



HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

21 JULY 2021

The legally binding text is the original French opinion version

alogliptin

VIPIDIA 6.25 mg, 12.5 mg, 25 mg film-coated tablets

alogliptin/metformin

VIPDOMET 12.5 mg/1,000 mg film-coated tablets

linagliptin

TRAJENTA 5 mg film-coated tablets

linagliptin/metformin

JENTADUETO 2.5 mg/1,000 mg film-coated tablets

saxagliptin

ONGLYZA 5 mg film-coated tablets

saxagliptin/metformin

KOMBOGLYZE 2.5 mg/1,000 mg film-coated tablets

sitagliptin

JANUVIA 25 mg, 50 mg, 100 mg film-coated tablets

XELEVIA 25 mg, 50 mg, 100 mg film-coated tablets

sitagliptin/metformin

JANUMET 50 mg/1,000 mg film-coated tablets

VELMETIA 50 mg/1,000 mg film-coated tablets

vildagliptin

GALVUS 50 mg tablets

vildagliptin/metformin

EUCREAS 50 mg/1,000 mg film-coated tablets

Re-evaluation

► Key points

The Committee reassessed 12 proprietary medicinal products containing 5 different gliptin substances, including 6 as fixed-dose combinations with metformin. This re-evaluation concerns the indication in the treatment of type 2 diabetes mellitus in adults to improve glycaemic control in combination with other antidiabetic medicinal products and following the failure of diet and exercise followed by first-line medicinal treatment with metformin or a sulfonylurea.

The Committee returned:

- In the indications previously recommended for reimbursement by the Committee,
 - a favourable opinion for maintenance of reimbursement only in combination with other antidiabetic medicinal products (dual therapy in combination with metformin or a sulfonylurea or triple therapy in combination with metformin and a sulfonylurea or with metformin and insulin), for the following proprietary medicinal products:
 - * alogliptin (VIPIDIA and VIPDOMET), except as triple therapy in combination with metformin and a sulfonylurea;
 - * linagliptin (TRAJENTA and JENTADUETO)
 - * saxagliptin (ONGLYZA and KOMBOGLYZE)
 - * sitagliptin (JANUVIA/XELEVIA and JANUMET/VELMETIA)
 - * and vildagliptin (GALVUS and EUCREAS).

Nonetheless, the clinical benefit of these proprietary medicinal products is now moderate in all the indications, except for saxagliptin (ONGLYZA) and its fixed-dose combination with metformin (KOMBOGLYZE) and for vildagliptin (GALVUS) and its fixed-dose combination with metformin (EUCREAS), for which it is low. Previously, the clinical benefit was substantial for all these proprietary medicinal products, except in a minority of clinical situations for which the clinical benefit was low or moderate.

- In the indications previously not recommended for reimbursement, the Committee maintained:
 - an unfavourable opinion for reimbursement as monotherapy, except for sitagliptin (JANUVIA/XELEVIA) at the 25 mg and 50 mg strengths appropriate for patients with type 2 diabetes mellitus with moderate, severe or end-stage renal disease, which retains a favourable opinion for reimbursement (with a now moderate clinical benefit),
 - unfavourable opinion for reimbursement in the indication as dual therapy with insulin.

► What therapeutic improvement?

No clinical added value in the therapeutic strategy for type 2 diabetes in the situations recommended for reimbursement.

► 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. Lifestyle and dietary measures must be maintained alongside medicinal treatment. 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.

Role of gliptins in the care pathway

Gliptins are characterised by a modest effect in terms of reducing HbA1c levels, a neutral effect on body weight and a low risk of occurrence of hypoglycaemia. In cardiovascular studies with alogliptin, linagliptin, saxagliptin and sitagliptin, none of these drug substances demonstrated any superiority compared to placebo.

The data from these studies is reassuring in terms of their cardiovascular safety profile (with only non-inferiority compared to placebo having been demonstrated for the 3P-MACE or 4P-MACE endpoint in cardiovascular studies). However, it is necessary to highlight a lower level of evidence based on a meta-analysis for vildagliptin, with demonstration of a lack of difference in terms of the number of cardiovascular events compared to placebo or other antidiabetic medicinal products with no formal demonstration of non-inferiority.

