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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Zinbryta

INN/active substance: daclizumab

Procedure number: EMEA/H/A-20/1456/C/003862/0010

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

On 7 June 2017, the European Commission (EC) was informed of a fatal case of fulminant liver failure in a patient treated with daclizumab in an ongoing observational study, despite monthly liver function testing performed in accordance with recommendations in the product information. In addition, 4 cases of serious liver injury were reported from clinical trials, in the first periodic safety update report (PSUR).

Transaminases elevations and serious hepatic injury are known risks associated to treatment with Zinbryta (daclizumab) and several risk minimisation measures (RMMs) were implemented in this regard at the time of the initial marketing authorisation, including monthly liver function monitoring. However, in view of the seriousness of the reactions reported, leading in one case to a fatal outcome despite adherence to the RMMs, the EC considered that the impact of the risk of liver injury on the benefit-risk balance of the medicinal product and the adequacy of the related RMMs should be reviewed.

On 9 June 2017 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Zinbryta (daclizumab) and to issue a recommendation on whether the marketing authorisation should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Daclizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that modulates Interleukin-2 (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 multiple sclerosis (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 central nervous system (CNS) pathology in MS and thereby reduce the occurrence of relapses and disability progression.

Zinbryta (daclizumab) is authorised in the European Union (EU)/European Economic Area (EEA) since 1 July 2016. As of 30 April 2017, 2,236 patients had received Zinbryta in the clinical development program and 960 were included in a long-term extension study. The post-marketing exposure in the EEA is estimated at 2,421 patients (872 patient years) and worldwide at 3,513 patients (1,262 patient years). In the EEA, as of 30 April 2017, daclizumab had been marketed in Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Slovenia, Sweden and United Kingdom and used in 10 of these countries. At the time of referral of the matter to the PRAC, it was indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

At time of initial marketing authorisation, transaminases elevations and serious hepatic injury were reflected in the risk management plan (RMP) of Zinbryta as important identified risks. Routine and additional RMMs have been implemented to mitigate these risks, such as a monthly monitoring of liver enzymes, recommendations on interruption and discontinuation of treatment, guidance on

investigation of other causes and recommended observation period for hepatic signs and symptoms. A physician guide and a patient card have also been implemented.

This procedure under Article 20 of Regulation (EC) No 726/2004 was initiated to review the risk of liver injury, its impact on the benefit-risk balance of the medicinal product and the adequacy of the related RMMs further to the report of a fatal case of fulminant liver failure in a patient treated with daclizumab in an ongoing observational study (ZEUS), despite monthly liver function testing performed in accordance with recommendations in the product information. In addition, 4 cases of serious liver injury were reported from clinical trials, in the first PSUR, covering the period 27 May 2016 to 26 November 2016.

Whilst the impact of these cases on the overall risk of liver injury and on the benefit-risk balance of daclizumab was not fully elucidated, based on the preliminary information available in July 2017, the PRAC considered that provisional measures were needed while the issue was being further reviewed[1]. The PRAC considered that as a precautionary measure the use of daclizumab should be restricted to adult patients with highly active relapsing disease despite a previous 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. The PRAC also considered that daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment. In addition, the Committee recommended, as provisional measures to further minimise the risk of liver injury, to strengthen the current warnings to take due account that all patients should be monitored for signs and symptoms of hepatic injury and that liver functions testing should be performed at least monthly, to promptly refer patients to an hepatologist in case of signs or symptoms suggestive of such injury and that treatment initiation is not recommended in patients with other autoimmune conditions. Caution should also be used when medicinal products of known hepatotoxic potential are used concomitantly. In addition, consideration should be given to discontinue treatment if an adequate therapeutic response is not achieved. The European Commission issued a decision on the provisional measures on 14 July 2017 which was corrected on 29 August 2017, to take account of a minor revision of the PRAC recommendation.

Acute liver failure (ALF), interchangeably referred to as fulminant hepatic failure, is rare, but is serious as it can result in the need for liver transplantation and has a high fatality rate. Drug-induced liver injury (DILI) is the leading cause of ALF in the developed world (Bernal, 2010 [2]; Blackmore, 2015 [3]). Most cases of DILI resolve spontaneously with the cessation of the offending drug. However, approximately 10% of DILI cases will progress to ALF and among those as many as 80% will have a fatal outcome or require liver transplantation (Bernal 2010 [1]).

2.2. Data on safety

The PRAC reviewed detailed information provided by the MAH on all cases of liver injury that occurred among the 2,236 subjects enrolled and dosed at least once with daclizumab across 6 interventional phase 2 or 3 studies and among the 3,513 patients administered daclizumab in post-marketing settings. Five of the 6 studies were completed[4] and one still ongoing[5] at the time of this report. A summary of the relevant information is included below.

[1] More information is available in the published assessment report on provisional measures
[2] Bernal W, Auzinger G, Dhawan A, et al. Acute liver failure. Lancet. 2010;376(9736):190-201.
[3] Blackmore L, Bernal W. Acute liver failure. Clin Med (Lond). 2015;15(5):468-72.
[4] 205MS201/SELECT Phase 2, double-blind, placebo-controlled, dose-ranging; 205MS202/SELECTION Phase 2, double-blind, extension; 205MS203/SELECTED Phase 2b, open-label, single-arm, long-term extension; 205MS301/DECIDE Phase 3, double-blind, parallel group, active control; 205MS302/OBSERVE Phase 3, single-arm, open-label, with extension.
[5] 205MS303 /EXTEND Phase 3, single-arm, open-label extension.

