Type 2 diabetes
Sectors: Retail and hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 JULY 2021

The legally binding text is the original French opinion version

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dulaglutide
TRULICITY 0.75 mg, 1.5 mg, 3 mg, 4.5 mg solution for injection

exenatide
BYETTA 5 µg, 10 µg solution for injection
BYDUREON 2 mg powder and solvent for solution for infusion

liraglutide
VICTOZA 6 mg/mL solution for injection
liraglutide/insulin degludec
XULTOPHY 100 units/mL solution for injection

lixisenatide
LYXUMIA, 10 µg, 20 µg solution for injection
lixisenatide/insulin glargine
SULIQUA 100 units/mL+ 33 micrograms, 100 units/ml+50 micrograms solution for injection

semaglutide
OZEMPIC 0.25 mg, 0.5 mg, 1 mg solution for injection
RYBELSUS 3 mg, 7 mg, 14 mg tablets

Re-evaluation

- Key points

The Committee reassessed nine proprietary medicinal products, including two fixed-dose combinations with insulins, containing five different GLP-1 analogues, indicated in the treatment of type 2 diabetes mellitus (see SMP), and recommended, for some of them, in specific situations:

- if the difference with respect to the target is > 1% HbA1c,

- and if the BMI ≥ 30 kg/m² or if weight gain under insulin or the occurrence of hypoglycaemic episodes are of concern,

- and only in combination with other medicinal products for the treatment of diabetes (as dual or triple therapy).

The Committee maintained a favourable opinion for maintenance of reimbursement in the indications previously recommended for the following GLP-1 analogues:

*** dulaglutide (TRULICITY), except as dual therapy with a sulfonylurea,**

*** exenatide (BYDUREON / BYETTA), except as triple therapy with insulin and metformin for BYDUREON**

*** liraglutide (VICTOZA) and the fixed-dose liraglutide/insulin degludec combination (XULTOPHY)**

*** semaglutide for injection (OZEMPIC), except as dual therapy with a sulfonylurea and as triple therapy with insulin and metformin.**

The clinical benefit of these proprietary medicinal products remains substantial, except for semaglutide for injection (OZEMPIC), which now has a moderate clinical benefit.

In the indications previously not recommended for reimbursement, the Committee maintained an unfavourable opinion for reimbursement as monotherapy or as dual therapy with insulin.

Finally, the unfavourable opinion for reimbursement of lixisenatide (LYXUMIA), of lixisenatide/insulin glargine (SULIQUA) and of oral semaglutide (RYBELSUS) was maintained.

What therapeutic improvement?

The proprietary medicinal products with a favourable opinion for reimbursement provide:

- a therapeutic improvement in the treatment of type 2 diabetes mellitus for TRULICITY (dulaglutide), VICTOZA (liraglutide) and XULTOPHY (liraglutide/insulin degludec).

- no clinical added value in the therapeutic strategy for type 2 diabetes mellitus for BYDUREON (exenatide), BYETTA (exenatide) and OZEMPIC (semaglutide).

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, GLP-1 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.

Role of the medicinal product in the care pathway

GLP-1 analogues are characterised by a substantial effect in terms of reducing HbA1c levels and an effect on weight loss. Only two substances from this class - dulaglutide and liraglutide - have demonstrated a clinical value in terms of cardiovascular benefit on the 3P-MACE cardiovascular composite endpoint (superiority versus placebo demonstrated in cardiovascular studies). The other substances only demonstrated non-inferiority versus placebo for this 3P-MACE endpoint. Although data from meta-analyses suggest a cardiovascular benefit for the entire analogue class, without formal evidence, this non-inferiority data only provides reassurance in terms of the cardiovascular safety of these substances without demonstrating a cardiovascular benefit. As regards semaglutide, the level of evidence provided by oral or injectable semaglutide is lower than for the other substances due to the choice of a non-inferiority margin of 1.8 instead of 1.3 as was the case for all the other substances.

Their safety profile is characterised by gastrointestinal events (nausea, vomiting, diarrhoea), headache, cholelithiasis and pain at the injection site.

