HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 DECEMBER 2020

The legally binding text is the original French opinion version

semaglutide

RYBELSUS 3 mg, 7 mg, 14 mg tablets

First assessment

Key points

Unfavourable opinion for reimbursement in insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications,

- in combination with other medicinal products for the treatment of diabetes.

Role in the care pathway?

The objective of treatment of type 2 diabetes is to prevent the numerous serious and disabling complications, such as microangiopathy (affecting the retina, nerves, heart and kidneys) and sudden complications of macroangiopathy, such as myocardial infarction, stroke, etc. Diabetes promotes the development of heart failure.

The Committee also highlights the importance of ensuring patients are well informed and of their compliance with treatment for successful management of the disease.

The initial management of type 2 diabetes is based on non-medicinal interventions and, in particular, the implementation of lifestyle and dietary measures.

In the event of failure to meet the blood glucose target, medicinal treatment with metformin or, in the event of contraindications, a sulfonylurea is recommended as first-line therapy, in addition to these measures. Drug combinations are envisaged following the failure of monotherapy.

Following the failure of monotherapy with metformin or a sulfonylurea, a new treatment line with an antidiabetic drug from a different therapeutic class will be added to the first-line treatment. The choice between the different drug families that can be used as second or third-line treatment (gliflozins, gliptins, alphaglucosidase inhibitors, GLP1 analogues and insulins) will notably be determined on the basis of the safety profile of the medicinal products, the availability of conclusive cardiovascular or renal morbidity and mortality study results and the preferences of patients after they have been given appropriate information.

As regards GLP-1 analogues, various injectable drugs currently have a limited role in the care pathway for type 2 diabetes:
- If the BMI ≥ 30 kg/m² or if weight gain under insulin is a concern
At the dual therapy stage, if the difference from the target is > 1% HbA1c, a GLP-1 analogue may be combined with metformin or a sulfonylurea (if metformin is not tolerated or is contraindicated).
At the triple therapy stage, a GLP-1 analogue may be combined with metformin + sulfonylurea dual therapy if the blood glucose target is not met:
- despite metformin + sulfonylurea dual therapy and if the difference from the HbA1c target is > 1%,
- despite oral triple therapy including metformin + sulfonylurea.
In the absence of type 2 diabetes control by dual therapy combining basal insulin and metformin, the therapeutic options are addition of a GLP-1 analogue or intensification of insulin therapy.

Role of the medicinal product in the care pathway:

RYBELSUS (semaglutide) is the first GLP-1 analogue to be administered orally, although the drug substance is already known and available in its injectable form in the proprietary medicinal product OZEMPIC.

Considering:

- demonstration of only the non-inferiority of oral semaglutide compared to placebo for the 3P-MACE composite endpoint, with methodological limitations, in particular the choice of a non-inferiority threshold deemed to be not very challenging (i.e. 1.8),

- the absence of demonstration of the superiority of oral semaglutide compared to placebo for this cardiovascular endpoint in the PIONEER 6 study, which contrasts with the positive results obtained with other antidiabetic drugs belonging either to the same therapeutic class or to another therapeutic class, and demonstrates a lower level of evidence for RYBELSUS (semaglutide) in terms of efficacy on cardiovascular endpoints,

- the results of the other clinical studies, concerning only an intermediate laboratory endpoint, change in HbA1c, in studies versus an active comparator or versus placebo, the latter now being considered to be of less value in a disease in which numerous clinically relevant comparators are available, with additional data on cardiovascular morbidity and mortality,

- the absence of a study versus the subcutaneous injection form of semaglutide (OZEMPIC) as weekly administrations,

- and despite the potential value of an oral form in the management of diabetic patients to improve quality of life and treatment compliance, the Committee points out that the semaglutide dose required by the oral route is extremely high compared to the subcutaneous dose required, with a very low bioavailability, therefore, and a high between- and within-individual variability, requiring that the medicinal product be taken at a distance from meals, which is not conducive to good treatment compliance,

RYBELSUS (semaglutide) has no role in the care pathway for type 2 diabetes as monotherapy and in combination with other medicinal products for the treatment of diabetes, in view of the alternatives.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Diabetes is a chronic disease with potentially serious complications, particularly cardiovascular. The objective of treatment of type 2 diabetes is to prevent its numerous, serious and often disabling complications, that are often insidious, such as microangiopathy (affecting the retina, nerves, heart and kidneys) and sudden complications of macroangiopathy, such as myocardial infarction, stroke, etc. Diabetes promotes the development of heart failure.

◗ This proprietary medicinal product is a preventive treatment for complications of diabetes.

◗ Given the absence of conclusive data with respect to morbidity and mortality endpoints in a context in which other drugs have this type of data (superiority study), the efficacy/adverse effects ratio of RYBELSUS (semaglutide) is inadequately established compared to the alternatives.

◗ There are therapeutic alternatives.

◗ RYBELSUS (semaglutide) has no role in the care pathway for type 2 diabetes as monotherapy and in combination with other antidiabetic drugs (see arguments in the dedicated section above).

Public health impact

Considering:

- the seriousness of the disease and, in particular, the microvascular and macrovascular complications associated with this disease,
- the high and constantly increasing prevalence of type 2 diabetes,
- the medical need in type 2 diabetes, currently met by medicinal products having all demonstrated an efficacy on an intermediate laboratory endpoint (and not a surrogate endpoint), change in HbA1c, as well as medicinal products, including gliflozins, having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, only in combination and following the failure of monotherapy with metformin or a sulfonylurea.
- the unmet need to have access to an antidiabetic drug having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improves patients' compliance and adhesion to treatment, with a satisfactory safety profile,
- the absence of demonstration of an impact of RYBELSUS (semaglutide) on quality of life, despite the potential value of an oral form,
- the absence of an additional response of RYBELSUS (semaglutide) in view of the efficacy data available, i.e. clinical studies based on an intermediate laboratory endpoint, change in HbA1c, conducted versus placebo or an active comparator, the safety data available, with, in particular, the absence of an additional risk of cardiovascular events by demonstration of the non-inferiority of semaglutide compared to placebo on the 3P-MACE composite endpoint with a margin of 1.8, but without demonstration of a superiority of semaglutide compared to placebo for this same endpoint, and the absence of data concerning the reduction in morbidity and mortality risk with RYBELSUS (semaglutide),
- the lack of data provided relative to a potential impact on the organisation of care of RYBELSUS (semaglutide),

RYBELSUS (semaglutide) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RYBELSUS (semaglutide) is insufficient to justify public funding cover:

- **in the MA indications,**
- **including within the reimbursement scope sought by the pharmaceutical company, i.e. only in combination:**

- **as dual therapy with metformin,**
- **as triple therapy with metformin and a sulfonylurea or with metformin and insulin.**

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indications and dosages.