In the absence of demonstration of a superiority compared to placebo in these studies, these drug substances have not therefore demonstrated a clinical benefit in the prevention of cardiovascular events in type 2 diabetics at cardiovascular risk in primary and secondary prevention, in a context in which gliflozins and two GLP-1 analogues (dulaglutide, liraglutide) have demonstrated evidence of a clinical benefit in these at-risk populations (demonstrated superiority in cardiovascular studies versus placebo).

In addition, their safety profile remains favourable, with, however, an identified risk of pancreatitis and a rare but serious risk of bullous pemphigoid. For saxagliptin, the additional risk of hospitalisation due to cardiac failure suggested in the SAVOR-TIMI 53 study was not confirmed in subsequent data and study analyses and in the post-marketing follow-up data.

In this context, the 5 drug substances re-evaluated - alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin - remain treatment options for type 2 diabetes in adults, only as second or third-line drug therapy, i.e. when 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
- as dual therapy with a sulfonylurea (except for linagliptin, in the absence of conclusive data),
- as triple therapy with a sulfonylurea and metformin (except for alogliptin, in the absence of conclusive data),
- as triple therapy with metformin and insulin.

The fixed-dose combinations with metformin, VIPDOMET (alogliptin/metformin), JENTADUETO (linagliptin/metformin), JANUMET/VELMETIA (sitagliptin/metformin), EUCREAS (vildagliptin/metformin), must be used in the context of the recommended combinations.

If prescription of a gliptin is envisaged, the choice should be made on the basis of the efficacy data, the safety profile and the patient's preferences. Demonstration of the cardiovascular safety of vildagliptin with a lower level of evidence than for the other gliptins is an element to be taken into consideration.

Given the suggested additional risk of hospitalisation due to cardiac failure with saxagliptin in the SAVOR-TIMI 53 study, caution is recommended when ONGLYZA (saxagliptin) or KOMBOGLYZE (saxagliptin/metformin) are used in patients with known risk factors for hospitalisation due to cardiac failure, such as a history of cardiac failure or moderate to severe renal failure. Patients must be informed of the symptoms characteristic of cardiac failure and immediately report any such symptoms.

Linagliptin, saxagliptin, sitagliptin and vildagliptin have an MA as monotherapy. However, in the absence of conclusive data, they still have no role in the care pathway at this stage, with the exception of sitagliptin at the 25 mg and 50 mg strengths, which retains a role in patients with renal failure, particularly in the event of failure of or contraindication to metformin and sulfonylureas and before the initiation of insulin.

It should be noted that, in combination with other antidiabetic medicinal products, ONGLYZA (saxagliptin), JANUVIA (sitagliptin), GALVUS (vildagliptin) and TRAJENTA (linagliptin) may be prescribed in the event of mild, moderate or severe renal failure, with adjustment of the dosage.

Finally, in the absence of conclusive clinical data, gliptins have no role in the care pathway for patients with type 2 diabetes mellitus as dual therapy in combination with insulin. The oral antidiabetic agents recommended in combination with insulin therapy are metformin or a sulfonylurea.

COMMITTEE'S CONCLUSIONS

VIPIDIA (alogliptin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, but only demonstration of non-inferiority versus a sulfonylurea, glipizide, the reassuring safety data available concerning the cardiovascular safety of alogliptin, the absence of identification of any new safety signals specific to alogliptin, the efficacy/adverse effects ratio of VIPIDIA (alogliptin) is moderate only:

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

In the absence of conclusive clinical data, the efficacy/adverse effects ratio of VIPIDIA (alogliptin) is inadequately established:

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

► There are numerous therapeutic alternatives.

► VIPIDIA (alogliptin) is a medicinal treatment for type 2 diabetes in adults, only as second or third-line drug therapy, i.e. when 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 or with a sulfonylurea,
- as triple therapy with metformin and insulin.

VIPIDIA (alogliptin) has no role in the care pathway as dual therapy with insulin and as triple therapy with metformin and a sulfonylurea in the absence of conclusive clinical data.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile.

- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with alogliptin having demonstrated its superiority versus placebo or a non-inferiority versus a sulfonylurea for this endpoint,
 - the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

VIPIDIA (alogliptin) is unlikely to have an additional impact on public health.

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

- **moderate only in the following indications:**
 - as dual therapy with metformin,
 - as dual therapy with a sulfonylurea,
 - as triple therapy only with metformin and insulin.
- **insufficient to justify public funding cover in the following indications:**
 - as dual therapy with insulin,
 - as triple therapy with metformin and a sulfonylurea.

The Committee issues the following opinions:

- **favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in this indications “as dual therapy with metformin or with a sulfonylurea and as triple therapy only with metformin and insulin” and at the MA dosages,**
- **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 indications “as dual therapy with insulin and as triple therapy with metformin and a sulfonylurea”.**

► Recommended reimbursement rate: 30%

Clinical Added Value

In the treatment of adults with type 2 diabetes mellitus inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

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

considering,

- demonstration of non-inferiority only versus placebo (non-significant analysis for superiority), 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, in the EXAMINE study,
- initial data having demonstrated a modest efficacy of alogliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, or the non-inferiority compared to a sulfonylurea, without any studies demonstrating a superiority compared to a clinically relevant comparator,
- the safety profile of alogliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
- the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,

the Committee considers that VIPIDIA (alogliptin) provides no clinical added value (CAV V).

VIPDOMET (alogliptin/metformin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, but only demonstration of non-inferiority versus a sulfonylurea, glipizide, the reassuring safety data available concerning the cardiovascular safety of alogliptin, the absence of identification of any new safety signals specific to alogliptin, the efficacy/adverse effects ratio of VIPDOMET (alogliptin/metformin) is moderate.

► There are numerous therapeutic alternatives.

► VIPDOMET (alogliptin/metformin) is an additional treatment:

- in patients inadequately controlled on their maximal tolerated dose of metformin alone,
- in patients already being treated with the combination of alogliptin and metformin as separate tablets,
- in combination with other antidiabetic medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products, only:
 - in combination with insulin.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with alogliptin having demonstrated its superiority versus placebo or a non-inferiority versus a sulfonylurea for this endpoint,
 - the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

VIPDOMET (alogliptin/metformin) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of VIPDOMET (alogliptin/metformin) is moderate.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

► **Recommended reimbursement rate: 30%**

Clinical Added Value

Considering,

- demonstration of non-inferiority only versus placebo (non-significant analysis for superiority), 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, in the EXAMINE study,
- initial data having demonstrated a modest efficacy of alogliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, or the non-inferiority compared to a sulfonylurea, without any studies demonstrating a superiority compared to a clinically relevant comparator,
- the absence of clinical data specifically relating to these fixed-dose combinations,
- the safety profile of alogliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
- the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,

the Committee considers that VIPDOMET (alogliptin/metformin) provides no clinical added value (CAV V) in the treatment of type 2 diabetes.

TRAJENTA (linagliptin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, the reassuring safety data available concerning the cardiovascular safety of linagliptin, the absence of identification of any new safety signals specific to linagliptin, the efficacy/adverse effects ratio of TRAJENTA (linagliptin) is moderate only:

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

In the absence of conclusive clinical data, the efficacy/adverse effects ratio of TRAJENTA (linagliptin) is inadequately established:

- as monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.
- as dual therapy in combination with insulin.

► There are numerous therapeutic alternatives.

► TRAJENTA (linagliptin) is a medicinal treatment for type 2 diabetes in adults, only as second or third-line drug therapy, i.e. when 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 in combination with metformin,
- as triple therapy in combination with metformin and a sulfonylurea,
- as triple therapy in combination with insulin and metformin.

TRAJENTA (linagliptin) has no role in the care pathway as monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment and as dual therapy in combination with insulin, in the absence of conclusive clinical data.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:

- the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with linagliptin having demonstrated its superiority versus placebo for this endpoint,
- the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

TRAJENTA (linagliptin) is unlikely to have an additional impact on public health.