In this context, five of the seven proprietary medicinal products with single substances re-evaluated - TRULICITY (dulaglutide), BYETTA (exenatide), BYDUREON (exenatide), VICTOZA (liraglutide) and OZEMPIC (semaglutide) - remain treatment options for type 2 diabetes mellitus in adults only as second or third-line medicinal treatment and recommended in specific situations: if the difference with respect to the target is > 1% HbA1c and if the BMI ≥ 30 kg/m² or if weight gain under insulin or the occurrence of hypoglycaemic episodes are of concern and the disease is inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in combination only:
- as dual therapy with metformin in the event of intolerance or contraindication to sulfonylureas,
- as dual therapy with a sulfonylurea, except for TRULICITY (dulaglutide) and for OZEMPIC (semaglutide), in the absence of conclusive data,
- as triple therapy in combination with a sulfonylurea and metformin,
- as triple therapy with metformin and insulin, except for BYDUREON (exenatide) and OZEMPIC (semaglutide), in the absence of conclusive data.

If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec).

BYETTA (exenatide) and BYDUREON (exenatide) are therefore second-line GLP-1 analogues, due to the absence of a demonstrated cardiovascular benefit. Given the lower level of evidence

provided by the cardiovascular study (with a non-inferiority margin of 1.8), OZEMPIC (semaglutide) should not be favoured within its class.

In the context of a specialised opinion, XULTOPHY, which enables administration of insulin degludec and liraglutide as a daily injection, has a role in the care pathway for type 2 diabetes, in combination with metformin, for patients not controlled by dual therapy with basal insulin and metformin. The Committee considers that it may be relevant to carry out a treatment optimisation phase for triple therapy with metformin + basal insulin + liraglutide as a free-dose combination before prescribing XULTOPHY (liraglutide/insulin degludec).

In the absence of conclusive new data, RYBELSUS (oral semaglutide), LYXUMIA (lixisenatide) and SULIQUA (lixisenatide/insulin glargine) have no role in the care pathway for type 2 diabetes.

In the absence of relevant clinical data as monotherapy and in combination with basal insulin alone, GLP-1 analogues have no role in the care pathway for type 2 diabetes in these treatment lines.

Liraglutide (VICTOZA) and dulaglutide (TRULICITY) may be prescribed in patients with mild, moderate or severe renal impairment, in contrast with prolonged-release exenatide (BYDUREON), which is not recommended in patients with moderate renal function impairment (creatinine clearance of 30 to 50 ml/min). Exenatide is not recommended in patients with end-stage renal disease or severe renal function impairment (creatinine clearance < 30 ml/min).

COMMITTEE'S CONCLUSIONS

TRULICITY (dulaglutide)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ Given all the clinical data available, which highlight a demonstrated benefit on cardiovascular endpoints with dulaglutide versus placebo, and data from clinical studies with variation in HbA1c as the primary endpoint, and with meta-analyses for which interpretation is limited suggesting a class effect for this endpoint, the efficacy/adverse effect ratio of TRULICITY (dulaglutide) proprietary medicinal products is high as dual therapy with metformin, as triple therapy with metformin and a sulfonylurea and as triple therapy with metformin and insulin.
The efficacy/adverse effects ratio of TRULICITY (dulaglutide) proprietary medicinal products cannot be qualified as monotherapy or as dual therapy with insulin, in the absence of conclusive clinical data.

◗ There are numerous therapeutic alternatives.

◗ If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec).

◗ 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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- **the additional response to the identified medical need:**

    - an additional impact expected on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and new safety data for dulaglutide that has not revealed any new signals,
    - the lack of impact on quality of life in the absence of data,
- the expected but not demonstrated additional impact on the organisation of care,

TRULICITY (dulaglutide) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of TRULICITY (dulaglutide) is:

- **substantial in the indication in addition to other medicinal products for the treatment of diabetes, including insulin, where the current treatment, combined with diet and exercise, does not provide adequate glycaemic control, only:**
    - **as dual therapy in combination with metformin,**
    - **as triple therapy in combination with metformin and insulin,**
    - **as triple therapy in combination with metformin and a sulfonylurea.**
- **insufficient to justify public funding cover:**
    - **for the treatment of adults with 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,**
    - **as dual therapy in combination with a sulfonylurea**
    - **as dual therapy in combination with insulin**

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only:

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

The Committee issues an unfavourable opinion for inclusion:

- **for the treatment of adults with 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,**
- **as dual therapy in combination with a sulfonylurea**
- **as dual therapy in combination with insulin**

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

As dual therapy with metformin, as triple therapy with metformin and a sulfonylurea and as triple therapy with metformin and insulin.

