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**Ocrelizumab
(multiple sclerosis) –
Addendum to Commission A18-06¹**

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator treatment
BSC	Best supportive Care
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN	Interferon
IM	intramuscular
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MID	Minimal Important Difference
PCS	Physical Component Summary
PPMS	primary progressive multiple sclerosis
RMS	relapsing multiple sclerosis
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 12 June 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-06 (Ocrelizumab – Benefit assessment according to §35a Social Code Book V) [1].

In Module 4 A [2] of its dossier on ocrelizumab, the pharmaceutical company (hereinafter referred to as “the company”) presented the studies OPERA I and OPERA II for the assessment of the added benefit in patients with active relapsing multiple sclerosis (RMS); for patients with early primary progressive multiple sclerosis (PPMS), it presented the ORATORIO study. All 3 studies were used for the benefit assessment of ocrelizumab [1].

For research question 2 (pretreated patients with highly active RMS), the company presented results of subpopulations of the studies OPERA I and OPERA II in its dossier [2]. However, information particularly on type and duration of the prior therapies were missing for these subpopulations. Whether a change within the basic therapeutic agents had been performed for all patients as requested in the G-BA’s appropriate comparator therapy (ACT) could thus only be assessed based on the data of the total population. Due to the resulting uncertainty, the certainty of conclusions for research question 2 was downgraded. The company provided further data only after the oral hearing.

Moreover, the company’s dossier contained various responder analyses for the outcome “health-related quality of life” recorded with the Short Form (36) Health Survey (SF-36). These responder analyses were not used for the benefit assessment because they were not prespecified and could neither be derived from the literature presented by the company.

The G-BA commissioned IQWiG with the assessment of the data on research question 2 subsequently submitted by the company. Moreover, the commission included the assessment of the extent to which deviating results for the benefit assessment result from the analyses submitted on the SF-36 under consideration of the Minimal Important Difference (MID) of 5.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The following 3 research questions were investigated in the benefit assessment of ocrelizumab [1]:

- Research question 1: treatment-naive and pretreated patients with non-highly active RMS
- Research question 2: pretreated patients with highly active RMS
- Research question 3: Patients with early PPMS

The benefit assessment used the studies OPERA I and OPERA II for the assessment of the added benefit of ocrelizumab in comparison with the ACT in patients with RMS; the ORATORIO study was used for patients with early PPMS. The OPERA I and OPERA II studies included adults (18 to 55 years) with at least 2 documented relapses during the last 2 years or 1 relapse within the last year before study inclusion and a maximum Expanded Disability Status Scale (EDSS) score of 5.5. Both studies compared ocrelizumab with interferon (IFN) β 1a. Adults (18 to 55 years) with PPMS and an EDSS score of 3 to 6.5 points were included in the ORATORIO study. The study compared ocrelizumab with placebo; all patients additionally received Best supportive Care (BSC). The studies are described in detail in dossier assessment A18-06 [1].

Section 2.1 of the present addendum starts with the assessment of the data on research question 2 subsequently submitted by the company. Assessment of the responder analyses of the SF-36 can be found in Section 2.2.

2.1 Assessment of the subsequently submitted data on research question 2 (pretreated patients with highly active RMS)

Only a subpopulation of the studies OPERA I and OPERA II is relevant for research question 2 (pretreated patients with highly active RMS). In its dossier, the company only presented few data on the characteristics of the included patients for this subpopulation. Information on the disease severity and on duration and type of the prior therapies was completely lacking [2]. Therefore, it remained unclear whether the G-BA's ACT (change within the basic therapeutic agents) had been adequately implemented for the patients included in the subpopulation. This situation and the resulting consequences are described in detail in dossier assessment A18-06 [1]. Although the limitations of the analyses presented by the company in its dossier were clearly stated in dossier assessment A18-06, the company did not submit the missing information [3] with its written comment. In the framework of the oral hearing [4] it became clear that the missing information was mandatory for the assessment of the added benefit for research question 2, and after the oral hearing the company provided further data on the pretreatment of the patients in the subpopulations of the OPERA studies. These are shown in Table 1 presented below. The data comprise the pretreatments the patients had received in the last 2 years before study inclusion and which they had discontinued before study inclusion.