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

- **moderate only:**
 - as dual therapy in combination with metformin,
 - triple therapy in combination with metformin and a sulfonylurea,
 - as triple therapy in combination with insulin and metformin.
- **insufficient to justify public funding cover in the following indications:**
 - as monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment,
 - as dual therapy in combination with insulin.

The Committee issues the following opinions:

- **favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications “as dual therapy in combination with metformin, as triple therapy in combination with insulin and metformin” and at the MA dosages,**
- **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 indications “as monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment and as dual therapy in combination with insulin”.**

► Recommended reimbursement rate: 30%

Clinical Added Value

In the treatment of adults with type 2 diabetes mellitus inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

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

considering,

- **demonstration of non-inferiority only versus placebo (non-significant analysis for superiority), 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, in the CARMELINA study versus placebo and the CAROLINA study versus glimepiride,**
- **initial data having demonstrated a modest efficacy of linagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, without any studies demonstrating a superiority compared to a clinically relevant comparator,**
- **the safety profile of linagliptin which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,**
- **the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,**

the Committee considers that TRAJENTA (linagliptin) provides no clinical added value (CAV V).

JENTADUETO (linagliptin/metformin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, the reassuring safety data available concerning the cardiovascular safety of linagliptin, the absence of identification of any new safety signals specific to linagliptin, the efficacy/adverse effects ratio of JENTADUETO (linagliptin/metformin) is moderate.

► There are numerous therapeutic alternatives.

► JENTADUETO (linagliptin/metformin) is a treatment as an adjunct to diet and exercise in adults with type 2 diabetes mellitus to improve glycaemic control:

- in patients inadequately controlled on their maximal tolerated dose of metformin alone,
- in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products.
- in patients already being treated with the combination of linagliptin and metformin as separate tablets.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with linagliptin having demonstrated its superiority versus placebo for this endpoint,
 - the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

JENTADUETO (linagliptin/metformin) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of JENTADUETO (linagliptin/metformin) is moderate in the MA indication.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and at the MA dosages.

Clinical Added Value

Considering,

- demonstration of non-inferiority only versus placebo (non-significant analysis for superiority), 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, in the CARMELINA study versus placebo and the CAROLINA study versus glimepiride,
- initial data having demonstrated a modest efficacy of linagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, without any studies demonstrating a superiority compared to a clinically relevant comparator,
- the safety profile of linagliptin which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
- the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,

the Committee considers that JENTADUETO (linagliptin/metformin) provides no clinical added value (CAV V) in the treatment of type 2 diabetes.

ONGLYZA (saxagliptin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, but only demonstration of superiority compared to placebo or non-inferiority versus a sulfonylurea or sitagliptin, the reassuring safety data available concerning the cardiovascular safety of saxagliptin, the additional risk of hospitalisation due to cardiac failure suggested in the SAVOR-TIMI 53 study with saxagliptin, but not confirmed in subsequent data and study analyses and in the post-marketing follow-up data, the absence of identification of any new safety signals specific to saxagliptin, the efficacy/adverse effects ratio of ONGLYZA (saxagliptin) is low 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.

In the absence of conclusive clinical data, the efficacy/adverse effects ratio of ONGLYZA (saxagliptin) is inadequately established:

- as monotherapy,
- as dual therapy with insulin.

► There are numerous therapeutic alternatives.

► ONGLYZA (saxagliptin) is a medicinal treatment for type 2 diabetes in adults, only as second or third-line drug therapy, i.e. when 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 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.

ONGLYZA (saxagliptin) has no role in the care pathway as monotherapy or as dual therapy with insulin, in the absence of conclusive clinical data.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with saxagliptin having demonstrated its superiority versus placebo for this endpoint, or the non-inferiority versus a sulfonylurea or sitagliptin, the additional risk of hospitalisation due to cardiac failure suggested with saxagliptin in the SAVOR-TIMI 53 study, but not confirmed in subsequent data, this additional risk not having been demonstrated with gliptins following significant experience of their use,
 - the lack of impact on quality of life in the absence of data,
 - the lack of data on a potential impact on the organisation of care,
- ONGLYZA (saxagliptin) is unlikely to have an additional impact on public health.**

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

- **low only in the following indications:**
 - 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.
- **insufficient to justify public funding cover in the following indications:**
 - as monotherapy,
 - as dual therapy in combination with insulin.