2.2.1. Clinical safety data

The cumulative incidence and incidence rates for liver enzyme elevations and serious liver injury were calculated using exposure from these 6 studies including long-term extension studies, through to 26 May 2017. A total of 2,236 patients have been enrolled in clinical trials with a follow-up time of 8,309 patient-years of exposure. In the clinical trials 1.7% of the subjects suffered at least 1 serious liver injury event, corresponding to a rate of 4.45 events per 1000 patient-years. Almost 50% of patients included in the clinical trial setting and treated with daclizumab 150 mg and 65% on daclizumab 300 mg experienced at least one episode of liver enzymes elevation (> 1x upper limit of normal (ULN)). Peak alanine transaminase (ALT) or aspartate transaminase (AST) increase based on laboratory data observed in clinical trials in patients treated with daclizumab 150 mg, compared to patients treated with interferon beta-1a and with placebo is presented in the below table. The median time to onset (TTO) of the first hepatic event was 488.5 days, ranging from 1 to 1,965 days, including up to 6 months after stopping treatment. In clinical trials, 13.5% of patients had transaminase elevations above 3 times the ULN, out of which 17% had a further elevation. The proportion of patients with hepatic events (defined as those preferred terms in the Standardised MedDRA Queries (SMQ) "drug related hepatic disorders") accrued at a constant rate up to week 216 on daclizumab treatment.

Table 1. Cumulative incidences of peak ALT or AST increase (based on laboratory data) observed in clinical trials

	Daclizumab 150 mg (N=1943)	Interferon beta-1a (N=922)	Placebo (N=204)
Total exposure (subject-years)	7011	1884	210
≥ 3 x ULN	13.6%	8.5%	3.4%
> 5 x ULN	9.0%	3.4%	0.5%
> 10 x ULN	4.3%	1.3%	0.0%
> 20 x ULN	1.4%	0.4%	0.0%
AST or ALT ≥ 3 x ULN AND total bilirubin ≥ x 2 ULN	0.77%	0.1%	0.5%

The MAH also provided subgroup analyses of safety by disease activity from the controlled clinical studies (see definitions of high disease activity in section 2.3. data on efficacy). In study 205MS301, the incidence of hepatic events in the 150 mg daclizumab arm was 16% (91 subjects) in subjects with low/unknown disease activity and 15% (53 subjects) in those with high disease activity and in the Interferon beta-1a (IFN β-1a) group the incidence was 16% in subjects with high disease activity and 13% in subjects with low disease activity. The incidence of serious hepatic events was low (<1%) in both the IFN β-1a and daclizumab treatment arms and was similar in the disease activity subgroups within each treatment arm. The incidences of hepatic and serious hepatic events in the subset of subjects with highly active disease treated with daclizumab were also similar to those for the overall population of the same treatment arm (16% and 1%, respectively) (Kappos, 2015 [6]).

Maximum values for liver function tests were also similar in the high and low disease activity groups. Most subjects in both disease activity subgroups had maximum values for serum transaminases (worst

[6] Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. The New England journal of medicine. 2015;373(15):1418-28

of ALT or AST) that were <3×ULN. The incidence of maximum values >5×ULN was similar between the disease activity subgroups and the daclizumab (high disease activity, 4%; low disease activity, 8%) and IFN β-1a arms (4% and 3%, respectively). Also in the analyses of elevations of serum transaminases >5×ULN, no difference was evident between subjects with high disease activity and the general population exposed to daclizumab (incidence of elevations of serum transaminases >5×ULN 6%).

Serious cases of liver injury

In the six clinical studies, besides a high number of cases with increases of liver enzymes, 39 cases of serious liver injury were observed in patients exposed to daclizumab. Among these 39 cases, 23 were considered probable or possibly related to daclizumab treatment, 6 cases were classified as unlikely related due to concomitant hepatotoxic medication with a more plausible temporal association (duloxetine/tizanidine, valproic acid, methylprednisolone, azytromicine and sertraline), but in which the role of daclizumab could not totally be ruled out. High levels of hepatic enzymes were observed in 5 out of the 6 cases; biopsies were not available. In addition, 10 cases were unassessable or considered as not related due to alternative causal agent, negative rechallenge or other pathological process.

In the cases assessed as probably or possibly related 14 patients were female and 9 male, aged between 20 and 57 years old. The TTO ranged from 2 to 73 months (mean TTO ≈ 1000 days; median 886 days (Range 59 to 2410). Mean and median number of daclizumab doses to the first serious event was 34.1 and 28.0 doses (Range 3 to 85). Four cases of liver injury occurred 2 to 5 months following study termination per protocol or the treatment discontinuation due to experience the adverse event toxicodermia. Most of the related cases occurred under 150 mg treatment, in only two instances the patient was being treated with the dose of 300 mg at the event onset and in 3 cases the patient had received the higher daclizumab dose in a previous treatment. The number of 150 mg daclizumab-treated patients in clinical trials was roughly 7 times the number of 300 mg treated patients and the follow-up exposure expressed in patient-years was 5 times greater. Most patients (18/23) reported no sign or symptoms of liver injury and the reaction was detected either through monthly monitoring or when hospitalised due to a MS relapse or other clinical condition. Pre-existing liver conditions or comorbidities have not been reported for these patients, which could be explained by the exclusion criteria of the studies. Twenty-one cases resolved upon treatment interruption, one was not resolved and one was fatal.

An hepatocellular pattern was observed in all but one (22/23) patient (classified as cholestatic), and in seven cases autoimmune components were identified (positive autoantibodies, increases in serum IgG, fluctuations of liver enzymes, improvement with immunosupressive therapy, clinical features suggestive of autoimmune injury such as delayed onset of the adverse drug reactions (ADR) could be attributed to immunological nature of the event). The clinical manifestations of the damage vary from raises of liver enzymes to acute hepatitis.

Most of the 23 patients were taking concomitant medications related to symptomatic treatment of the underlying disease or for associated disorders. In 4 cases no concomitant medication were reported at the event onset. The medications most frequently used by these patients were CNS acting agents (e.g. escitalopram, sumatriptan, tramadol/paracetamol, carbamacepine, venlafaxine and lorazepam). In addition, antibiotics, oral contraceptive therapy and medicines employed to treat MS relapses are frequently reported. In cases where patients were taking concomitant hepatotoxic medications, in some instances the subject had already been on that treatment for a long period of time, including before starting treatment with daclizumab, whereas in others multiple previous short expositions to hepatotoxic agents were present with no alterations of the hepatic enzymes.

