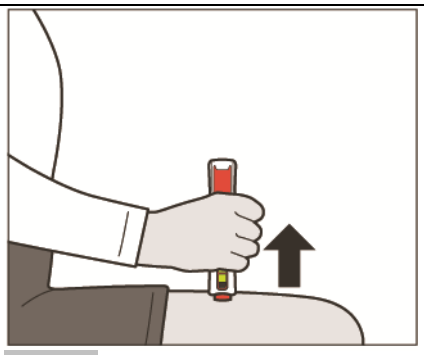


Figure I

Step 8: Check to make sure you have received your full dose of Zinbryta (see Figure J).

a. Check the injection status window. You should see green ticks.

b. Check the medicine window. You should see a yellow plunger.

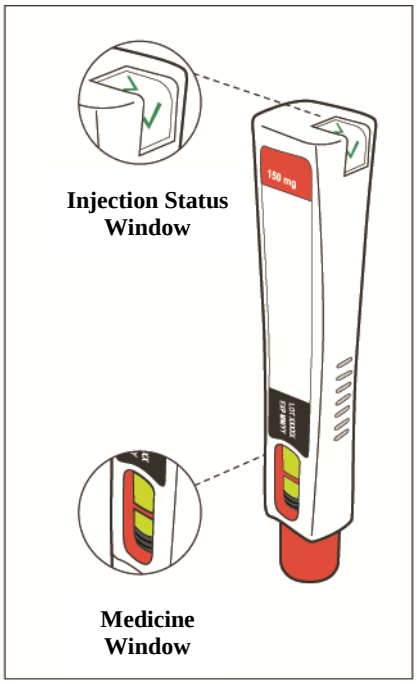


Figure J

After your injection

After Use – Parts of your Zinbryta Pen (see Figure K):

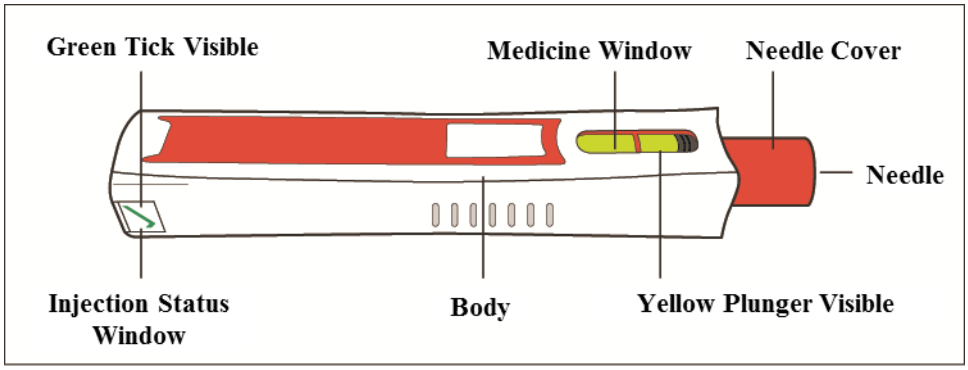


Figure K

Note: After the pen has been removed from the injection site, the needle cover will lock to protect against needle injury. **Do not re-cap the pen.**

Step 9: Disposing of used Zinbryta Pens

- Check with your doctor, pharmacist or nurse about the right way to throw away the used pen.
- **Do not re-cap the pen.**

Step 10: Care for your injection site

- If needed, apply a gauze pad, adhesive bandage or plaster to the injection site.

Storage

- Recommended storage is controlled refrigeration 2°C to 8°C in the closed original carton to protect from light.
- If needed, Zinbryta may be stored in the closed original carton without refrigeration up to 30°C for up to 30 days.
- **Do not** place Zinbryta pen back into the refrigerator after warming to room temperature.
- **Do not** freeze or expose to high temperatures.
- **Keep Zinbryta pen and all medicines out of reach and sight of children.**