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Saxagliptin and saxagliptin/metformin (type 2 diabetes mellitus) –

Addendum to Commissions A16-42 and A16-43[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SPC	Summary of Product Characteristics
SU	sulfonylurea
TZD	thiazolidindione

1 Background

On 7 November 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for the commissions A16-42 (Saxagliptin – Benefit assessment according to §35a Social Code Book V) [1] and A16-43 (Saxagliptin/metformin – Benefit assessment according to §35a Social Code Book V) [2].

In the commenting procedure on the assessment of saxagliptin and saxagliptin/metformin, the pharmaceutical company (hereinafter referred to as "the company") submitted further data to the G-BA [3-6] that went beyond the information provided in the dossiers on saxagliptin [7-10] and saxagliptin/metformin [11,12]. The G-BA commissioned IQWiG to assess the analyses of hypoglycaemic events (study SAVOR-TIMI 53) submitted by the company with the written comment.

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

2.1 Data subsequently submitted

With its comment, the company subsequently submitted the following data of the SAVOR-TIMI 53 study relevant for the present addendum:

- Analyses on hospitalizations due to hypoglycaemia and symptomatic confirmed (blood glucose level < 50 mg/dL) hypoglycaemic events; these analyses were available in the original dossier only for saxagliptin and were subsequently submitted for saxagliptin/metformin.
- Analyses on severe hypoglycaemic events, operationalized as hospitalizations due to hypoglycaemia or intravenous glucose infusion or/and administration of glucagon for the treatment of hypoglycaemia; these analyses were not available in the original dossier for saxagliptin or for saxagliptin/metformin and were subsequently submitted both for saxagliptin and for saxagliptin/metformin.
- Analyses on the dependence of the risk of hypoglycaemia on the pretreatment; these analyses were not available in the original dossier for saxagliptin or for saxagliptin/metformin and were subsequently submitted both for saxagliptin and for saxagliptin/metformin.

The analyses on severe hypoglycaemic events, on hospitalization due to hypoglycaemia and on symptomatic confirmed hypoglycaemic events are assessed in the following Section 2.2. The analyses on the dependence of the risk of hypoglycaemia on the pretreatment are assessed in Section 2.3.

2.2 Assessment of the data on severe hypoglycaemic events, on hospitalizations due to hypoglycaemia and on symptomatic confirmed hypoglycaemic events

Table 1 summarizes the results on symptomatic confirmed hypoglycaemic events, on severe hypoglycaemic events, on hospitalizations due to hypoglycaemia and in the SAVOR-TIMI 53 study for the total population and for the saxagliptin/metformin subpopulation created by the company. For reasons of completeness, the data subsequently submitted with the comment are presented as well as the data already reported in dossier assessment A16-42.

In addition to the results shown in Table 1, the company presented analyses on the outcomes mentioned in relation to the research questions both for saxagliptin and for saxagliptin/ metformin (i.e. analyses on the comparison with the appropriate comparator therapy specified by the G-BA for the respective research question, see dossier assessments A16-42 [1] and A16-43 [2]). These analyses conducted by the company in relation to the research questions were not interpretable or not relevant for the reasons stated in the dossier assessments A16-42 and A16-43.

Table 1: Results on hypoglycaemic events – SAVOR-TIMI 53

Study Population Outcome	Saxagliptin N	Saxagliptin Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Saxagliptin vs. placebo RR [95% CI]; p-value
SAVOR-TIMI 53					
Total population					
Symptomatic, confirmed hypoglycaemia[a]	8280	703 (8.5)	8212	578 (7.0)	1.21 [1.09; 1.34] < 0.001
Severe hypoglycaemia[b]	8280	110 (1.3)	8212	96 (1.2)	1.14 [0.87; 1.49]; 0.530[c]
Hospitalization due to hypoglycaemia	8280	53 (0.6)	8212	43 (0.5)	HR: 1.22 [0.82; 1.83]; 0.327[d]
Saxagliptin/metformin population[e]					
Symptomatic, confirmed hypoglycaemia[a]	2994	279 (9.3)	2925	199 (6.8)	1.37 [1.15; 1.63]; < 0.001[c]
Severe hypoglycaemia[b]	2994	33 (1.1)	2925	21 (0.7)	1.54 [0.89; 2.65]; 0.130[c]
Hospitalization due to hypoglycaemia	2994	17 (0.6)	2925	9 (0.3)	HR: 1.85 [0.84; 4.33]; 0.127[f]

a: According to the information provided by the company in Module 5, these events presented a blood glucose level of < 50 mg/dL and a hypoglycaemic AE or a corresponding entry in the case report form.
b: Defined as hospitalization due to hypoglycaemia or intravenous glucose infusion or/and administration of glucagon for the treatment of hypoglycaemia.
c: Institute's calculation, unconditional exact test (CSZ method according to [13]).
d: Effect and CI: Cox proportional hazards model; Institute's calculation of p-value.
e: According to the company defined as patients who were receiving metformin at a dosage of ≥ 1700 mg at the start of the study and had a creatinine clearance of ≥ 60 mL/min; the documents presented by the company were contradictory, however; see also text below.
f: Effect and CI: Cox proportional hazards model; p-value: log-rank test.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RR: relative risk; vs.: versus

Total population of the SAVOR-TIMI 53 study

The results on the outcomes "symptomatic confirmed hypoglycaemia" and "hospitalization due to hypoglycaemia" for the total population of the SAVOR-TIMI 53 study were already presented in dossier assessment A16-42 [1]. A statistically significant result to the disadvantage of saxagliptin was shown for symptomatic confirmed hypoglycaemia. The result on hospitalizations due to hypoglycaemia pointed in the same direction, but was not statistically significant.