The fatal case concerned a 46 years old woman, with a body mass index (BMI) of 27, diagnosed with MS in June 2000. She received a total of 13 doses of daclizumab 300mg between June 2009 and May 2010 during which the results of her hepatic test were observed within reference range. In May 2010 she presented with transaminase elevations (ALT 63U/L and AST 58 U/L) and was randomised to a 5 months washout period, transaminase values normalised a month later. Eight additional doses were planned from November 2010. At the third dose, transaminases were elevated (ALT 195, AST 141, alkaline phosphatase (ALP) and total bilirubin (TB) normal), and further increased at the following dose (which was the last) without symptoms (ALT 419 U/L, AST 420 U/L, TB 1.35mg/dL, ALP 222 U/L and gamma-glutamyltransferase (GGT) 297 U/L). The liver results progressively worsened and peaked three months later, the subject continued to deteriorate clinically and died the following month. Five days prior to death antinuclear antibody (ANA), anti-mitochondrial antibody and anti-smooth muscle antibody were negative while IgE was 1042.6 U/ml (normal <165.3), IgA 5.21 g/L (normal <4.00), IgG 17.9 g/L (normal <17.65) and IgM 6.77 g/L (normal <2.3). Serum alpha-1 antitrypsin, and ceruloplasmin values were normal. Post-mortem examination revealed an autoimmune hepatitis, fulminant form.

2.2.2. Post-marketing safety data

In the post-marketing setting through to 30 April 2017 the MAH has estimated 3,513 exposed patients with a follow-up time of 1,262 person-years. Although figures cannot be directly compared to those from clinical trial, a relatively similar magnitude is noted with regards to the reporting rate of serious liver injury which was estimated to be 0.45% (12.6 events per 1000 patient-years). In post-marketing 21% of patients experienced at least one episode of liver enzymes elevation (> 1x ULN).

Council for international organizations of medical sciences (CIOMS) forms were provided for the 84 cases (106 events) concerning hepatotoxicity, including 22 serious cases, reported from marketing to 26 June 2017. Most of these cases were reported in Germany and the United States (US). Information is limited for these cases but the 22 serious cases also reported a compatible temporal association. For 12 cases where this information was available, and that had not been previously included in clinical studies, TTO ranged between 1 and 5 doses (mean 2.9 doses). No relevant medical history is provided in most of the cases. Thyroidal disease was reported in the fatal case from an observational study (ZEUS), previous abnormal liver function tests and hepatitis A were each reported in one case. Seventeen (17) cases reported raised liver tests or liver injury: 11 cases do not provide ALT or AST levels; the remaining 6 cases presented more than 5 times the ULN of ALT (considering a normal value of ALT as 35), from 191 to 1,312. Two cases reported jaundice, with unknown liver values. Three cases reported autoimmune hepatitis, two with autoantibodies positive (one fatal described below) and one with autoantibodies negative. Information on presence or absence of symptoms is not available in some cases. Seven cases referred symptoms and in 6 the liver injury seemed to be detected through liver monthly monitoring. In most of the cases treatment was discontinued and the reaction resolved or, for some, not yet resolved at the time of the report, one case was fatal. Six patients did not stop treatment despite reporting serious liver injury.

In the 7 cases where concomitant treatment was provided, scarce information on dates is available. In the fatal case tizanidine treatment started 2 months before onset of the reaction; in the second patient treated with tizanidine, it was started at the same time than daclizumab, 4 months before occurrence of liver injury. Other concomitant treatments were reported without information on timing of treatment, antidepressants in 4 patients (trimipramine, citalopram, escitalopram or amitriptyline), antihypertensive drugs (enalapril, valsartan, lercanidipine) and treatments to alleviate symptoms of MS such as baclofen, gabapentine, metamizole, or ropinirole.

Insufficient information to assess causality was reported in 15 cases. In the 5 well documented cases the causality was considered possible or probable. Cases where liver enzymes values were available supported a hepatocellular pattern. Necropsy from the fatal case is also compatible with autoimmune hepatitis.

The fatal case of fulminant liver failure occurred in a patient diagnosed with relapsing multiple sclerosis, who started treatment with daclizumab the same month in an observational study (ZEUS) and received a total of 4 doses. This patient had a 5.5 score on the Expanded Disability Status Scale (EDSS) and was given daclizumab as a first DMT. Monthly liver test monitoring was conducted while on daclizumab, and all results were within normal limits, including laboratory tests conducted 6 days prior to the last daclizumab dose. Relevant medical history included autoimmune thyroiditis and obesity (BMI = 30 to 35 kg/m^2). The patient had no reported medical history of liver disease; however, 2.5 weeks prior to initiation of daclizumab treatment, serum transaminases were mildly elevated with AST 42.2 U/L (reference range <35) and ALT 84.8 U/L (reference rage <35), which was attributed to treatment for MS which included high dose intravenous steroids. Daclizumab treatment was started the day following the lowering of serum transaminases within the reference range. Concomitant medications included oral contraceptives and 2 mg/day doses of tizanidine (started over a month later). The patient became ill 25 days following the last dose of daclizumab, developed jaundice two days later and was admitted to hospital where liver failure was diagnosed 30 days after the last dose (AST 3041 U/L, ALT 4760 U/L, ALP 204 U/L and TB 8.8 mg/dL with a hepatocellular pattern; ANA and antineutrophil cytoplasmic antibody (ANCA) levels highly elevated). Liver transplant took place the day following admission. The patient experienced graft dysfunction, haemorrhagic shock secondary to gastroesophageal junction ulcer Forrest Ib and died 37 days after the last dose of daclizumab. Death was attributed to haemorrhagic shock, secondary to upper gastrointestinal bleeding and systemic inflammatory response syndrome, both of which were considered caused by liver failure.

