09 August 2017
EMA/453660/2017 Rev. 1
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report on provisional measures

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 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 Zinbryta (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, 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 recommended 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 relevant marketing authorisations should be maintained, varied, suspended or revoked. In addition, the EC requested the Agency to give its opinion, as to whether provisional measures were necessary to protect public health.

The current report relates only to provisional measures recommended by the PRAC for daclizumab based on the preliminary data available at this time. These provisional measures are without prejudice to the outcome of the ongoing review under Article 20 procedure.

Following adoption of the PRAC recommendation and issuance of the European Commission decision on provisional measures, the PRAC recommendation was revised in view of discrepancies across sections of the summary of product characteristics.

2. Scientific discussion

2.1. Introduction

Daclizumab is a humanised IgG1 monoclonal antibody that 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 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) 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 European Union, as of 30 April 2017, daclizumab had been marketed in Austria, Belgium, Denmark, Finland, Germany, Ireland, Netherland, Norway, Sweden and United Kingdom. It is 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, recommendation on 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 review 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, 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.

Acute liver failure (ALF), interchangeably referred to as fulminant hepatic failure, is rare, but has a high fatality rate, and can result in the need for liver transplantation and/or death. Drug-induced liver injury (DILI) is the leading cause of ALF in the developed world (Bernal, 2010 [1]; Blackmore, 2015 [2]). 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 die or require liver transplantation (Bernal 2010 [1]).

2.2. Data on safety

The MAH provided data, albeit currently incomplete, on the fatal case of fulminant liver failure as well as on the 4 serious clinical trial cases of liver injury from the ongoing extension study 205MS303 reported in the first PSUR, and a preliminary analysis of cases received between 27 November 2016 and 26 May 2017 (second PSUR).

Risk of hepatic injury in the clinical development program

During the clinical development, transaminases elevations and serious hepatic injury were identified as important identified risks. The majority of findings were asymptomatic transaminases elevations. In the clinical development program, the incidence of hepatic AEs (identified using the drug-related hepatic disorders standardized MedDRA query) was 16%. Discontinuations and withdrawals due to hepatic events were 5% and 3%, respectively. Severe events occurred in 2% and serious hepatic events occurred in 1% of patients treated with daclizumab. As of 26 May 2017, in clinical studies one (0.04%) patient had died of drug-related autoimmune hepatitis in the 300 mg daclizumab dose group after a planned 6-month treatment interruption period and reinitiation of treatment (incidence rate of fatal hepatic injury calculated as 12.04 [95% CI: 0.30 to 67.04] per 100,000 patient-years). This patient had a medical history of chronic pyelonephritis and received concomitant tizanidine and methylprednisolone. Across all studies, of patients who had interruption of study drug due to hepatic transaminases elevations, 77% experienced no further hepatic enzyme elevations when the drug was re-started. In clinical trials, time to onset of serious liver injury ranged from 59 to 2,410 days (mean: 1000.6 days, median: 886.0 days).

To better understand the hepatic findings observed during the clinical trials, the MAH convened an external independent Hepatic Adjudication Committee (HAC) to provide recommendations and to evaluate any hepatic events that met the biochemical criteria of Hy's Law (ALT or AST value ≥ 3 times the upper limit of normal (ULN) and an elevated total bilirubin > 2 times ULN, indicative of a risk of drug-induced severe liver injury). The HAC reviewed 20 subjects including 18 in daclizumab treatment

[1] Bernal W, Auzinger G, Dhawan A, et al. Acute liver failure. Lancet. 2010;376(9736):190-201.
[2] Blackmore L, Bernal W. Acute liver failure. Clin Med (Lond). 2015;15(5):468-72.

groups. Out of these, 3 (0.13%) were assessed as “probable” Hy’s Law: 1 subject in the daclizumab 300 mg/washout/300 mg group with fatal autoimmune hepatitis; 1 subject with non-fatal acute hepatic failure who had also received treatment with valproic acid, carbamazepine containing products and herbal supplements (Herbalife), and 1 subject with concurrent autoimmune thyroiditis who experienced non-fatal events of elevated liver function tests (LFTs) and icterus. The cases were assessed as probably related to daclizumab treatment by the HAC.

Following the case of fatal autoimmune hepatitis, monthly LFT monitoring in clinical trials was implemented with testing prior to administration of the next dose. In addition, following the non-fatal acute hepatic failure, study protocols were updated to limit concomitant treatment with specific medications associated with hepatotoxicity (e.g. carbamazepine, valproate, lamotrigine, phenytoin, isoniazid, propylthiouracil and nimesulide).