Considering:

- **demonstration of the superiority of dulaglutide as a weekly injection compared to placebo in the REWIND study for a clinically relevant cardiovascular endpoint, i.e. the reduction in events in the 3P-MACE composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), in type 2 diabetic patients, primarily as primary prevention with an HR = 0.88, 95% CI [0.79; 0.99]**
- **initial data having demonstrated the efficacy of dulaglutide, a GLP-1 analogue, versus clinically relevant comparators, on reduction of the intermediate laboratory endpoint, HbA1c, in combination with other medicinal products for the treatment of diabetes as dual or triple therapy,**
- **new safety data for dulaglutide that has not revealed any new signals,**
- **the unmet medical need to have access to antidiabetic drugs having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improve patients' compliance and adhesion to treatment, with a satisfactory safety profile,**

and despite:

- **the reduction in absolute cardiovascular risk judged to be low in the REWIND study,**

the Committee considers that TRULICITY (dulaglutide) provides a minor clinical added value (CAV IV), in the same way as liraglutide (VICTOZA), in the treatment of adults with type 2 diabetes mellitus to improve glycaemic control, in addition to other medicinal products for the treatment of diabetes, including insulin, where the current treatment, combined with diet and exercise, does not provide adequate glycaemic control, only:

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

BYDUREON (exenatide)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ Given all the clinical data available, i.e. clinical studies concerning the laboratory endpoint of HbA1c variation, the absence of clinical study results demonstrating a cardiovascular benefit and although meta-analyses for which interpretation is limited suggest a class effect for this endpoint, the absence of new safety signals with exenatide, the efficacy/adverse effects ratio ofBYDUREON (exenatide) is high.

◗ There are numerous therapeutic alternatives.

If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec). BYDUREON (exenatide) is therefore a second-line GLP-1 analogue, due to the absence of a demonstrated cardiovascular benefit.

◗ <u>Public health impact:</u>
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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- the lack of additional response to the identified medical need:
    - the lack of a demonstrated additional impact on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and despite available new safety data with exenatide that does not reveal any new signals,
    - the lack of impact on quality of life in the absence of data,
- the non-demonstrated additional impact on the organisation of care,

BYDUREON (exenatide) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BYDUREON is:

- **substantial only:**

- as dual therapy in combination with metformin,
- as dual therapy in combination with a sulfonylurea,
- as triple therapy in combination with metformin and a sulfonylurea,
in adults having failed to achieve adequate glycaemic control at the maximum tolerated doses of these oral treatments and at the MA dosages.

- **insufficient to justify public funding cover in combination with a basal insulin with or without metformin for adults having failed to achieve adequate glycaemic control with these medicinal products.**

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only:

- **as dual therapy in combination with metformin,**
- **as dual therapy in combination with a sulfonylurea,**
- **as triple therapy in combination with metformin and a sulfonylurea,**

in adults having failed to achieve adequate glycaemic control at the maximum tolerated doses of these oral treatments and at the MA dosages.

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 indication in combination with a basal insulin with or without metformin for adults having failed to achieve adequate glycaemic control with these medicinal products.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

As dual therapy with metformin, as dual therapy with a sulfonylurea and as triple therapy with metformin and a sulfonylurea

Considering:

- **the absence of demonstration of the superiority of exenatide compared to placebo in the EXSCEL study on a clinically relevant cardiovascular composite endpoint, i.e. reduction of the 3P-MACE composite endpoint including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, with only non-inferiority having been demonstrated for this endpoint,**
- **initial data having demonstrated the efficacy of exenatide in combination with other medicinal products for the treatment of diabetes, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo or to active comparators,**
- **the unmet medical need to have access to antidiabetic drugs having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improve patients' compliance and adhesion to treatment, with a satisfactory safety profile,**

and despite

- **new data from meta-analyses suggesting a cardiovascular benefit for GLP-1 analogues, although this effect has not been confirmed by robust clinical studies,**
- **new safety data for exenatide that does not reveal any new signals,**

the Committee considers that BYDUREON (exenatide) provides no clinical added value (CAV V) in the treatment of type 2 diabetes mellitus, as dual therapy with metformin, as dual therapy with a sulfonylurea and as triple therapy with metformin and a sulfonylurea.