The MAH provided an analysis of the factors that led to the identification of the cases of serious liver injury in post-marketing settings, through to 26 June 2017, for the 29 serious hepatic events in 25 post-marketing cases that reported adverse events coding to Medical Dictionary for Regulatory Activities preferred terms (MedDRA PT) in one of the following SMQs (search in the MAH database as of 15 August 2017): cholestasis and jaundice of hepatic origin, hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, hepatitis, non-infectious, liver malignant tumours, liver neoplasms, benign (including cysts and polyps), liver related investigations, signs and symptoms, liver tumours of unspecified malignancy and Liver-related coagulation and bleeding disturbances. In 7 cases only laboratory tests were abnormal, 3 cases presented clinical symptoms first and in 4 cases there were only clinical symptoms, in one cases both symptoms and liver test abnormalities were reported without information on timing, and in 10 cases information was insufficient on these aspects.

2.2.3. Discussion on safety

During clinical trials with daclizumab, transaminase elevations and serious hepatic injury was determined to be an important identified risk with daclizumab. In addition, a rare but increased risk of developing progressive and clinically important liver injuries that may include liver failure resulting in transplant or fatal outcome was noted.

Based on the thorough review of the cases, it is apparent that liver injuries caused by daclizumab are not dose-dependent and can occur throughout treatment and up to 6 months after treatment. No time window of a higher risk can be identified. In the post-marketing cases, time to onset was shorter than in cases from clinical trials.

An analysis of the effect of potentially hepatotoxic concomitant medications on transaminase elevations showed no increases in categorical elevations in transaminases in clinical trial subjects who were treated with potentially hepatotoxic medicinal products compared to those who did not receive such medicinal products. Analyses were also conducted to assess if the timing of initiation of potentially hepatotoxic medications had any impact on the risk of transaminase elevations with daclizumab. A similar incidence of transaminase elevations in subjects who initiated hepatotoxic medication prior to the start of daclizumab treatment and those who initiated hepatotoxic medication while already receiving daclizumab was observed. In most serious liver injury cases no concomitant hepatotoxic medication with a plausible temporal association was reported. No common medications or group of medications or pattern of administration has been identified acting as a risk or contributing factor or triggering the daclizumab-induced liver injury. Elevations of hepatic enzymes have been observed in daclizumab-treated subjects who took hepatotoxic medication and in those who did not. There is no evidence suggesting a drug-drug interaction nor that hepatotoxic medication increases liver damage of daclizumab. Available data is insufficient to conclude on the role of concomitant hepatotoxic medication for the risk of liver injury in patients treated with daclizumab, nevertheless it is reasonable to diminish potential liver injury by not exposing daclizumab-treated patients to drugs known to be hepatotoxic, including non-prescription products and herbal remedies.

Other comorbidities, such as prior history of immune disorders or other potential genomic risk factors, that may play a role on the occurrence of liver damage have not been identified. Factors that may influence the occurrence of liver injury could not be identified from the analysis of the data from clinical trials. No relationship with biochemical markers has been established. Symptoms suggestive of hepatitis were seldom present, and abnormalities were mostly found through biochemical testing in clinical trials. Liver enzymes returned to normal levels upon treatment discontinuation and, in some cases, upon treatment with steroids, but two fatal cases have been reported in the framework of clinical studies and some cases had not yet resolved at the time of the report. Based on the limited information on the identification of the cases based on laboratory values or clinical signs and symptoms in post-marketing settings, it appears that both monthly liver monitoring test and information about prompt recognition of signs and symptoms of liver disease are important to minimize the risk of liver injury.

Data on IgG, IgE, anti-liver antibody levels, extended auto-immune profiling, histology and immunohistochemistry were not available in all the cases adjudicated to daclizumab which limits any conclusions in this regard. However the phenotype of drug-induced liver injury attributed to this product shows a quite consistent pattern typical of autoimmune hepatitis with mostly hepatocellular pattern of liver damage. These features are in the range of those reported for other medical products which characteristically induce an autoimmune-like phenotype yet only in a proportion of cases (De Boer 2017 [7]). No characteristic phenotype was detected that could be used to identify patients where treatment with steroids would be the most appropriate. Available data on all cases analysed is highly suggestive of an immune-mediated mechanism of serious liver injury caused by daclizumab. Necropsy from the fatal case observed in an observational study is also compatible with autoimmune hepatitis, and the same mechanism is highly suggestive for the cases observed in the clinical trials. This was further supported by the scientific advisory group (SAG), which was consulted during the course of this procedure (see section 3). The SAG was of the view that daclizumab's actions on the IL-2 receptor and pathway and its effect on regulatory T (Treg) cells is most probably the mechanism that is linked to the cases of DILI. Based on its mechanism of action it could be hypothesised that this immune-mediated injury is probably a result of dysregulation of the IL-2 pathway, resulting in quantitative and or qualitative reduction in the function of Tregs.

[7] De Boer, Kosinski AS, Urban TJ, Zhao Z, Long N, Chalasani N et al. Features of Autoimmune Hepatitis in Patients With Drug-induced liver injury. Clin Gastroenterol Hepatol. 2017;15:103-112

The mechanism of action of daclizumab causes the reduction in Treg cells, and increase and activation of $CD56^{bright}$ NK cells. Taken together with the evidence of the role of immune tolerance in autoimmune hepatitis, both are important backgrounds that may explain the development of autoimmune hepatitis in some subjects receiving daclizumab, when other unidentified risk factors are still present. Additionally, it is unknown whether the reduction in circulating Treg cells and the expansion of the $CD56^{bright}$ NK cells could be involved in other autoimmune disorders. Immune-mediated or autoimmune conditions such as type I diabetes, colitis, autoimmune thyroiditis, pancreatitis, glomerulonephritis, were reported in low numbers during clinical trials, and haemolytic anaemia is already an important identified risk.

Therefore, although the exact physiopathological mechanism for the development of serious liver injury is unknown, the characteristics are highly suggestive of an immune-mediated mechanism and the role of prior history of immune disorders or potential consequences on the development of other autoimmune disorders are unknown. It was further noted that at least two serious cases of liver injury occurred in patients with pre-existing autoimmune conditions other than MS. The PRAC therefore considered that treatment initiation should not be recommended in these patients.