Serious cases of liver injury reported since the marketing authorisation

Fatal case of fulminant liver failure

The case occurred in a patient diagnosed with relapsing multiple sclerosis, who started treatment with daclizumab the same month in an observational study 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 disease modifying treatment. 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, and was admitted to hospital where liver failure was diagnosed 30 days after the last dose. Liver transplant took place the day following admission, and the patient died 37 days after the last dose of daclizumab. Death was attributed to hemorrhagic shock, secondary to upper gastrointestinal bleeding and systemic inflammatory response syndrome, both of which were considered caused by liver failure.

Pathology findings of the explanted liver are described as demonstrating “major tissue degeneration in the presence of necrosis with concomitant severe florid inflammation, consistent with the clinical reports of acute drug-induced/toxic liver failure”. It was further noted that the liver weighed 890 g which is low in proportion of the patient weight. Signs of minor chronic and acute cholecystitis were also observed in the gallbladder. Microscopy report, noted mixed-cell inflammatory infiltrates, with lymphocytes, plasma cells and neutrophils, which in some places was severe. Causal association with daclizumab was established. It is noted however that final autopsy results were not available as the neuropathological investigations were still ongoing. In addition, some findings such as the low weight of the liver (considering the weight of the patient) need further consideration. The histological investigations did not exclude some potential underlying liver diseases in the patient. Although there is some suggestion that this case may be a form of autoimmune hepatitis, there is insufficient evidence at this time to confirm with certainty that this is the case.

With 1 fatal hepatic injury case among the estimated 3,351 patients exposed in the post-marketing setting, the calculated post-marketing reporting rate of fatal hepatic events is 79.24 (95% CI: 2.01 to 440.69) per 100,000 patient-years. This calculated rate is higher than observed in clinical trials;

however, this rate should be interpreted with caution in view of the wide confidence interval and limited post-marketing experience.

Other serious cases of liver injury reported since the marketing authorisation

In the first Zinbryta PSUR covering between 27 May 2016 through 27 November 2016, 4 serious cases from clinical trials (ongoing extension study 205MS303) were reported. In all 4 cases, the hepatic events resolved, and were not considered by the investigator to be life-threatening. Review of these cases determined that the reported liver events in all 4 cases were confounded by concomitant drugs associated with liver toxicity, including citalopram, azithromycin, acyclovir; carbamazepine, baclofen, diazepam and sertraline. One case was referred to the HAC for review. In this case, the HAC did not attribute the reported event of hepatic necrosis to daclizumab as the event occurred 5 months after discontinuing the study drug. In another case, a temporal association and a positive dechallenge with sertraline suggested that causality to daclizumab was unlikely related. In the remaining 2 cases, the events were limited to transaminases elevations without accompanying elevations in total bilirubin.

In addition, the MAH provided a summary of data regarding the risk of transaminases elevations and serious hepatic injury that became available between 27 November 2016 and 26 May 2017. However, this data analysis is preliminary and may change. Eighty six initial events were identified (18 serious) reported in 74 initial case reports received during the period, including 3 serious events in 2 cases from interventional clinical trials, 1 non-serious AE in 1 case from non-interventional study, 20 events (5 serious and 15 non-serious) in 15 spontaneously reported cases, and 62 events (10 serious and 52 non-serious) from 47 solicited case sources, none of the cases were fatal. The first of the two serious events reported from clinical trials was a drug induced liver injury in a patient with increased ALT/AST after 40 doses of daclizumab, abdominal ultrasound showed no evident liver pathology, the event resolved. The second case was a liver injury in a patient hospitalised due to prolonged fever with "hepatic lesion" and elevated transaminases. In both cases, bilirubin levels were reported to be within reference range and the events were reported as related to daclizumab. Limited data was provided regarding 15 serious hepatic events reported in the post-marketing setting, but appeared to be aligned with the events observed in the pre-marketing clinical trials.

Therefore, in total 6 non-fatal well described cases from clinical trials during the post-marketing setting, and one fatal case of fulminant liver failure were observed. There is no evidence that the current liver functions monitoring recommendations have not been followed in any of these cases. Time to onset for developing the ADR ranged from 1 month to 69 months after starting daclizumab treatment and in five out of the six cases the episode was driven or occurred concomitantly to the intake of other medications known to induce liver damage. Causality assessment performed by the investigator at the event onset was considered related for five of the cases. The frequency of serious hepatic events in clinical trials is therefore increased to common (1.7%) as of May 2017.

2.3. Data on efficacy

The clinical efficacy of daclizumab in the authorised indication was established during the initial marketing authorisation application based on the assessment of data from two pivotal clinical trials, studies 205MS201 and 205MS301, described in table 1 below and a supportive phase 2 dose ranging study (DAC-1012). In addition there were two extension studies for study 205MS201, i.e. study 202 (one year extension, completed) and study 203, extension to study 202, ongoing.