The analyses on severe hypoglycaemia subsequently submitted by the company also showed a result that pointed in the same direction, but was not statistically significant. There was therefore neither an advantage nor a disadvantage of saxagliptin versus placebo (each in addition to "standard treatment") for the outcome "severe hypoglycaemia".

Saxagliptin/metformin population in the SAVOR-TIMI 53 study

The results of the saxagliptin/metformin population created by the company are consistent with those of the total population: A statistically significant result to the disadvantage of saxagliptin/metformin was shown for the outcome "symptomatic confirmed hypoglycaemia". In each case, the result on the outcome "severe hypoglycaemia" and on the outcome "hospitalization due to hypoglycaemia" pointed in the same direction, but was not statistically significant.

The information provided by the company on the creation of the saxagliptin/metformin population was contradictory, however. In the dossier and in its comment, the company stated that it had used the following criteria for the creation of an approval-compliant population in accordance with the Summary of Product Characteristics (SPC) of the fixed combination of saxagliptin/metformin [14]:

- treatment with metformin at a dose of 1700 mg or higher
- creatinine clearance ≥ 60 mL/min

This was in contrast to the baseline data of the saxagliptin/metformin population created by the company subsequently submitted with the comment. It can be inferred from these data that either no threshold value or a threshold value notably below 60 mL/min was chosen for creatinine clearance because, based on these data, the minimum value was 50.1 mL/min for patients in the saxagliptin group, and 46.5 mL/min for patients in the placebo group. Due to the contradictory information, it remains unclear how exactly the company created the saxagliptin/metformin population.

2.3 Assessment of the analyses on the dependence of the risk of hypoglycaemia on the pretreatment

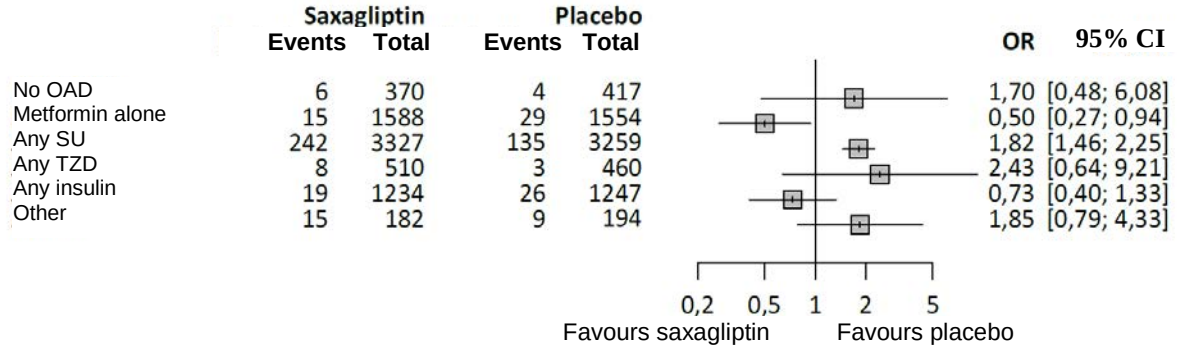
With its comment, the company presented analyses on confirmed symptomatic hypoglycaemic events depending on the pretreatment. The company used these analyses to prove that the risk of hypoglycaemia under saxagliptin and saxagliptin/metformin is only increased for patients with concomitant sulfonylurea treatment.

The analyses presented by the company were not usable for several reasons:

- There were overlaps between the subgroups created by the company and no completely disjunct groups can be formed from the information provided by the company. For example, the company formed the subgroups "any SU" and "any TZD", comprising patients either pretreated with a sulfonylurea (SU) or with a thiazolidindione (TZD). The group of patients with any SU treatment was not compared with an analysis for the group of all patients without any concomitant SU medication. The treatment effect can therefore not be calculated independently for the group of patients without SU medication. Hence it is not possible to compare the groups with versus without SU treatment.

- The subgroups created by the company were incomplete. It can be inferred from the patient numbers cited in the analysis that fewer than 7211 of the 8280 patients in the saxagliptin arm were considered. The upper limit of 7211 resulted from adding the patient numbers of the groups individually cited by the company. The exact number of patients is unclear because these groups were not disjunct. Also in the placebo arm, a patient number of a similar magnitude was not considered.
- The analysis presented by the company only considered a small proportion of the symptomatic confirmed hypoglycaemic events. Only at most 305 of the 703 (see also Table 1) of the events were used for saxagliptin, for example. The upper limit of 305 resulted from adding the events reported by the company for each subgroup. The exact number of events is unclear because the groups were not disjunct. Also in the placebo arm, an event number of a similar magnitude was not considered.

To illustrate the reasons mentioned, Figure 1 shows the figure presented by the company for the analysis on saxagliptin.



CI: confidence interval; OAD: oral antidiabetic; OR: odds ratio; SU: sulfonylurea; TZD: thiazolidindione

Figure 1: Figure of the company for the analysis of the risk of hypoglycaemia in dependence on the pretreatment (page 68 of the comment on saxagliptin)

Overall, it cannot be inferred from the analyses presented by the company that saxagliptin increases the risk of hypoglycaemia only in patients with SU pretreatment.

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