Regarding the latest fatal case reported from an observational study, the rapid evolution of the liver damage despite medicinal product withdrawal was remarkable. The patient was undergoing the recommended monthly monitoring of liver enzymes. The histological examination and the reduced weight of the liver observed in the autopsy are typical of acute liver failure owing to the parenchymal necrosis and liver structure collapse. Immunological features were also reported (ANA and ANCA were highly elevated). No pre-existing liver disease was mentioned by the pathologist. The patient was also taking tizanidine, a concomitant medication also reported in other non-fatal serious cases of liver injury, and oral contraceptives since an unknown date, none of which have been associated with immune-related liver injury. Oral contraceptives are reported to produce a cholestasis normally early on treatment, a pattern different from that observed in this and most of the cases of serious liver injury (hepatocellular pattern). Thus, in this fatal case no specific conditions/comorbidities or concomitant medication different from those described in the other cases of serious liver injury with daclizumab that could justify the rapid and fatal evolution of the case were identified. It is of concern that the RMMs in place did not prevent the fatal evolution.

Analyses from the controlled clinical trials in both subgroups with highly and non-highly active disease showed that the incidence of hepatic and serious hepatic adverse events and elevations of serum transaminases and serum markers of liver function does not appear to be impacted by the degree of multiple sclerosis activity.

Patients with a known history of or positive screening test result for hepatitis C virus (HCV) or hepatitis B virus (HBV) were excluded from clinical trials to avoid confounding the assessment of the safety of daclizumab. Therefore no correlation has been established between pre-existing HBV or HCV infections and the development of serious liver injury in relation to daclizumab at present. In view of the uncertainties around the exact mechanism of action of the immune-mediated liver injury and as the risk of hepatitis B reactivation with daclizumab has not been characterised, patients tested positive for these viruses prior to treatment initiation should be recommended to consult with a physician with expertise in the treatment of these conditions.

2.3. Data on efficacy

The efficacy of daclizumab was demonstrated in two pivotal studies in subjects with relapsing-remitting multiple sclerosis (RRMS), which led to the authorised indication in relapsing multiple sclerosis. Study 205MS201 was a placebo-controlled study, and study 205MS301 an active-controlled study versus

interferon beta-1a (IFN β-1a). Both trials enrolled a range of RRMS subjects who had recent relapse activity and were representative of the broader population of patients with RMS. Both studies demonstrated an effect of daclizumab on the primary efficacy endpoint of the annualized relapse rate: a 54% reduction versus placebo in Study 201 and a 45% reduction versus IFN β-1a in Study 301 (p <0.0001 for both). The risk of relapse was reduced by 55% over 1 year in daclizumab versus placebo-treated subjects in Study 201 (p <0.0001) and by 39% over 1 year and by 41% over 2 to 3 years in daclizumab versus IFN β-1a-treated subjects in Study 301 (p <0.0001 for both).

The MAH has made a subgroup analysis in both studies for patients with highly active disease and patient with non-highly active disease, for the following endpoints by baseline disease activity level: annualized relapse rate (using independent neurology evaluation committee (INEC) confirmed relapses), number of new or newly enlarging T2 lesions and 6-month sustained disability progression.

Patients with highly active disease have been defined by the MAH for these analyses as: (1) Subjects with 2 or more relapses in 1 year, and with 1 or more Gadolinium (Gd)-enhancing lesions on brain magnetic resonance imaging (MRI) or (2) Subjects who failed to respond to a full and adequate course (at least 1 year of treatment) of any DMT or specifically IFN-β, 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. The MAH has provided three different analyses: failure to a full and adequate course of IFN β or any DMT and a third analysis in rapidly evolving severe disease, combining the previous population.

Results from the placebo controlled study (205MS201) are limited by the small sample size and the relatively small proportion of subjects with highly active disease (around 20%, corresponding to 121 out of 600), therefore, results of study 205MS301 were considered more relevant and are presented below. The study 205MS301 which had a duration of 2 to 3 years provides data of approximately 40% of patients with highly active disease (744 out of 1841).

Table 2. Study 205MS301 highly active disease by failure of prior IFN β with or without criteria for rapidly evolving severe disease

	% reduction in daclizumab (DAC) vs. IFN β-1a (95% CI)		
	Highly active disease	Non-highly active disease	Overall population (INF 922; DAC 919)
Annualised relapse rate (at 3 years)	50 (38, 60)	39 (23, 51)	45 (36-53)
Number of new/newly enlarging T2 lesions at MRI (at 2 years)	54 (42, 63)	52 (41, 61)	54 (47-61)
Risk of 6-month confirmed disability progression (at 3 years)	43 (13, 63)	11 (-32, 39)	27 (2-45)

Table 3. Study 205MS301 highly active disease by failure of prior any DMT with or without criteria for rapidly evolving severe disease

	% reduction in daclizumab vs. IFN β-1a (95% CI)		
	Highly active disease	Non-highly active disease	Overall population (INF 922; DAC 919)
Annualised relapse rate (at 3 years)	48 (36, 58)	40 (24, 53)	45 (36-53)
Number of new/newly enlarging T2 lesions at MRI (at 2 years)	54 (43, 62)	51 (40, 61)	54 (47-61)
Risk of 6-month confirmed disability progression (at 3 years)	40 (11, 60)	10 (-37, 40)	27 (2-45)

Table 4. Study 205MS301 highly active disease criteria for rapidly evolving severe disease

	% reduction in daclizumab vs. IFN β-1a (95% CI)		
	Highly active disease	Non-highly active disease	Overall population (INF 922; DAC 919)
Annualised relapse rate (at 3 years)	58 (43, 69)	39 (26, 49)	45 (36-53)
Number of new/newly enlarging T2 lesions at MRI (at 2 years)	48 (34, 60)	53 (44, 61)	54 (47-61)
Risk of 6-month confirmed disability progression (at 3 years)	32 (-29, 64)	28 (0, 48)	27 (2-45)

2.3.1. Discussion on efficacy

The PRAC noted the clinically meaningful and statistically significant reductions in relapse rate and slowing of the accumulation of neurological disability observed in two controlled studies with daclizumab. These clinical effects were supported by robust and substantial treatment effects in reducing key brain MRI parameters of acute and chronic inflammatory and destructive CNS disease activity.