Table 1. Overview of key efficacy data submitted in support of the initial marketing authorisation

Study ID and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main results
Study 205MS201 to determine the safety and efficacy of daclizumab (Zinbryta) as a monotherapy treatment in subjects with relapsing-remitting multiple sclerosis.					
Study 205MS201 Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging Biogen Idec Ltd.	Superiority over placebo Primary endpoint: annualized relapse rate	Treatments groups: - Placebo n=204 - Daclizumab 150mg n=208 - Daclizumab 300mg n=209	Main inclusion criteria: Patients with RMS, at least 1 relapse (clinical and/or MRI) during the year prior to randomisation, and had an EDSS score between 0 and 5.0.	- Placebo SC every 4 weeks, for 1 year - Daclizumab 150mg every 4 weeks, for 1 year - Daclizumab 300mg every 4 weeks, for 1 year	Annualized relapse rate (95% CI): - Placebo 0.458 (0.370-0.566) - Daclizumab 150mg 0.211 (0.155-0.287) - Daclizumab 300mg 0.230 (0.172-0.308) Placebo vs. Daclizumab 150 mg ARR ratio: 0.461 (0.318 0.668) P< 0.0001
Study 205MS301 to determine the efficacy and safety of daclizumab high yield process versus Avonex (Interferon β-1a) in patients with relapsing-remitting multiple sclerosis					
Study 205MS301 Multicenter, double-blind, randomized, parallel-group, monotherapy, active-control study Biogen Idec Ltd.	Superiority over IFN β-1a	Treatments groups: - IFN β-1a n=922 - Daclizumab n=919	Main inclusion criteria: 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 and at least 2 relapses (one of which was a clinical relapse) within	- IFN β-1a 30 µg IM every week, for 96-144 weeks - Daclizumab 150 mg SC every 4 weeks, for 96-144 weeks	Annualized relapse rate (95% CI): - IFN β-1a 0.393 (0.353, 0.438) – Daclizumab 0.216 (0.191, 0.244) % reduction Daclizumab vs. IFN β-1a 0,550 (0.469, 0.645) P<0.0001

			the prior 3 years.		

It was established that Zinbryta reduces the annualised relapse rate (ARR), as well as the risk of 24-week confirmed disability progression. However the extrapolation of annualised relapse rate to more than the study period adds significant uncertainty, therefore the magnitude and duration of efficacy over non-RMS (efficacy on secondary progressive MS) was considered uncertain.

3. Benefit-risk balance

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

The PRAC considered the preliminary new safety data from a recent fatal case of fulminant liver failure and from cases of serious liver injury that occurred since the marketing authorisation, in the context of the data generated during the clinical development of daclizumab.

The efficacy of daclizumab was demonstrated in two pivotal studies in subjects with relapsing remitting multiple sclerosis that led to the indication in relapsing multiple sclerosis.

During the clinical development, transaminases elevations and serious hepatic injury were identified as important identified risks. The majority of findings were asymptomatic transaminases elevations, however a low incidence of serious liver events and a rare incidence of fatal liver failure (autoimmune hepatitis) were acknowledged as important risks with daclizumab. Since the initial marketing authorisation further serious cases of liver injury have been reported, including a fatal case despite an attempted liver transplant. Notable for this fatal case was the occurrence of rapid fulminant liver failure in the setting of recommended liver function monitoring and concomitant use of another medicinal product known to be associated with hepatotoxicity (tizanidine) and oral contraceptive use. Tizanidine has a labelled risk of hepatic failure and a known drug-drug interaction with oral contraceptives.

The risk minimisation measures (RMMs) implemented, in particular the monthly liver testing, have not been effective to prevent the fatal case of fulminant hepatic failure. While liver function monitoring continues to be an important measure to detect liver injury, and likely reduce the incidence of severe cases, it is unclear at this stage whether any alternative monitoring regimen would necessarily prevent further severe cases. Therefore, while the magnitude and nature of the risk are being reviewed in depth, having considered the seriousness of the risk and that further RMMs that would be effective in preventing with certainty any new severe cases cannot be identified at this stage, the PRAC considered that it is necessary to provisionally limit the use of daclizumab through restriction of the indication and through preventing its use in patients potentially predisposed to liver injury and provide further recommendations to healthcare professionals (HCPs) and patients in the management of this risk.

The PRAC took under consideration the alternative treatment options for the different stages or manifestations of RMS and that limiting access to daclizumab may deny some patients a treatment option for this disease. Further, the PRAC took into consideration that interrupting treatment in patients whose disease is well-controlled with daclizumab may induce relapses. Thus, considering the serious risk of hepatic injury along with the benefit that daclizumab may bring to RMS patients, the PRAC recommended that the use of daclizumab should be provisionally restricted to adult patients with highly active RMS 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.