Table 1: Characteristics of the subpopulation, pretreatment – RCT, direct comparison: ocrelizumab vs. IFN β 1a (pretreated patients with highly active disease)

Study Characteristics Category	Ocrelizumab	IFNβ1a
OPERA I^a	N = 53	N = 59
INF β 1a, IM	17 (32.1)	19 (32.2)
INF β 1a, SC	5 (9.4)	3 (5.1)
INF β 1b, SC	10 (18.9)	15 (25.4)
Glatiramer acetate	28 (52.8)	23 (39.0)
Immunoglobulin	1 (1.9)	1 (1.7)
Mycophenolate mofetil	0 (0)	1 (1.7)
OPERA II^a	N = 57	N = 46
INF β 1a, IM	11 (19.3)	18 (39.1)
INF β 1a, SC	2 (3.5)	4 (8.7)
INF β 1b, SC	20 (35.1)	6 (13.0)
Glatiramer acetate	25 (43.9)	25 (54.3)
Natalizumab	1 (1.8)	0 (0)
Fingolimod	1 (1.8)	0 (0)
Azathioprine	1 (1.8)	0 (0)
OPERA I + OPERA II^a	N = 110	N = 105
INF β 1a, IM	28 (25.5)	37 (35.2)
INF β 1a, SC	7 (6.4)	7 (6.7)
INF β 1b, SC	30 (27.3)	21 (20.0)
Glatiramer acetate	53 (48.2)	48 (45.7)
Natalizumab	1 (0.9)	0 (0)
Fingolimod	1 (0.9)	0 (0)
Immunoglobulin	1 (0.9)	1 (1.0)
Mycophenolate mofetil	0 (0)	1 (1.0)
Azathioprine	1 (0.9)	0 (0)
a: Pretreatment was recorded for the last 2 years before the start of the study. Considered were only those drugs that had been discontinued before administration of the study medication.		
IM: intramuscular; IFN β : interferon beta; MS: multiple sclerosis; n: number of patients in the category; N: number of included patients; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus		

The pretreatments of the patients were largely balanced between the study arms of the two studies. In the OPERA I study, the proportion of patients pretreated with glatiramer acetate was slightly higher in the ocrelizumab arm (about 53%) than in the IFN β 1a arm (about 39%). In the OPERA II study, the proportion of patients pretreated with IFN β 1a (intramuscular, IM) was almost twice as high in the IFN β 1a arm (39%) as in the ocrelizumab arm (about 19%).

Overall, the data showed that the ACT had not been adequately implemented in a relevant proportion of patients in both studies; thus, the subpopulation presented by the company was not usable for the benefit assessment. This is justified below.

ACT not adequately implemented

The ACT for research question 2 was alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (IFN β 1a or IFN β 1b or glatiramer acetate under consideration of the approval). The company chose IFN β 1a as ACT. To fulfil the criterion “change within the basic therapeutic agents”, pretreatment of the patients included in the relevant subpopulation with IFN β 1a before study inclusion was not allowed. The G-BA also considered mere change of the administration form (from IM to SC) or the dosage to be no change within the basic therapeutic agents in the sense of the ACT [5].

In dossier assessment A18-06 [1], the proportion of the relevant subpopulation for research question 2, i.e. patients pretreated with IFN β 1a, was estimated to be < 20% of the total population. Due to this estimation, the subpopulation was used for the benefit assessment under consideration of the resulting uncertainty.

The treatment received immediately before study inclusion would be particularly relevant to assess whether a change within the basic therapies had actually taken place upon study inclusion. However, the company’s data comprised all therapies the patients had received in the last 2 years before study inclusion. Due to possible double counting, only a range of patients can be stated who had been pretreated with IFN β 1a before study inclusion and thus experienced no change within the basic therapy. The presently available information demonstrates that the proportion of patients pretreated with IFN β 1a in the subpopulation presented by the company ranged between 29.5% and 39.3% in the OPERA I study; in the OPERA II study it was between 23.3% and 34.0%. The ACT specified by the G-BA was thus not adequately implemented in a relevant proportion of patients in this subpopulation. The subpopulation presented by the company can thus not be used for the benefit assessment. Analyses of the subpopulation excluding patients pretreated with IFN β 1a (IM or SC) would be required.

Analyses presented by the company on only one outcome

Also after the oral hearing, the company presented analyses of a subpopulation that only included patients who had been pretreated with glatiramer acetate or IFN β 1b. These were 78 patients in the ocrelizumab arm and 64 patients in the IFN β 1a arm. Analyses of these patients provide an adequate representation of the subpopulation relevant for research question 2 and could be used for the benefit assessment.

However, the company presented such analysis only for the outcome “relapses”, operationalized as “annualized relapse rate”, and even this only pooled for the two OPERA studies. Analyses on the basis of the individual studies and on all other patient-relevant outcomes are missing.

The approach of the company was inadequate. The company obviously knew which patients are to be included in the subpopulation relevant for the benefit assessment. Moreover, the company knew the outcomes relevant for the benefit assessment. It is unclear why the company selectively reported only one outcome.