BYETTA (exenatide)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ Given all the clinical data available, i.e. clinical studies concerning the laboratory endpoint of HbA1c variation, the absence of clinical study results demonstrating a cardiovascular benefit, although meta-analyses for which interpretation is limited suggest a class effect for this endpoint, the absence of new safety signals with exenatide, the efficacy/adverse effects ratio of BYETTA (exenatide) is high.

◗ There are numerous therapeutic alternatives.

◗ If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec). BYETTA (exenatide) is therefore a second-line GLP-1 analogue, due to the absence of a demonstrated cardiovascular benefit.

◗ <u>Public health impact:</u>

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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- the lack of additional response to the identified medical need:
    - the lack of a demonstrated additional impact on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and despite available new safety data with exenatide that does not reveal any new signals,
    - the lack of impact on quality of life in the absence of data,
- the non-demonstrated additional impact on the organisation of care,

BYETTA (exenatide) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BYETTA (exenatide) is:

- **substantial only in combination: with metformin, with a sulfonylurea, with metformin and a sulfonylurea and in adults having failed to achieve adequate glycaemic control at the maximum tolerated doses of these oral treatments**
- **insufficient in combination with a basal insulin in adults having failed to achieve adequate glycaemic control with this medicinal product.**

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only:

- **as dual therapy in combination with metformin,**
- **as dual therapy in combination with a sulfonylurea,**
- **as triple therapy in combination with metformin and a sulfonylurea,**
- **as triple therapy in combination 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:

- **for the treatment of adults with 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,**
- **as dual therapy in combination with a basal insulin in adults having failed to achieve adequate glycaemic control with this medicinal product.**

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

As dual therapy with metformin, as dual therapy with a sulfonylurea, as triple therapy with metformin and a sulfonylurea and as triple therapy with metformin and insulin

Considering:

- **the absence of demonstration of the superiority of exenatide compared to placebo in the EXSCEL study on a clinically relevant cardiovascular composite endpoint, i.e. reduction of the 3P-MACE composite endpoint including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, with only non-inferiority having been demonstrated for this endpoint,**
- **initial data having demonstrated the efficacy of exenatide in combination with other medicinal products for the treatment of diabetes, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo or to active comparators,**
- **the unmet medical need to have access to antidiabetic drugs having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improve patients' compliance and adhesion to treatment, with a satisfactory safety profile,**

and despite:

- **new data from meta-analyses suggesting a cardiovascular benefit for GLP-1 analogues, although this effect has not been confirmed by robust clinical studies,**
- **new safety data for exenatide that does not reveal any new signals,**

the Committee considers that BYETTA (exenatide) provides no clinical added value (CAV V) in the treatment of type 2 diabetes mellitus, as dual therapy with metformin, as dual therapy with a sulfonylurea, as triple therapy with metformin and a sulfonylurea and as triple therapy with metformin and insulin.

VICTOZA (liraglutide)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ Given all the clinical data available, which highlight a demonstrated benefit on cardiovascular endpoints with liraglutide, and data from clinical studies with variation in HbA1c as the primary endpoint, as well as meta-analyses for which interpretation is limited suggesting a class effect for this endpoint, the efficacy/adverse effect ratio of VICTOZA (liraglutide) proprietary medicinal products is high as dual therapy with metformin, as triple therapy with metformin and a sulfonylurea and as triple therapy with metformin and insulin.
The efficacy/adverse effects ratio of VICTOZA (liraglutide) proprietary medicinal products cannot be qualified as monotherapy or dual therapy with insulin, in the absence of conclusive clinical data.

◗ There are numerous therapeutic alternatives.

◗ If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec).

