The draft opinion adopted by the Transparency Committee on 3 September 2014 was examined at a hearing on 5 November 2014

VOKANAMET 50/1000 mg, film-coated tablet
B/60 tablets (CIP: 34009 278 938 0 3)

VOKANAMET 150/1000 mg, film-coated tablet
B/60 tablets (CIP: 34009 278 940 5 3)

Applicant: JANSSEN

<table>
<thead>
<tr>
<th>INN</th>
<th>Canagliflozin and metformin</th>
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<td>ATC code (2014)</td>
<td>A10BD16 (combinations of oral blood glucose lowering drugs)</td>
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<td>Reason for the request</td>
<td>Inclusion</td>
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<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)</td>
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Indications concerned

“VOKANAMET is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:
- in patients not adequately controlled on their maximally tolerated doses of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets.”
| Actual Benefit | - substantial in patients not adequately controlled on their maximally tolerated doses of metformin alone, or in combination with a sulfonylurea;  
|               | - moderate in patients on their maximally tolerated doses of metformin along with insulin, when these do not provide adequate glycaemic control;  
|               | - substantial as replacement of the free combination of canagliflozin and metformin, at the same doses. |
| Improvement in Actual Benefit | Taking into account the lack of clinical benefit shown by the fixed-dose combination compared with the free combination of metformin and canagliflozin or other oral blood glucose lowering drugs, the Committee considers that the VOKANAMET proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the treatment of patients with type 2 diabetes, whose treatment includes the free association of canagliflozin and metformin, or as part of a triple therapy in patients not adequately controlled on their maximum doses of metformin in combination with a sulfonylurea or an insulin. |
| Therapeutic use | VOKANAMET is a supplemental therapeutic means in type 2 diabetes not adequately controlled:  
|               | - in patients not adequately controlled on their maximally tolerated doses of metformin alone,  
|               | - in combination with a sulfonylurea or an insulin as part of a triple therapy,  
|               | - as a replacement of a free combination of canagliflozin and metformin. |
01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>Date initiated: 23 April 2014 (centralised procedure, rapporteur: Germany);</th>
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| Prescribing and dispensing conditions/special status | List I  
Medicine for initial annual prescription reserved for specialists in endocrinology, diabetes and metabolic disorders or internal medicine. |

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<th>ATC Classification</th>
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<td>Blood glucose lowering drugs, excl. insulins</td>
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<tr>
<td>A10BD</td>
<td>Combinations of oral blood glucose lowering drugs</td>
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<td>A10BD16</td>
<td>metformin and canagliflozin</td>
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02 BACKGROUND

This is an application for inclusion of the proprietary medicinal products VOKANAMET, fixed-dose combinations of two oral blood glucose lowering drugs, canagliflozin 50 or 150 mg and metformin 1000 mg, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

Canagliflozin is a sodium-glucose cotransporter type 2 inhibitor, partially blocking the renal reabsorption of glucose and resulting in glycosuria. The application for inclusion of the canagliflozin-based proprietary medicinal products INVOKANA is being assessed by the Transparency Committee in parallel.

03 THERAPEUTIC INDICATIONS

"VOKANAMET is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients not adequately controlled on their maximally tolerated doses of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets."
**04 DOSAGE**

"Posology"

The dose of glucose-lowering therapy with VOKANAMET should be individualised on the basis of the patient’s current regimen, effectiveness, and tolerability, while not exceeding the maximum recommended daily dose of 300 mg of canagliflozin and 2000 mg of metformin orally.

**For patients inadequately controlled on maximal tolerated dose of metformin**

For patients not adequately controlled on metformin, the recommended starting dose of VOKANAMET should provide canagliflozin dosed at 50 mg twice daily plus the dose of metformin already being taken or the nearest therapeutically appropriate dose. For patients who are tolerating a VOKANAMET dose containing canagliflozin 50 mg who need tighter glycaemic control, the dose can be increased to VOKANAMET containing 150 mg canagliflozin twice daily (see below and section 4.4).