Based on the result of only one single, selectively reported outcome, a balancing of benefit and risk for the benefit assessment was not possible. The isolated result presented by the company for the outcome “relapses” was not used for the assessment. The result on this outcome is presented in Appendix A as supplementary information.

Results on added benefit

The data presented by the company in its dossier [2] and after the oral hearing [6] are not relevant for the assessment of the added benefit of ocrelizumab in comparison with the ACT in pretreated patients with highly active RMS. This resulted in no hint of an added benefit of ocrelizumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit

An added benefit is not proven because the company presented no relevant data for the assessment of the added benefit of ocrelizumab in comparison with the ACT for pretreated patients with highly active RMS.

2.2 Analysis of the responder analyses of the SF-36

In its dossier [2], the company presented responder analyses of the SF-36 sum scores (Mental Component Summary [MCS] and Physical Component Summary [PCS]) for all 3 research questions. These responder analyses were prespecified neither in the OPERA I and II studies, nor in the ORATORIO study. It cannot be incurred from the literature cited by the company [7] whether the response criteria used by the company are substantiated for the present indication. Hence, the responder analyses presented by the company are not relevant for the benefit assessment, however, the analyses of the mean differences planned a priori presented in the benefit assessment are relevant. The responder analyses on the response criterion “deterioration by ≥ 5 points” are provided in Appendix B as supplementary information for research question 1 and research question 3. Relevant analyses on the SF-36 are not available for research question 2 (see Section 2.1).

Influence of the responder analyses on the result of the benefit assessment

In compliance with the commission, the text below will explain how the result of the benefit assessment would change under consideration of the responder analyses on the SF-36.

As shown in Appendix B, analyses on the PCS and the MCS were available, and there were also analyses with and without imputation of missing values for each component summary.

The meta-analysis of the OPERA studies (research question 1) showed a statistically significant difference in favour of ocrelizumab for the PCS in the analyses without imputation of missing

values, the analysis with imputation of missing values showed no statistically significant difference between the treatment groups. The results on the PCS are therefore not robust. For the MCS, none of the analyses included in the meta-analysis of the OPERA studies showed statistically significant differences between the treatment groups.

There were no statistically significant differences between the treatment groups for the PCS or the MCS in the ORATORIO study (research question 3).

Overall, the result of the benefit assessment would change neither for research question 1 nor for research question 3, even under consideration of the responder analyses and irrespective of the validity of the response criterion.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of ocrelizumab from dossier assessment A18-06 for research question 2 (pretreated patients with highly active RMS): An added benefit is not proven for these patients. For the other research questions, there was no change in comparison with dossier assessment A18-06.

The following Table 2 shows the result of the benefit assessment of ocrelizumab under consideration of dossier assessment A18-06 and the present addendum.

Table 2: Ocrelizumab – probability and extent of added benefit

Research question	Subindication	ACT ^a	Probability and extent of added benefit ^b
1	Adults with RMS who had not yet received disease-modifying therapy or patients with non-highly active disease pretreated with disease-modifying therapy	Interferon beta (IFNβ)1a or 1b or glatiramer acetate under consideration of the approval	Age < 40 years: proof of considerable added benefit
			Age \geq 40 years: proof of minor added benefit
2	Adults with highly active RMS despite treatment with a disease-modifying therapy ^c	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (IFNβ1a or IFN β 1b or glatiramer acetate under consideration of the approval)	Added benefit not proven
3	Adults with early PPMS	BSC ^d	Indication of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

b: Changes in comparison with the dossier assessment are printed in **bold**.

c: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months.

d: Best supportive Care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.

ACT: active comparator treatment; BSC: Best supportive Care; G-BA: Federal Joint Committee; IFN β 1a: interferon alpha; IFN β : interferon beta; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis

The G-BA decides on the added benefit.

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The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A – Results on the outcome “relapses” (research question 2)Table 3: Results (morbidity, annualized relapse rate) – RCT, direct comparison: ocrelizumab vs. IFN β 1a (pretreated patients with highly active RMS)

Outcome category	Ocrelizumab			IFN β 1a			Ocrelizumab vs. IFN β 1a
Outcome	N	n/patient years	Annualized relapse rate [95% CI] ^a	N	n/patient years	Annualized relapse rate [95% CI] ^a	Rate ratio [95% CI]; p-value ^a
Morbidity							
Relapses							
Annualized relapse rate							
OPERA I ^b					ND		
OPERA II ^b					ND		
Total ^b	78	19/134.9	0.14 [0.08; 0.25]	64	33/100.0	0.32 [0.18; 0.57]	0.43 [0.20; 0.94]; 0.034 ^c
<p>a: Adjusted annualized relapse rate, effect measure, CI and p-value: presumably negative binomial model, adjusted for region and EDSS at the start of the study.</p> <p>b: Patients pretreated with glatiramer acetate and betaferon.</p> <p>c: Calculation using IPD meta-analysis.</p> <p>CI: confidence interval; EDSS: Expanded Disability Status Scale; IFNβ1a: interferon alpha; IFN-β: interferon beta; IPD: individual patient data; N: number of analysed patients; n: number of relapses; ND: no data; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis; vs.: versus</p>							