The PRAC noted that the hepatic findings observed during the clinical development program had led at time of the initial marketing authorisation to the inclusion of a warning in the product information that treatment of patients with pre-existing severe hepatic impairment is not appropriate and that those with pre-existing mild or moderate hepatic impairment should be monitored. Considering the lack of clinical data in patients with pre-existent significant hepatic diseases as these were excluded from clinical trials, the new serious hepatic cases, and that a mild elevation of serum transaminases was reported prior to treatment initiation in the patient who died of fulminant liver failure, the PRAC recommended as a provisional measure that daclizumab should be contraindicated in all patients with pre-existing hepatic disease or hepatic impairment, while the pattern of hepatotoxicity and possible mechanism of action is further investigated.

In view of the restricted indication and contraindication in patients with pre-existing hepatic disease or hepatic impairment, the PRAC recommended that physicians should re-evaluate promptly whether daclizumab continues to be an appropriate treatment option for each of their patients currently treated with this medicinal product, taking into account the provisional measures recommended by the PRAC.

In the fatal case under review, the finding of normal serum transaminases levels prior to the dose of daclizumab did not prevent the occurrence of liver failure. Therefore, monitoring of serum transaminases levels should continue to be performed at least monthly and more frequently as clinically indicated, further, bilirubin levels should also be tested. In addition, prompt recognition of signs and symptoms of liver injury is a key component of risk minimisation for liver injury with daclizumab and these should be monitored in all patients. Patients exhibiting signs and symptoms suggestive of liver injury should be promptly referred to a hepatologist.

Analyses performed in the clinical development program to assess potential interactions of daclizumab with potentially hepatotoxic medications showed no clear evidence of increased risk of liver injury with concomitant hepatotoxic medications. However, a number of serious hepatic events in patients in daclizumab groups occurred in the setting of concomitant drugs with known hepatotoxic potential, including one fatal autoimmune hepatitis (tizanidine) and one non-fatal hepatic failure (valproic acid and carbamazepine) assessed by the HAC as probable Hy's Law. This was also noted in serious cases that occurred since the marketing authorisation, including the fatal case, therefore while the role of concomitant hepatotoxic medication is not fully elucidated, concomitant use with daclizumab should be cautious. It was also noted that autoimmune thyroiditis was reported in the recent fatal case as well as in one of the Hy's law adjudicated cases; therefore treatment initiation is not recommended in patients with history of concurrent autoimmune conditions. Finally, physicians should consider discontinuing daclizumab treatment if an adequate therapeutic response has not been achieved.

HCPs and patients should be informed of the post-marketing fatal case of fulminant liver failure, the common risk of hepatitis and the updated frequency of serious cases of hepatic injury in the light of the new cases. Cases of serious liver injury occurred at any time point between early after treatment initiation to several month after discontinuation and no window of susceptibility to could be defined from cases observed in clinical trials. 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 above provisional measures should be reflected in the product information of daclizumab and communicated to HCPs via a dedicated letter. The adequacy of these provisional measures will be reviewed as part of the ongoing Article 20.

4. Risk management

4.1.1. Amendments to the product information

The PRAC considered that routine RMMs 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 include amendments to sections 4.1, 4.2, 4.3, 4.4, 4.5 and 4.8 of the SmPC.

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

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 Package Leaflet was amended accordingly.

4.1.2. Direct Healthcare Professional Communications and Communication plan

The PRAC adopted the content of a Direct Healthcare Professional Communication (DHPC) to inform HCPs of the restrictions of use for Zinbryta (daclizumab) and strengthened the warning related to the risk of liver injury. The PRAC also agreed on a communication plan.

5. Grounds for Recommendation on provisional measures

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, in particular regarding the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Zinbryta (daclizumab).
- The PRAC reviewed the preliminary data provided by the marketing authorisation holder on cases of serious liver injury reported since the initial marketing authorisation, in the context of available safety data from clinical trials submitted in support of the initial marketing authorisation in relation to the overall risk of liver injury with daclizumab.
- The PRAC noted that a fatal case of fulminant liver failure occurred despite adherence to the terms of the marketing authorisation and the risk minimisation measures recommended, including the liver function monitoring. In view of this and while the magnitude and nature of the risk of liver injury is being further investigated, the PRAC considered that provisional measures are needed to limit the use of daclizumab.
- The PRAC recommended as provisional measure, amendment to the indication of daclizumab to restrict its use 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 PRAC 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.

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

This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.