**For patients switching from separate tablets of canagliflozin and metformin**

For patients switching from separate tablets of canagliflozin and metformin, VOKANAMET should be initiated at the same total daily dose of canagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Dose titration with canagliflozin (added to the optimal dose of metformin) should be considered before the patient is switched to VOKANAMET.

In patients tolerating VOKANAMET containing canagliflozin 50 mg who need tighter glycaemic control, increasing the dose to VOKANAMET containing canagliflozin 150 mg may be considered.

Care should be taken when increasing the dose of VOKANAMET containing 50 mg of canagliflozin to 150 mg of canagliflozin in patients ≥ 75 years of age, patients with known cardiovascular disease, or other patients for whom the initial canagliflozin-induced diuresis poses a risk (see section 4.4). In patients with evidence of volume depletion, correcting this condition prior to initiation of VOKANAMET is recommended (see section 4.4).

When VOKANAMET is used as add-on therapy with insulin or an insulin secretagogue (e.g., a sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

**Special populations**

**Elderly patients (≥ 65 years old)**

Because metformin is eliminated in part by the kidney and elderly patients are more likely to have decreased renal function, VOKANAMET should be used with caution as age increases. Regular assessment of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients. The risk of volume depletion associated with canagliflozin should be taken into account (see sections 4.3 and 4.4).

**Patients with renal impairment**

For patients with an estimated glomerular filtration rate (eGFR) 60 ml/min/1.73 m² to < 90 ml/min/1.73 m² or creatinine clearance (CrCl) of 60 ml/min to < 90 ml/min, no dose adjustment is needed.

VOKANAMET must not be used in patients with moderate or severe renal impairment (eGFR < 60 ml/min/1.73m² or CrCl < 60 ml/min) due to the active substance metformin (see sections 4.3, 4.4 and 5.2).
Patients with hepatic impairment
VOKANAMET is not recommended in patients with hepatic impairment due to the active substance metformin (see sections 4.3 and 5.2). There is no clinical experience with VOKANAMET in patients with hepatic impairment.

Paediatric population
The safety and efficacy of VOKANAMET in children under 18 years of age have not been established. No data are available.

Method of administration
For oral use. VOKANAMET should be taken orally twice daily with meals to reduce the gastrointestinal undesirable effects associated with metformin. Tablets are to be swallowed whole. If a dose is missed, it should be taken as soon as the patient remembers unless it is nearly time for the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time."
The objective of treatment in type 2 diabetes is to reduce morbidity and mortality, in particular using the correct glycaemic control. The short-term objective is the improvement of symptoms (thirst, polyuria, asthenia, emaciation and blurred vision) and prevention of acute complications (infections and hyperosmolar state). The longer-term objective is the prevention of chronic microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, strokes and obliterating arteriopathy of the legs) complications and reduction of mortality.

According to the 2013 HAS guidelines, the glycaemic target of type 2 diabetes patients should be defined for each patient based on comorbidities and life expectancy: the target HbA1c varies from 6.5% to 8%. It turns out that a target HbA1c less than or equal to 7% is recommended for most patients. The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%. Diabetes is progressive and treatment should be regularly re-assessed in all its components: lifestyle and dietary measures, therapeutic education and drug treatment.

Special cases: for patients in whom diabetes has been newly diagnosed, with a life expectancy of more than 15 years and with no history of cardiovascular events, a target ≤ 6.5% is recommended, subject to it being achieved by the implementation or reinforcement of lifestyle and dietary measures then, in case of failure, by oral monotherapy.

There is a certain number of special cases where the glycaemic target is less demanding: age > 75 years; history of macrovascular complication; chronic renal failure; proven serious comorbidity; limited life expectancy (< 5 years); long-lasting diabetes (> 10 years) and whose target of 7% proves difficult to achieve because the increase in drugs causes severe hypoglycaemia.

Implementation of effective lifestyle and dietary measures is a necessary prerequisite for glycaemic control medication.

Drug strategy:
According to general HAS guidelines, if the glycaemic target is not achieved despite the implementation of lifestyle and dietary measures, monotherapy should be initiated with metformin as first-line treatment or, in case of contraindications, sulfonylureas (for contraindications for both substances, repaglinide or alpha-glucosidase inhibitors are recommended).