The PRAC noted that in the three subgroup analyses confidence intervals were wide for the annualized relapse rate, number of new or newly enlarging T2 lesions and 6-month sustained disability progression endpoints, which may be due to the small sample size available for the different subgroup analyses and overlap among subgroups. In addition, patients included in the interferon-controlled study have previously failed to respond to INF beta-1a therapy and almost 80% of patients with high disease activity at baseline based on the criterion of failure to any DMT were due to failure to INF-beta. Nonetheless in patients with highly active disease at baseline, despite a full and adequate course of treatment with at least one DMT, there seem to be no differences in the clinical and radiological outcomes compared to patients with non-highly active disease, regardless of the criterion of highly active disease.

3. Expert consultation

The PRAC consulted the neurology scientific advisory group (SAG) which provided advice on a number of issues.

The SAG experts considered that daclizumab's actions on the IL-2 receptor and pathway and its effect on Treg cells is most probably the mechanism that is linked to the cases of DILI. Based on its mechanism of action it could be hypothesised that this immune-mediated injury is probably a result of dysregulation of the IL-2 pathway, resulting in quantitative and or qualitative reduction in the function of Tregs. In addition, the fact that there were DILI events in patients having received numerous treatment doses and long time after the end of treatment, are both indicative of an immune-mediated mechanism.

It was noted that limited data are available to derive firm conclusions on the risk of developing other autoimmune diseases in the context of daclizumab use in MS, but it would be important to be aware of this possibility. The experts also considered that the very limited data available did not allow concluding on any synergistic hepatotoxic effects in patients taking concomitant hepatotoxic drugs and that it would be unfeasible to completely exclude these medicines from the clinical management of MS patients. The SAG experts could not define any factors that would help identify at risk patients.

The SAG experts agreed that as a precautionary measure, discontinuation of daclizumab therapy when levels of ALT or AST reach >3x ULN should be recommended, although it was recognised that this measure has no predictive value on the risk of developing severe and potential fatal DILI. The SAG experts were split on the usefulness of increasing the frequency of investigation of LFTs and the majority of the members considered this to be impractical and with very limited predictive value for preventing a potentially serious DILI. The SAG agreed that in case of signs and symptoms suggestive of liver injury the referral to a hepatologist without any delay for treatment or examination was critical. The SAG experts insisted to highlight in the product information that the risk of unpredictable, rapidly evolving and potentially fatal DILI exists, and no clinical or para-clinical investigations could be identified that could help predict or prevent DILI.

The SAG experts recommended that a treatment initiation form was needed to be filled by all patients before starting treatment with daclizumab, and by those currently treated with daclizumab in order to ensure that information on the risks as well as the possibility of having to switch therapy (and possible implications) in case of levels of ALT or AST reaching >3x ULN has been communicated.

The experts noted that data were limited at present, and that additional post-marketing data should be collected in the future with the aim to better characterise the risk of liver injury.
The SAG experts concluded that a small number of MS patients would benefit from daclizumab treatment, even with the unpredictable, rapidly evolving and potentially fatal risk of DILI. A patient representative also supported that this medicine should be available for people that have no therapeutic alternatives. The group agreed that this population could be described in the indication as follows:

"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 two disease modifying therapies (DMT) and who are unsuitable for treatment with other DMT or,*
- *with rapidly evolving severe relapsing multiple sclerosis, who are unsuitable for treatment with other DMT."*

The unsuitability for other DMT treatments may be defined by a strict contraindication or a severe intolerance or the reconsideration of another DMT due to severe potential risks (e.g. risk of PML for a JC positive patient).

4. Benefit-risk balance

Zinbryta (daclizumab) is a centrally authorised medicinal product indicated at the start of this review in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

The PRAC considered all the data provided by the MAH on cases of liver injury that occurred since the marketing authorisation, including a recent fatal case of fulminant liver failure, as well as safety and efficacy data from clinical trials with daclizumab, in relation to the overall risk of liver injury with daclizumab. The PRAC also considered the views expressed by experts consulted during the course of the procedure (scientific advisory group (SAG) on neurology).

The efficacy of daclizumab was demonstrated in two pivotal studies in subjects with relapsing remitting multiple sclerosis (RRMS) that led to the indication in relapsing multiple sclerosis. Results from both studies demonstrated clinically meaningful and statistically significant reductions in relapse rate, the primary efficacy endpoint in each study. Daclizumab treatment also resulted in clinically meaningful slowing of the accumulation of neurological disability as measured by both clinician-assessed and patient-reported outcome measures. These clinical effects were supported by robust and substantial treatment effects in reducing all key brain magnetic resonance imaging (MRI) parameters of acute and chronic inflammatory and destructive central nervous system disease activity. Subgroup analyses of these studies, although of limited robustness, did not identify statistically significant differences in key efficacy outcomes in MS patients with high disease activity compared to patients with low disease activity.

The PRAC concluded that daclizumab is associated with a potentially fatal risk of immune-mediated liver injury. No time window of a higher risk could be identified and cases of liver injury have occurred throughout treatment and up to 6 months after the last dose of daclizumab. Risk or predictive factors that may play a role on the occurrence of liver damage such as comorbidities, relation with dose, timing, genetic or biochemical markers could not be identified by the PRAC or the SAG. Overall, considering the data available, the occurrence of daclizumab induced liver injury is considered to be unpredictable.

The occurrence of a fatal case of fulminant liver failure despite adherence to the risk minimisation measures implemented before this procedure, including monthly liver monitoring, was particularly of concern. The PRAC thus considered that further measures to those implemented as part of the provisional measures were justified to minimise this risk and, in view of its unpredictable and potentially fatal nature, to limit the use of the medicinal product.

Taking into account the conclusions from the SAG that the use of the medicinal product should be restricted to patients who are unsuitable for treatment with other DMT, the PRAC considered that the identification of sub-groups within the target population (i.e. with highly active disease and with rapidly evolving severe disease) was not warranted and that the restriction of the use would apply to all patients with RMS who are unsuitable for treatment with other DMT. Therefore PRAC recommended that the indication of daclizumab should be restricted to the treatment of adult patients with RMS who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable.