◗ 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 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 by medicinal products, gliflozins or SGLT2 inhibitors 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; and of 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 additional response to the identified medical need:
    - an additional impact expected on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and new safety data for liraglutide that has not revealed any new signals,
    - the lack of impact on quality of life in the absence of data,
- the expected but not demonstrated additional impact on the organisation of care,

VICTOZA (liraglutide) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of VICTOZA (liraglutide) is:

- **substantial only in the indication in addition to other medicinal products for the treatment of diabetes, including insulin, where the current treatment, combined with diet and exercise, does not provide adequate glycaemic control, only:**
  - **o as dual therapy in combination with metformin or with a sulfonylurea,**
  - **o as triple therapy with metformin and insulin or with metformin and a sulfonylurea.**
- **insufficient to justify public funding cover:**
  - **o for the treatment of adults with 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,**
  - **o as dual therapy in combination with insulin.**

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only:

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

The Committee issues an unfavourable opinion for inclusion:

- **for the treatment of adults with 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,**
- **as dual therapy in combination with insulin.**

◗ **Recommended reimbursement rate: 65%**

As dual therapy with insulin, as dual therapy with a sulfonylurea, as triple therapy with metformin and a sulfonylurea and as triple therapy with metformin and insulin

Considering:

- **demonstration of the superiority of liraglutide as a daily injection compared to placebo in the LEADER study for a clinically relevant cardiovascular endpoint, i.e. the reduction in events in the 3P-MACE composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), in type 2 diabetic patients, primarily as secondary prevention, with an HR = 0.86, 95% CI [0.77; 0.96],**
- **initial data having demonstrated the efficacy of dulaglutide, a GLP-1 analogue, versus clinically relevant comparators, on reduction of the intermediate laboratory endpoint, HbA1c, in combination with other medicinal products for the treatment of diabetes as dual or triple therapy,**
- **new safety data for liraglutide that has not revealed any new signals,**
- **the unmet medical need to have access to antidiabetic drugs having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improve patients' compliance and adhesion to treatment, with a satisfactory safety profile,**

and despite:

- **the reduction in absolute cardiovascular risk judged to be low in the LEADER study,**

the Committee considers that VICTOZA (liraglutide) provides a minor clinical added value (CAV IV), in the same way as dulaglutide (TRULICITY), in the treatment of adults with type 2 diabetes mellitus to improve glycaemic control, in addition to other medicinal products for the treatment of diabetes, including insulin, where the current treatment, combined with diet and exercise, does not provide adequate glycaemic control, only:

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

XULTOPHY (liraglutide/insulin degludec)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ The efficacy/adverse effects ratio of XULTOPHY (liraglutide/insulin degludec) proprietary medicinal products cannot be qualified as monotherapy or dual therapy with insulin, in the absence of conclusive clinical data. It is high as dual therapy with metformin, as triple therapy with metformin and a sulfonylurea or as triple therapy with metformin and insulin.

◗ There are numerous therapeutic alternatives.

◗ If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec).

◗ 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 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 by medicinal products, gliflozins or SGLT2 inhibitors 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; and of 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 additional response to the identified medical need:
    - an additional impact expected on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and new safety data for liraglutide that has not revealed any new signals,
    - the lack of impact on quality of life in the absence of data,
- the expected but not demonstrated additional impact on the organisation of care,

XULTOPHY (liraglutide/insulin degludec) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of XULTOPHY (liraglutide/insulin degludec) is:

- substantial

- **in patients in whom treatment with the free-dose combination of metformin/basal insulin and liraglutide has been optimised**
- **in patients not controlled by the metformin and basal insulin combination,**

- insufficient to justify public funding cover in patients with diabetes insufficiently controlled by a GLP-1 analogue and an oral glucose-lowering medicinal product

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only:

- **in patients in whom treatment with the free-dose combination of metformin/basal insulin and liraglutide has been optimised**
- **in patients not controlled by the metformin and basal insulin combination,**

The Committee issues an unfavourable opinion for inclusion in patients with diabetes insufficiently controlled by a GLP-1 analogue and an oral glucose-lowering medicinal product.

