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Dulaglutide
(Addendum to Commission A15-07)¹

Addendum

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List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OAD	oral antidiabetic
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 9 June 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-07 (Dulaglutide – Benefit assessment according to §35a Social Code Book [SGB] V).

In dossier assessment A15-07 [1], the pharmaceutical company (hereinafter referred to as "the company") presented, among other things, 3 adjusted indirect comparisons using the common comparator sitagliptin + metformin for research question B (dulaglutide in dual combination with an oral antidiabetic [OAD]) (Figure 1).

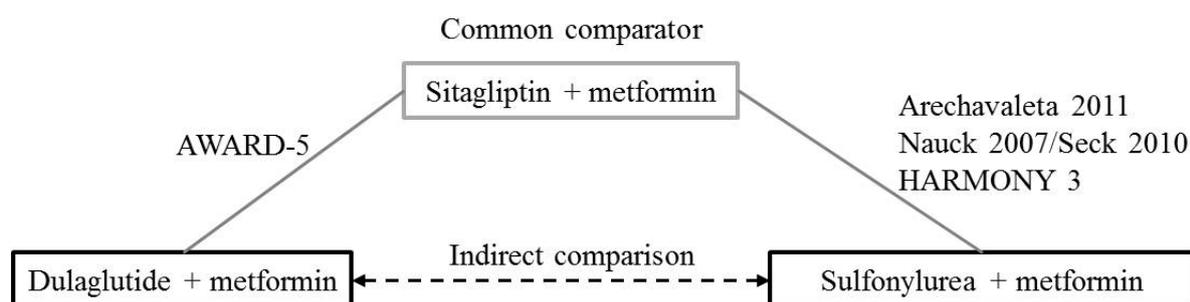


Figure 1: Data of the company for the indirect comparison using the common comparator sitagliptin + metformin in the therapeutic indication dulaglutide + metformin (A15-07; research question B)

The indirect comparison with the HARMONY 3 study was used for the assessment. The indirect comparisons with the studies Arechavaleta 2011 [2] and Nauck 2007/Seck 2010 [3,4] were unsuitable for the benefit assessment also because relevant data were not considered in the analyses presented by the company, and therefore no adequate balancing of positive and negative effects on the basis of these 2 indirect comparisons was possible.

The company presented further documents for the indirect comparison using the study Nauck 2007/Seck 2010 in the framework of the commenting procedure on the early benefit assessment of dulaglutide [5]. This indirect comparison investigated the added benefit of dulaglutide + metformin versus the sulfonylurea glipizide, which is not approved in Germany. The G-BA commissioned IQWiG to assess these documents.

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

2 Assessment of the data submitted with the comment

The company presented documents for the indirect comparison of dulaglutide + metformin (study AWARD-5) versus glipizide + metformin (study Nauck 2007/Seck 2010) in the framework of the commenting procedure on the early benefit assessment of dulaglutide [5].

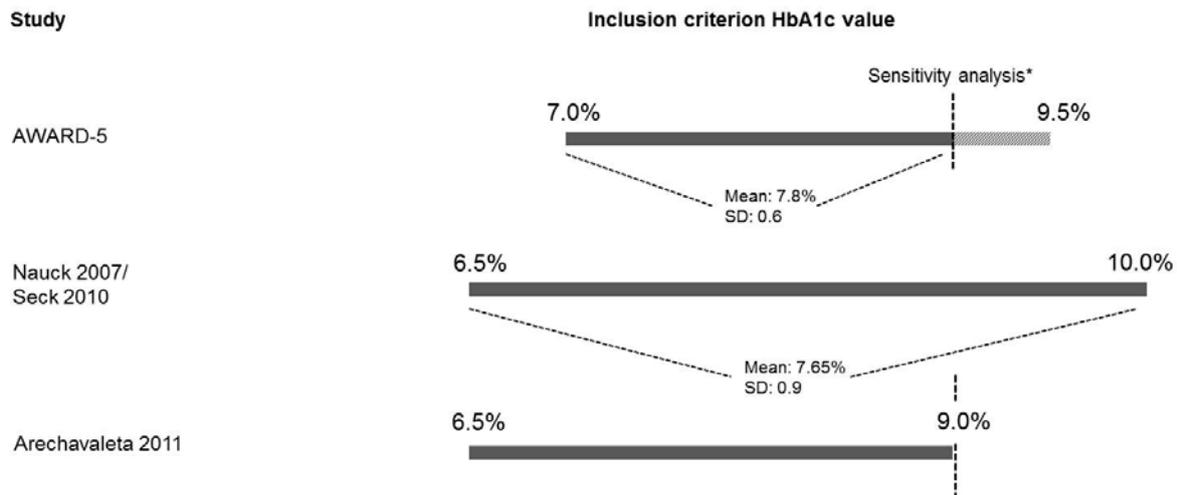
The indirect comparison submitted by the company is unsuitable for the derivation of the added benefit of dulaglutide. This is explained below.