The Committee issues the following opinions:

- **a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications:**
 - 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.
- **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 indications:**
 - as monotherapy,
 - as dual therapy in combination with insulin.

► Recommended reimbursement rate: 15%

Clinical Added Value

In the treatment of adults with type 2 diabetes mellitus inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

- as dual therapy with metformin or with a sulfonylurea,
 - as triple therapy in combination with metformin and a sulfonylurea or with metformin and insulin,
- considering,
- demonstration of the non-inferiority of saxagliptin only versus placebo (non-significant analysis for superiority), 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, in the SAVOR-TIMI 53 study,
 - initial data having demonstrated a modest efficacy of saxagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo or the non-inferiority compared to a sulfonylurea or sitagliptin, without any studies demonstrating a superiority compared to a clinically relevant comparator.
 - the safety profile of saxagliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
 - the additional risk of hospitalisation due to cardiac failure suggested in the SAVOR-TIMI 53 study, but not confirmed in subsequent data and study analyses and in the post-marketing follow-up data,
 - the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,
- the Committee considers that ONGLYZA (saxagliptin) provides no clinical added value (CAV V) in the treatment of type 2 diabetes.

KOMBOGLYZE (saxagliptin/metformin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, but only demonstration of superiority compared to placebo or non-inferiority versus a sulfonylurea or sitagliptin, the reassuring safety data available concerning the cardiovascular safety of saxagliptin, the additional risk of hospitalisation due to cardiac failure suggested in the SAVOR-TIMI 53 study with saxagliptin, which was not confirmed in subsequent data and study analyses and in the post-marketing follow-up data, the absence of identification of any new safety signals specific to saxagliptin, the efficacy/adverse effects ratio of KOMBOGLYZE (saxagliptin/metformin) is low.

► There are numerous therapeutic alternatives.

► KOMBOGLYZE (saxagliptin/metformin) is an additional treatment to improve glycaemic control as an adjunct to diet and exercise:

- in patients inadequately controlled on their maximally tolerated dose of metformin alone in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products,
- in patients already being treated with the combination of saxagliptin and metformin as separate tablets.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with saxagliptin having demonstrated its superiority versus placebo for this endpoint, or the non-inferiority versus a sulfonylurea or sitagliptin, the additional risk of hospitalisation due to cardiac failure suggested with saxagliptin in the SAVOR-TIMI 53 study, but not confirmed in

- subsequent data, this additional risk not having been demonstrated with gliptins following significant experience of their use,
 - the lack of impact on quality of life in the absence of data,
 - the lack of data on a potential impact on the organisation of care,
- KOMBOGLYZE (saxagliptin/metformin) is unlikely to have an additional impact on public health.**

Considering all these elements, the Committee deems that the clinical benefit of KOMBOGLYZE (saxagliptin/metformin) is low in the MA indications.

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 in the MA indications and at the MA dosages.

► Recommended reimbursement rate: 15%

Clinical Added Value

In the treatment of adults with type 2 diabetes mellitus inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

- as dual therapy with metformin or with a sulfonylurea,
 - as triple therapy in combination with metformin and a sulfonylurea or with metformin and insulin,
- considering,
- demonstration of the non-inferiority of saxagliptin only versus placebo (non-significant analysis for superiority), 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, in the SAVOR-TIMI 53 study,
 - initial data having demonstrated a modest efficacy of saxagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo or the non-inferiority compared to a sulfonylurea or sitagliptin, without any studies demonstrating a superiority compared to a clinically relevant comparator.
 - the safety profile of saxagliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
 - the additional risk of hospitalisation due to cardiac failure suggested in the SAVOR-TIMI 53 study, which was not confirmed in subsequent data and study analyses and in the post-marketing follow-up data,
 - the absence of clinical data specifically relating to the fixed-dose combination,
 - the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,
- the Committee considers that KOMBOGLYZE (saxagliptin/metformin) provides no clinical added value (CAV V) in the treatment of type 2 diabetes.