- **Recommended reimbursement rate: 65%**

In patients in whom treatment with the free-dose combination of metformin/basal insulin and liraglutide has been optimised and in patients not controlled by the metformin and basal insulin combination

Considering:

- **demonstration of the superiority of liraglutide as a daily injection compared to placebo in the LEADER study for a clinically relevant cardiovascular endpoint, i.e. the reduction in events in the 3P-MACE composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), in type 2 diabetic patients, primarily as secondary prevention, with an HR = 0.86, 95% CI [0.77; 0.96],**
- **initial data having demonstrated the efficacy of dulaglutide, a GLP-1 analogue, versus clinically relevant comparators, on reduction of the intermediate laboratory endpoint, HbA1c, in combination with other medicinal products for the treatment of diabetes as dual or triple therapy,**
- **new safety data for liraglutide that has not revealed any new signals,**
- **the unmet medical need to have access to antidiabetic drugs having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improve patients' compliance and adhesion to treatment, with a satisfactory safety profile,**

and despite:

- **the reduction in absolute cardiovascular risk judged to be low in the LEADER study,**

The Committee considers that XULTOPHY (liraglutide/insulin degludec) provides a minor clinical added value (CAV IV) in the treatment of adult patients with type 2 diabetes mellitus in whom treatment with the free-dose combination of metformin/basal insulin and liraglutide has been optimised and in patients not controlled by the metformin and basal insulin combination.

LYXUMIA (lixisenatide)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are 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), and the methodological limitations of studies having assessed the reduction in HbA1c, in the absence of new data, the efficacy/adverse effects ratio of LYXUMIA (lixisenatide) is inadequately established compared to the alternatives.

◗ There are numerous therapeutic alternatives.

◗ LYXYMIA (lixisenatide) has no role in the care pathway for adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin, when these, together, with diet and exercise, do not provide adequate glycaemic control.

◗ <u>Public health impact:</u>

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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. In addition, canagliflozin has demonstrated a reduction in renal morbidity and mortality. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- the lack of additional response to the identified medical need:
    - the lack of a demonstrated additional impact on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and despite available new safety data with lixisenatide that does not reveal any new signals,
    - the lack of impact on quality of life in the absence of data,
- the non-demonstrated additional impact on the organisation of care,

LYXUMIA (lixisenatide) is unlikely to have an additional impact on public health

Considering all these elements, the Committee deems that the clinical benefit of LYXUMIA (lixisenatide) is insufficient in the MA indications.

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.

SULIQUA (lixisenatide/insulin glargine)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ Given new data limited to a non-inferiority result versus insulin intensification in terms of HbA1c variation not accompanied by data relative to a cardiovascular or renal benefit with lixisenatide, in a context in which this type of data exists for other drug substances (superiority study), the efficacy/adverse effects ratio of SULIQUA (lixisenatide/insulin glargine) is inadequately established compared to the alternatives.

◗ There are numerous therapeutic alternatives.

◗ SULIQUA (lixisenatide/insulin glargine) has no role in the care pathway for type 2 diabetes.

◗ 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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. In addition, canagliflozin has demonstrated a reduction in renal morbidity and mortality. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- the lack of additional response to the identified medical need:
    - the lack of a demonstrated additional impact on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and despite available new safety data with lixisenatide that does not reveal any new signals,
    - the lack of impact on quality of life in the absence of data,
- the non-demonstrated additional impact on the organisation of care,

SULIQUA (lixisenatide/ insulin glargine) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of SULIQUA (lixisenatide/insulin glargine) is insufficient in the MA indications.

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

OZEMPIC (semaglutide)

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ These proprietary medicinal products are a preventive treatment for complications of diabetes.

◗ Given the results of the SUSTAIN 6 study with semaglutide for injection having demonstrated non-inferiority compared to placebo for the 3P-MACE primary composite endpoint with a predefined non-inferiority margin of 1.8 and not 1.3 as in the other studies, the demonstration provided by semaglutide is of a lower level of evidence compared to the other GLP1 analogues. In the absence of new data with a better level of evidence for this endpoint, the efficacy/adverse effects ratio of OZEMPIC (semaglutide) is moderate.

◗ There are numerous therapeutic alternatives.