Comparison of the study populations of the studies AWARD-5 and Nauck 2007/Seck 2010

The AWARD-5 study included patients with a baseline glycosylated haemoglobin A1c (HbA1c) value between 7.0% and 9.5%. The Nauck 2007/Seck 2010 study, in contrast, included patients with a baseline HbA1c value between 6.5% and 10%. Hence the Nauck 2007/Seck 2010 study included both patients with lower baseline HbA1c and patients with higher baseline HbA1c in comparison with the AWARD-5 study. The patients' baseline HbA1c values that actually existed in the study differed notably, however: Mean HbA1c was 8.15% (AWARD-5) and 7.65% (Nauck 2007/Seck 2010). The patient populations included were therefore not sufficiently similar.

Sensitivity analysis of the company on the AWARD-5 study

The company conducted a sensitivity analysis for the AWARD-5 study to adjust the relevant differences in baseline HbA1c of the patient populations between the 2 studies. The company claimed that it adapted the inclusion criteria of the AWARD-5 study to the ones of the Nauck 2007/Seck 2010 study. This was incorrect, however: Since the inclusion criteria of the AWARD-5 study were narrower both towards the lower threshold (7.0%) and towards the upper threshold (9.5%) than the inclusion criteria of the Nauck 2007/Seck 2010 study (6.5% and 10%), an adjustment to the inclusion criteria of the Nauck 2007/Seck 2010 study is not possible. However, it was clear from further documents presented by the company that the company did not adapt the inclusion criteria of the AWARD-5 study to the Nauck 2007/Seck 2010 study of interest, but to the Arechavaleta 2011 study. The company's approach is illustrated in Figure 2.



* The company conducted a sensitivity analysis for the AWARD-5 study. It adjusted the patient population of the AWARD-5 study to the population of the Arechavaleta 2011 study regarding the inclusion criterion HbA1c value.
 HbA1c: glycosylated haemoglobin A1c value; mean: mean baseline HbA1c value; SD: standard deviation

Figure 2: Inclusion criterion HbA1c value in the studies AWARD-5, Nauck 2007/Seck 2010 and Arechavaleta 2011 considered by the company in the therapeutic indication dulaglutide + metformin (A15-07, research question B)

Figure 2 shows that the company's approach did not result in an adjustment of the populations, but that, in contrast, the range of the included population differed even more greatly as a result than this was the case anyway based on the actual inclusion criteria of the 2 studies. Hence the company's sensitivity analysis increased the dissimilarity of the populations. This was also not changed by the fact that the mean baseline HbA1c (7.8%) approached the one of the Nauck 2007/Seck 2010 study rather by chance, because the similarity of the populations included is not only assessed based on the mean value, but also based on the distribution.

It should also be noted in this context that, according to the information on the Nauck 2007/Seck 2010 study, the study results differed particularly between the patient group with baseline HbA1c of more than 9% from the ones in patients with lower baseline HbA1c [3].

Summary

The populations included in the studies AWARD-5 and Nauck 2007/Seck 2010 were not sufficiently similar. Based on the range of the population included, the sensitivity analysis presented by the company on the AWARD-5 study even increased this difference. Hence the sensitivity analysis did not result in sufficient similarity of the populations. Overall, the indirect comparison using the studies AWARD-5 and Nauck 2007/Seck 2010 was unsuitable to derive conclusions on the added benefit of dulaglutide in dual combination with an OAD.

Irrespective of the suitability of this indirect comparison, the data submitted by the company did not change the assessment of the added benefit of dulaglutide in research question B because comparable results were shown versus the indirect comparison with the HARMONY 3 study: A positive effect regarding non-severe hypoglycaemia was offset by a negative effect in gastrointestinal adverse events. The data subsequently submitted by the company also did not increase the certainty of conclusions for the comparison of dulaglutide with the appropriate comparator therapy, particularly as the indirect comparison subsequently submitted referred to the sulfonylurea glipizide, which is not approved in Germany.

Overall, the documents on research question B subsequently submitted by the company did not change the assessment of the benefit assessment A15-07 [1]: There is no proof of added benefit of dulaglutide in the dual combination with metformin versus the appropriate comparator therapy metformin + sulfonylurea (glibenclamide or glimepiride) for patients with type 2 diabetes mellitus.

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