JANUVIA (sitagliptin), XELEVIA (sitagliptin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation (versus dapagliflozin in the CompoSIT-R study after 24 weeks of treatment in patients with mild renal failure), demonstration of non-inferiority versus a sulfonylurea or metformin, the reassuring safety data available concerning the cardiovascular safety of sitagliptin, the absence of identification of any new safety signals specific to sitagliptin, the efficacy/adverse effects ratio of JANUVIA/XELEVIA (sitagliptin) is moderate only:

- as monotherapy in patients with moderate, severe or end-stage renal disease only for JANUVIA/XELEVIA 25 mg, 50 mg (sitagliptin),
- as dual therapy with metformin,
- as dual therapy with a sulfonylurea,
- as triple therapy with metformin and a sulfonylurea,
- as triple therapy with metformin and insulin.

In the absence of conclusive clinical data, the efficacy/adverse effects ratio of JANUVIA/XELEVIA (sitagliptin) is inadequately established:

- as monotherapy only for the 100 mg strength,
- as dual therapy with insulin.

► There are numerous therapeutic alternatives.

► JANUVIA/XELEVIA (sitagliptin) is a medicinal treatment for type 2 diabetes in adults, only as second or third-line drug therapy, i.e. when 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 or with a sulfonylurea,
- as triple therapy with metformin and a sulfonylurea or with metformin and insulin.

JANUVIA/XELEVIA (sitagliptin) has no role in the care pathway as monotherapy (except for the 25 mg and 50 mg strengths in patients with moderate, severe or end-stage renal disease) and as dual therapy with insulin, in the absence of conclusive clinical data.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,

- the lack of additional response to the identified need in view of:
 - o the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with sitagliptin having demonstrated its superiority versus placebo or versus a clinically relevant comparator (versus dapagliflozin in the CompoSIT-R study after 24 weeks of treatment in patients with mild renal failure) as well as the non-inferiority versus a sulfonylurea or metformin for this endpoint,
 - o the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

JANUVIA/XELEVIA (sitagliptin) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of JANUVIA/XELEVIA (sitagliptin) is:

- **moderate only in the following indications:**
 - o as monotherapy in patients with moderate, severe or end-stage renal disease only for JANUVIA/XELEVIA 25 mg, 50 mg (sitagliptin),
 - o as dual therapy with metformin or with a sulfonylurea,
 - o as triple therapy with metformin and a sulfonylurea or with metformin and insulin.
- **insufficient to justify public funding cover in the following indications:**
 - o as monotherapy for the 100 mg strength,
 - o as dual therapy with insulin.

The Committee issues the following opinions:

- **favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications “as monotherapy in patients with moderate, severe or end-stage renal disease only for JANUVIA/XELEVIA 25 mg, 50 mg (sitagliptin), as dual therapy with metformin or with a sulfonylurea, as triple therapy with metformin and a sulfonylurea or with metformin and insulin” and at the MA dosages,**
- **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 indications “as monotherapy (only for the 100 mg strength) and as dual therapy with insulin”.**

► Recommended reimbursement rate: 30%

Clinical Added Value

In the treatment of adults with type 2 diabetes mellitus inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

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

or as monotherapy in patients with moderate, severe or end-stage renal disease only for JANUVIA/XELEVIA 25 mg, 50 mg (sitagliptin), considering,

- demonstration of non-inferiority only versus placebo (non-significant analysis for superiority), on a clinically relevant cardiovascular composite endpoint, i.e. reduction of the 4P-MACE composite endpoint including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, or unstable angina requiring hospitalisation, in the TECOS study,
- initial data having demonstrated a modest efficacy of sitagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, or the non-inferiority compared to a sulfonylurea or metformin, as well as superiority versus a clinically relevant comparator, dapagliflozin, in the CompoSIT-R study after 24 weeks of treatment in patients with mild renal failure,
- the safety profile of sitagliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
- the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,

the Committee considers that JANUVIA/XELEVIA (sitagliptin) provides no clinical added value (CAV V).