◗ If prescription of a GLP-1 analogue is envisaged, given the results observed in terms of reduction of the 3P-MACE endpoint with dulaglutide in the REWIND study, and with liraglutide in the LEADER study, the choice should preferentially lean towards TRULICITY (dulaglutide) and VICTOZA (liraglutide) or its fixed-dose combination XULTOPHY (liraglutide/insulin degludec). Given the lower level of evidence provided by the cardiovascular study (with a non-inferiority margin of 1.8), OZEMPIC (semaglutide) should not be favoured within its class.

◗ <u>Public health impact:</u>
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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- the lack of additional response to the identified medical need:
  - the lack of a demonstrated additional impact on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and despite available new safety data with semaglutide that does not reveal any new signals,
  - the lack of impact on quality of life in the absence of data,
- the non-demonstrated additional impact on the organisation of care,

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

Considering all these elements, the Committee deems that the clinical benefit of OZEMPIC (semaglutide) is:

- **Moderate**:
  - **• as dual therapy in combination with metformin,**
  - **• as triple therapy in combination with metformin and a sulfonylurea.**
- **Insufficient to justify public funding cover:**
  - **• as monotherapy**
  - **• as dual therapy in combination with a sulfonylurea,**
  - **• as dual therapy in combination with a basal insulin.**
  - **• as triple therapy in combination with a basal insulin and metformin.**

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only:

- **As dual therapy in combination with metformin**
- **As triple therapy in combination with metformin and a sulfonylurea**

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:

- **as monotherapy,**
- **as dual therapy in combination with a sulfonylurea,**
- **as dual therapy in combination with a basal insulin,**
- **as triple therapy in combination with a basal insulin and metformin.**

◗ **Recommended reimbursement rate: 30%**

Clinical Added Value

As dual therapy in combination with metformin and as triple therapy in combination with metformin and a sulfonylurea

Considering,

- the data previously examined by the Committee with, in particular:

- **initial data having demonstrated the efficacy of semaglutide in combination with other medicinal products for the treatment of diabetes, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo or to active comparators,**
- **the absence of demonstration of the superiority of semaglutide compared to placebo in the SUSTAIN 6 study on a clinically relevant cardiovascular composite endpoint, i.e. reduction of the 3P-MACE composite endpoint including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, but only demonstration of non-inferiority with a margin of 1.8 instead of 1.3 as with the other drug substances,**

- new data from meta-analyses suggesting a cardiovascular benefit for GLP-1 analogues, although this effect has not been confirmed by clinical studies,

- the absence of new safety signals with semaglutide,

- the unmet medical need to have access to antidiabetic drugs having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, which improve patients' compliance and adhesion to treatment, with a satisfactory safety profile,

the Committee considers that OZEMPIC (semaglutide) provides no clinical added value (CAV V) in the treatment of type 2 diabetes mellitus, as dual therapy with metformin and as triple therapy with metformin and a sulfonylurea.

RYBELSUS (semaglutide)

Considering all of this information and further to debate and voting, the Committee considers:

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 lack of identification of conclusive new data with respect to morbidity and mortality endpoints in a context in which other drugs have this type of data (superiority study), and the absence of reassuring data concerning the bioavailability of RYBELSUS (semaglutide), the efficacy/adverse effects ratio of RYBELSUS (semaglutide) remains 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.

◗ 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, currently partially met by medicinal products - gliflozins (canagliflozin, empagliflozin, dapagliflozin) and two GLP-1 analogues, dulaglutide and liraglutide - having demonstrated evidence of a reduction of cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. In addition, canagliflozin has demonstrated a reduction in renal morbidity and mortality. There is still an unmet need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, that improve patient compliance and adhesion to treatment with a satisfactory safety profile,
- the lack of additional response to the identified medical need:
    - the lack of a demonstrated additional impact on morbidity and mortality, in terms of reduction of cardiovascular events in the 3P-MACE composite endpoint, and despite available new safety data with semaglutide that does not reveal any new signals,
    - the lack of impact on quality of life in the absence of data,
- the expected but not demonstrated additional impact on the organisation of care,

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 its public funding cover in the MA indications.

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.