Appendix B – Responder analyses of the SF-36Table 4: Results (health-related quality of life, dichotomous) – RCT, direct comparison: ocrelizumab vs. IFN β 1a (treatment-naïve and pretreated patients with non-highly active RMS)

Outcome category Outcome Criterion Study	Ocrelizumab		IFN β 1a		Ocrelizumab vs. IFN β 1a RR [95% CI]; p-value ^a
	N	Patients with event n (%)	N	Patients with event n (%)	
Health-related quality of life					
SF-36 PCS					
Deterioration by ≥ 5 points (without imputation ^b)					
OPERA I	283	53 (18.7)	253	59 (23.3)	0.80 [0.58; 1.11]; 0.186
OPERA II	254	41 (16.1)	237	51 (21.5)	0.75 [0.52; 1.09]; 0.128
Total					0.78 [0.61; 0.99]; 0.044 ^c
Deterioration by ≥ 5 points (with imputation ^d)					
OPERA I	330	53 (16.1)	317	59 (18.6)	0.88 [0.63; 1.23]; 0.443
OPERA II	328	41 (12.5)	334	51 (15.3)	0.81 [0.56; 1.19]; 0.286
Total					0.84 [0.66; 1.09]; 0.190 ^c
SF-36 MCS					
Deterioration by ≥ 5 points (without imputation ^b)					
OPERA I	283	58 (20.5)	253	56 (22.1)	0.93 [0.67; 1.28]; 0.651
OPERA II	254	61 (24.0)	237	56 (23.6)	1.02 [0.74; 1.39]; 0.917
Total					0.97 [0.78; 1.22]; 0.815 ^c
Deterioration by ≥ 5 points (with imputation ^d)					
OPERA I	330	58 (17.6)	317	56 (17.7)	0.99 [0.71; 1.39]; 0.969
OPERA II	328	61 (18.6)	334	56 (16.8)	1.10 [0.79; 1.52]; 0.585
Total					1.05 [0.83; 1.32]; 0.702 ^c
a: Effect estimate, CI and p-value: adjusted for geographical region (US vs. RoW) and EDSS at the start of the study (< 4.0 vs. ≥ 4.0).					
b: Patients with missing value at baseline and/or missing value at week 96 were excluded from the analysis.					
c: Calculation using IPD meta-analysis.					
d: All patients with missing value at week 96, but available value at baseline, were imputed in the analysis as patients without event (i.e. “no deterioration”).					
CI: confidence interval; EDSS: Expanded Disability Status Scale; IFN β 1a: interferon alpha; IFN β : interferon beta; IPD: individual patient data; MCS: Mental Component Summary scale; n: number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis; RoW: Rest of World; RR: relative risk; SF-36: Short Form (36) Health Survey; US: United States; vs.: versus					

Table 5: Results (health-related quality of life, dichotomous) - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study Outcome category Outcome Criterion	Ocrelizumab + BSC		Placebo + BSC		Ocrelizumab + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
ORATORIO					
Health-related quality of life					
SF-36 PCS					
Deterioration by ≥ 5 points (without imputation ^b)					
No usable data ^c					
Deterioration by ≥ 5 points (with imputation ^d)					
	437	74 (16.9)	220	43 (19.5)	0.86 [0.62; 1.21]; 0.397
SF-36 MCS					
Deterioration by ≥ 5 points (without imputation ^b)					
No usable data ^c					
Deterioration by ≥ 5 points (with imputation ^d)					
	437	69 (15.8)	220	45 (20.5)	0.77 [0.55; 1.08]; 0.135
a: Effect estimate, CI and p-value: adjusted for geographical region (US vs. RoW) and age at the start of the study (≤ 45 vs. > 45).					
b: Patients with missing value at baseline and/or missing value at week 120 were excluded from the analysis.					
c: The data were not presented because the proportion of patients who were not considered in the analysis was $> 30\%$.					
d: All patients with missing value at week 120, but available value at baseline, were imputed in the analysis as patients without event (i.e. “no deterioration”).					
CI: confidence interval; BSC: Best supportive Care; MCS: Mental Component Summary scale; n: number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary scale; PPMS: primary progressive multiple sclerosis; RCT: randomized controlled trial; RoW: Rest of World; RR: relative risk; SF-36: Short Form (36) Health Survey; vs.: versus					