JANUMET (sitagliptin/metformin), VELMETIA (sitagliptin/metformin)

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, not revealing any demonstrated benefit on cardiovascular or renal endpoints, the available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation (versus dapagliflozin in the CompoSIT-R study after 24 weeks of treatment in patients with mild renal failure), demonstration of non-inferiority versus a sulfonylurea or metformin, the reassuring safety data available concerning the cardiovascular safety of sitagliptin, the absence of identification of any new safety signals specific to sitagliptin, the efficacy/adverse effects ratio of JANUMET/VELMETIA (sitagliptin/metformin) is moderate.

► There are numerous therapeutic alternatives.

► JANUMET/VELMETIA (sitagliptin/metformin) is an additional treatment:

- in patients inadequately controlled on their maximally tolerated dose of metformin alone or in patients already being treated with the sitagliptin/metformin combination.
- in combination with a sulfonylurea (triple therapy) when the maximally tolerated doses of metformin and sulfonylurea do not provide adequate glycaemic control.
- in addition to insulin (triple therapy) when stable doses of metformin and sulfonylurea alone do not provide adequate glycaemic control.

► **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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with sitagliptin having demonstrated its superiority versus placebo or versus a clinically relevant comparator (versus dapagliflozin in the CompoSIT-R study after 24 weeks of treatment in patients with mild renal failure) as well as the non-inferiority versus a sulfonylurea or metformin for this endpoint,
 - the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

JANUMET/VELMETIA (sitagliptin/metformin) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of JANUMET/VELMETIA (sitagliptin/metformin) is moderate in the MA indications.

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 in the MA indications and at the MA dosages.

► **Recommended reimbursement rate: 30%**

Clinical Added Value

Considering,

- demonstration of non-inferiority only versus placebo (non-significant analysis for superiority), on a clinically relevant cardiovascular composite endpoint, i.e. reduction of the 4P-MACE composite endpoint including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, or unstable angina requiring hospitalisation, in the TECOS study,
- initial data having demonstrated a modest efficacy of sitagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, or the non-inferiority compared to a sulfonylurea or metformin, as well as superiority versus a clinically relevant comparator, dapagliflozin, in the CompoSIT-R study after 24 weeks of treatment in patients with mild renal failure,
- the safety profile of sitagliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
- the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,

the Committee considers that JANUVIA/XELEVIA (sitagliptin) provides no clinical added value (CAV V) in the treatment of type 2 diabetes.

GALVUS (vildagliptin)

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, not including a robust study on cardiovascular endpoints but only a meta-analysis with a lower level of evidence, the absence of any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, but only demonstration of non-inferiority versus a sulfonylurea, glimepiride, the absence of identification of any new safety signals specific to vildagliptin, the efficacy/adverse effects ratio of GALVUS (vildagliptin) is low 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.

In the absence of conclusive clinical data, the efficacy/adverse effects ratio of GALVUS (vildagliptin) is inadequately established:

- as monotherapy,
- as dual therapy with insulin.

▮ There are numerous therapeutic alternatives.

▮ GALVUS (vildagliptin) is a medicinal treatment for type 2 diabetes in adults, only as second or third-line drug therapy, i.e. when 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 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.

GALVUS (vildagliptin) has no role in the care pathway as monotherapy or as dual therapy in combination with insulin, in the absence of conclusive clinical data.

▮ 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:

- the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with vildagliptin having demonstrated its superiority versus placebo or a non-inferiority versus a sulfonylurea for this endpoint,
- the lack of impact on quality of life in the absence of data,
- the lack of data on a potential impact on the organisation of care,

GALVUS (vildagliptin) is unlikely to have an additional impact on public health.

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

- **low only in the following indications:**
 - 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.
- **insufficient to justify public funding cover in the following indications:**
 - as monotherapy,
 - as dual therapy in combination with insulin.

The Committee issues the following opinions:

- **a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications:**
 - 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.
- **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 indications:**
 - as monotherapy,
 - as dual therapy in combination with insulin.