In addition, considering the lack of clinical data in patients with pre-existent significant hepatic diseases as these were excluded from clinical trials, the seriousness of the hepatic adverse reaction, and the increased susceptibility of patients with basal hepatic disease to experience worsening of the hepatic impairment, the PRAC considered that daclizumab should be contraindicated in all patients with pre-existing hepatic disease or hepatic impairment.

It was also noted that autoimmune thyroiditis was reported in the recent fatal case as well as in one of the adjudicated cases. Considering that immune-mediated conditions and autoimmune conditions have been reported in clinical trials, that the effect of daclizumab on other autoimmune disorders and the role of such disorder on daclizumab-induced liver injury is unknown, as also highlighted by the SAG, the PRAC considered that daclizumab treatment should not be recommended in patients with history of concurrent autoimmune conditions other than multiple sclerosis.

Cases of liver injury were identified both through signs and symptoms and through laboratory values, therefore patient serum transaminase and total bilirubin levels should be monitored at least monthly and as close as possible before each administration, and more frequently if clinically indicated during treatment. As the risk has been shown to persist for up to six months after the last dose of daclizumab, this monitoring should be continued for the same period after the end of treatment. Although it was recognised that this measure has no predictive value on the risk of developing severe and potential fatal liver injury, the SAG considered that as a precautionary measure discontinuation of therapy should be recommended when patients levels of ALT or AST reach over 3 times the upper limit of normal. This view was supported by the PRAC who recommended that this stricter discontinuation criterion, regardless of bilirubin levels, should be applied. To complement the laboratory follow-up, it was considered key by the SAG and the PRAC, that patients should be informed about the risk of hepatic injury, and warned about signs or symptoms suggestive of hepatic dysfunction. If a patient develops such signs or symptoms suggestive of livery injury they should be promptly referred to a hepatologist. Patients should also be explained the importance of adhering to the periodic liver monitoring. To facilitate the discussion between physicians and patients on this topic and ensure patients have understood information provided on the risk, following the view of the SAG, the PRAC required the introduction of an acknowledgment form. The acknowledgement form needs to be provided by physicians to all patients, including those currently on treatment. Physicians should consider discontinuing therapy if an adequate response has not been achieved or the patient fails to follow the requirement for scheduled liver test monitoring.

Based on the limited data available, any synergistic hepatotoxic effects in patients taking concomitant hepatotoxic medications on the liver injury caused by daclizumab could not be fully elucidated. Daclizumab is not expected to be metabolised by the liver and the experts noted that it would be unfeasible to completely exclude hepatotoxic medications from the clinical management of MS patients. The PRAC concluded therefore that caution should be exercised when using such medicines concomitantly with daclizumab.

Patients with hepatitis C virus (HCV) or hepatitis B virus (HBV) were excluded from clinical trials and no correlation has been established between pre-existing infections with these viruses and daclizumab-induced serious liver injury at present. In view of the uncertainties around the exact mechanism of action of the immune-mediated liver injury and as the risk of hepatitis B reactivation with daclizumab has not been characterised, the PRAC recommended that patients should be screened for these viruses prior to treatment initiation. Patients tested positive should be recommended to consult with a physician with expertise in the treatment of these conditions.

Autoimmune hepatitis and fulminant hepatitis should be added as adverse drug reactions to the product information respectively with the frequencies uncommon and not known. In addition the frequency of transaminase increases and liver function tests abnormal should be updated to very

common. The description of hepatic injury in the product information should be brought up to date in line with current knowledge.

Finally the threshold of transaminases elevation for patients not included in clinical trials, and therefore in which treatment initiation is not recommended, should be corrected from above two times the upper normal limit to above or equal to two times that limit.

The PRAC concluded that the benefit-risk balance remained positive, provided that Zinbryta is only used in the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable and that changes are implemented in the product information to minimise the risk of serious liver injury. The existing educational materials should also be updated with these recommendations and complemented with an acknowledgement form.

5. Risk management

The MAH should operate a risk management system described in a Risk Management Plan which has been endorsed as part of the current review procedure. The PRAC considered that the important identified risk “transaminase elevations and serious hepatic injury” should be renamed “serious hepatic injury including autoimmune hepatitis”.

5.1. Pharmacovigilance activities

5.1.1. Specific adverse drug reaction follow-up questionnaires

The PRAC considered that analyses of the data collected via the existing targeted follow-up forms for serious hepatic injury should be presented in future periodic safety update reports (PSURs).

5.1.2. Non-interventional studies

A protocol for a phase IV observational study in the EU to assess adherence to the liver function testing schedule and a feasibility study of assessing important potential risks using MS registries are under assessment. The MAH should take into account the present recommendations in the upcoming submission of the revised protocol and revised feasibility study.

PRAC noted that the MAH has undertaken with the US FDA to conduct a nested case-control study among patients enrolled in the Zinbryta (daclizumab) risk evaluation and mitigation strategy registry, with the primary objective of determining which clinical attributes are risk factors or protective factors for developing liver disorders and serious skin reactions. It will also aim at determining whether there are biomarkers that are earlier indicators of liver injury than standard liver function tests. Patient blood samples will need to be analysed at baseline, 3 months, and 6 months after initiating therapy and possibly when ending therapy. This study should be added to the RMP of daclizumab as a category 3 study. The final study report is currently estimated to be available by end of 2028. This timeline may be adjusted upon completion of the protocol review by the US FDA.

5.2. Risk minimisation measures

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to further minimise the risk of liver injury associated with the use of Zinbryta (daclizumab). These changes refined and completed those implemented in the provisional measures in July 2017[1] and include amendments to sections 4.1, 4.2, 4.3, 4.4, 4.5, and 4.8 of the SmPC.

The indication was restricted to the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable (see section 4.4).

In addition, the PRAC considered that Zinbryta use should be contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

Further warnings and precautions of use relating to the risk of liver injury associated with the use of Zinbryta were strengthened and information regarding undesirable events updated with the new cases.