► Recommended reimbursement rate: 15%

Clinical Added Value

In the treatment of adults with type 2 diabetes mellitus inadequately controlled by metformin or a sulfonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

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

considering,

- **the absence of a clinical study demonstrating a benefit of vildagliptin compared to placebo, 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,**
- **demonstration of the cardiovascular safety of vildagliptin based on a meta-analysis only, with a lower level of evidence than demonstration provided by a clinical study,**
- **the absence of identified data suggesting a benefit for a cardiovascular endpoint with vildagliptin,**
- **initial data having demonstrated a modest efficacy vildagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, or the non-inferiority compared to a sulfonylurea, without any studies demonstrating a superiority compared to a clinically relevant comparator,**
- **the safety profile of vildagliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,**
- **the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,**

the Committee considers that GALVUS (vildagliptin) provides no clinical added value (CAV V).

EUCREAS (vildagliptin/metformin)

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, not including a robust study on cardiovascular endpoints but only a meta-analysis with a lower level of evidence, the absence of any demonstrated benefit on cardiovascular or renal endpoints, the absence of available efficacy results demonstrating a superiority versus a clinically relevant comparator for an intermediate laboratory endpoint, HbA1c variation, but only demonstration of non-inferiority versus a sulfonylurea, glimepiride, the absence of identification of any new safety signals specific to vildagliptin, the efficacy/adverse effects ratio of EUCREAS (vildagliptin/metformin) is low.

► There are numerous therapeutic alternatives.

► EUCREAS (vildagliptin/metformin) is an additional treatment:

- in the treatment of adult patients with inadequate glycaemic control on their maximally tolerated dose of metformin as oral monotherapy, or in patients who are already being treated with the combination of vildagliptin and metformin, as separate tablets.
- in combination with a sulfonylurea (i.e. triple therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulfonylurea.
- as triple therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

► 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 in cardiovascular morbidity and mortality only in combination and following the failure of metformin or a sulfonylurea as monotherapy. Canagliflozin has also 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, with improved patient compliance and adherence to treatment, and with a satisfactory safety profile,
- the lack of additional response to the identified need in view of:
 - the absence of an impact on morbidity and mortality, with, in particular, the absence of any demonstrated benefit on cardiovascular or renal endpoints, and in a context in which the existence of a correlation between a reduction in HbA1c and a reduction in microangiopathies has still not been formally demonstrated, with vildagliptin having demonstrated its superiority versus placebo or a non-inferiority versus a sulfonylurea for this endpoint,
 - the lack of impact on quality of life in the absence of data,

- the lack of data on a potential impact on the organisation of care,
EUCREAS (vildagliptin/metformin) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of EUCREAS (vildagliptin/metformin) is low in the MA indications.

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 in the MA indications and at the MA dosages.

► **Recommended reimbursement rate: 15%**

Clinical Added Value

Considering,

- the absence of a clinical study demonstrating a benefit of vildagliptin compared to placebo, 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,
- demonstration of the cardiovascular safety of vildagliptin based on a meta-analysis only, with a lower level of evidence than demonstration provided by a clinical study,
- the absence of identified data suggesting a benefit for a cardiovascular endpoint with vildagliptin,
- initial data having demonstrated a modest efficacy vildagliptin, in combination with other antidiabetic agents, on reduction of the intermediate laboratory endpoint, HbA1c, compared to placebo, or the non-inferiority compared to a sulfonylurea, without any studies demonstrating a superiority compared to a clinically relevant comparator,
- the safety profile of vildagliptin, which remains favourable, despite an identified risk of acute pancreatitis and bullous pemphigoid, a rare and serious event common to the gliptins,
- the unmet medical need to have access to antidiabetic medicinal products having shown evidence of a reduction in cardiovascular and renal morbidity and mortality, with improved patient compliance and adhesion to treatment, and with a satisfactory safety profile,

the Committee considers that EUCREAS (vildagliptin/metformin) provides no clinical added value (CAV V) in the treatment of type 2 diabetes.