The Annex II of the marketing authorisation was also updated to reflect the key elements to be included in the existing educational materials and in the newly introduced acknowledgment form, in relation to the risk of liver injury.

The Package Leaflet was amended accordingly.

5.2.2. Direct Healthcare Professional Communications and Communication plan (DHPC)

A DHPC was disseminated in July 2017 based on the preliminary data available to inform HCPs of the provisional measures to restrict the use for Zinbryta (daclizumab) and to strengthen the warnings related to the risk of liver injury. A DHPC with updated information further to the conclusion of the scientific assessment was considered needed. Therefore the PRAC adopted the wording of a DHPC to communicate the additional information identified during the review, including the risk of immune-mediated liver injury, the restriction of the indication to relapsing forms of multiple sclerosis (RMS) in adult patients who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable, the strengthened warnings regarding the risk of liver injury and the need to provide all patients with an acknowledgment form. The PRAC also agreed on a communication plan.

5.2.3. Educational materials

At time of the initial marketing authorisation, it was decided that prior to launch of Zinbryta in each Member State the MAH must agree 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. This program included a hepatic risk management guide and a patient card aimed at educating patients and physicians about the risk of severe hepatic injury and the procedures related to the appropriate management of this risk.

In light of the new information available on the risk of DILI, the hepatic risk management guide shall be revised to include detailed information on:

- The unpredictable risk of serious and potentially fatal hepatic injury at any time during treatment and up to several months after the last dose;
- The contraindication in all patients with pre-existing hepatic disease or hepatic impairment;
- The recommendation not to initiate treatment in patients with autoimmune disorders (other than multiple sclerosis);
- The need to screen for hepatitis B and C prior to treatment initiation and to recommend patients who test positive for HBV or HCV infection to consult with a physician with expertise in the treatment of those conditions;
- The recommendation not to initiate Zinbryta in patients with ALT or AST ≥ 2 times the ULN, and to discontinue treatment in patients with ALT or AST > 3 times the ULN;
- The importance of monitoring the liver function (AST, ALT and total bilirubin levels) at least monthly (or more frequently as clinically indicated) as close as possible before each treatment administration, and for up to six months after the last dose;
- The management of patients receiving Zinbryta and presenting with signs and symptoms of potential hepatic injury, including treatment discontinuation, potential consideration of additional therapy, and prompt referral to a hepatologist;
- The need to exercise caution regarding concomitant use of other hepatotoxic medications;
- The need to provide the patient with the Patient Card and the Acknowledgment Form, discuss their content before starting Zinbryta treatment, informing patients of the risk of hepatic injury, the need for periodic monitoring and the signs or symptoms suggestive of hepatic dysfunction.

The patient card shall be revised to include detailed information on:

- The unpredictable risk of serious and potentially fatal hepatic injury at any time during treatment and up to several month after treatment;
- The need for monitoring of liver function during treatment, and for up to 6 months after the last dose of Zinbryta;
- The importance of adhering to the monthly liver function tests (or more frequently, as clinically indicated during treatment).

In addition, it is essential that the patients are fully informed of the risks before making the decision to initiate treatment with daclizumab. For that reason the MAH has agreed with the PRAC to facilitate the information to the patient via the treating physician with the provision of an acknowledgment form. The form aims at highlighting the risk to the patients and ensuring they have understood them and been provided the patient card by their treating physician. The aim of the form is to protect patients by ensuring that they have been informed of, and understood the risk of liver injury and the signs and symptoms associated to it, as well as the associated need for regular monitoring during and up to 6 months after end of treatment. The form should also be provided to patients currently on daclizumab treatment. It should include the following elements:

- Confirmation of:
    - A discussion between the physician and the patient about the risk of serious and potentially fatal hepatic injury and the unpredictable nature of such reactions and about the possibility of having to switch treatment in case of levels of ALT or AST > 3 times the ULN;

    - Patient understanding of the risk information provided;
    - Receipt of a copy of the acknowledgement form;
    - Receipt of the Patient Card;
- The importance of the liver function monitoring, at least monthly during treatment (or more frequently as clinically indicated), and for up to 6 months after the last dose;
- The importance of detecting signs and symptoms which might indicate hepatic injury, and if any of these occur, to promptly contact their physician.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zinbryta (daclizumab).
- The PRAC reviewed the totality of the data provided by the marketing authorisation holder on cases of serious liver injury reported since the initial marketing authorisation and safety and efficacy data from clinical trials, in relation to the overall risk of liver injury with daclizumab. The PRAC also considered the views expressed by the scientific advisory group on neurology.
- The PRAC concluded that daclizumab is associated, during the treatment and for several months after the end of treatment, with an unpredictable and potentially fatal risk of immune-mediated liver injury. The PRAC noted that a fatal case had occurred despite the risk minimisation measures already implemented, including monthly liver monitoring. The PRAC thus considered that further measures are needed to minimise this risk including limiting the use of the product to situations where no other therapeutic options are suitable.
- As a consequence, the PRAC recommended restriction of the indication of daclizumab to the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable. The PRAC also considered that daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment.
- In addition, the PRAC recommended strengthening the current warnings to take due account that liver functions, including bilirubin levels, of all patients should be monitored at least monthly, close to each administration of daclizumab, and for six months after end of treatment and stricter discontinuation criteria in case of elevated transaminase should now be applied. Discontinuation should also be considered if an adequate response has not been achieved or if the liver function monitoring is not adhered to. Furthermore, PRAC recommended that all patients are informed about signs or symptoms suggestive of liver dysfunction and promptly referred to a hepatologist in case of such signs or symptoms.
- In addition, prior to treatment initiation, patients should be screened for hepatitis B and C infection and initiation is not recommended in patients with other autoimmune conditions. Administration of daclizumab with other medicinal products of known hepatotoxic potential should be done with caution.

- The PRAC also considered it necessary to introduce an acknowledgement form to ensure patients have been adequately informed on the risks of liver injury associated to daclizumab. The educational material in place should also be updated.

In view of the above, the Committee considers that the benefit-risk balance of Zinbryta (daclizumab) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Zinbryta (daclizumab).