In case of symptoms or very unbalanced diabetes with repeated blood glucose greater than 3 g/l or HbA1c greater than 10%, dual therapy or insulin therapy may be instituted from the outset.

Combinations recommended as dual therapy:
If the glycaemic target is not achieved with monotherapy, dual therapy is recommended, combining metformin and sulfonylureas as first-line treatment, monitoring weight and the occurrence of hypoglycaemia.

In the event of intolerance or contraindication to sulfonylureas, and if the deviation from the target is less than 1% HbA1c, the following treatment regimens may be proposed:

- metformin + repaglinide combination (if irregularity in intake of food),
- metformin + alpha-glucosidase inhibitors (if the occurrence of hypoglycaemia is a serious situation),
- metformin + dipeptidyl peptidase-4 inhibitors/gliptins (if the occurrence of hypoglycaemia or the increase in weight are serious).

In the event of intolerance or contraindication to metformin, and if the deviation from the target is less than 1% HbA1c, the following treatment regimens may be proposed:
- sulfonylurea + alpha-glucosidase inhibitor combination,
- sulfonylurea + DPP-4 inhibitor combination.

The use of GLP-1 analogues is possible at the dual therapy stage if the BMI is ≥ 30 kg/m² or if the increase in weight on insulin or the occurrence of hypoglycaemia are serious.

**Combinations recommended as triple therapy:**
If the glycaemic target is not achieved despite metformin + sulfonylurea dual therapy and if the deviation from the target is less than 1% HbA1c, the following treatment regimens can be proposed:
- metformin + sulfonylurea + alpha-glucosidase inhibitor combination
- metformin + sulfonylurea + DPP-4 inhibitor/gliptin combination.

**Combinations recommended with insulin therapy:**
The benefit of maintaining non-insulin blood glucose lowering drugs should be assessed depending on the expected benefits for each of the substances:
- metformin will be continued,
- the dosage of the sulfonylurea or repaglinide will be adapted, if necessary, according to the insulin regimen,
- the DPP-4 inhibitors and alpha-glucosidase inhibitors will be discontinued,
- the insulin + GLP-1 analogue combination is part of a specialist opinion.

In its guidelines, HAS specifies that the GLP-1/insulin combination is part of a specialist opinion.

**Sodium-glucose transporter type 2 inhibitors**
To date, this new therapeutic class includes two substances: dapagliflozin (FORXIGA) and canagliflozin (INVOKANA). Canagliflozin is currently being assessed by the Committee. No international guidelines oversee the prescription of this class of substances. However, according to the Transparency Committee opinion, dapagliflozin cannot be recommended as monotherapy or in dual therapy with insulin. It is, however, a supplemental therapeutic means for type 2 diabetes, in dual therapy with metformin or sulfonylureas, or in triple therapy after failure of combined insulin/metformin.

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5 Transparency Committee Opinion of 23 July 2014 on FORXIGA.
06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

No fixed-dose combination of metformin and sodium-glucose cotransporter type 2 inhibitor is currently available.

Comparators of the fixed-dose combination are:
- the free combination of canagliflozin and metformin in the context of a switch from this combination;
- the free combination in dual therapy with the maximally tolerated doses of metformin, and sulfonylureas, glinides, alpha-glucosidase inhibitors, GLP-1 analogues, and dapagliflozin,
- the free combination of canagliflozin and metformin in the context of triple therapy with insulin therapy or oral blood glucose lowering drugs;

The comparators are submitted in annex.

06.2 Other health technologies

Not applicable.

Conclusion
The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

VOKANAMET was granted a European MA on 23 April 2014. These proprietary medicinal products are not currently available in Europe or in the United States.
The application for reimbursement of the proprietary medicinal product VOKANAMET, fixed-dose combination of metformin and canagliflozin, is based on:
- phase I clinical studies on oral bioequivalence (DIA1051 and DIA1038) and bioavailability (DIA1037); the bioavailability study will not be submitted.
- a phase II study on dual therapy with metformin (DIA2003); considering the study of this combination in a phase III trial (see below), this study will not be submitted.
- phase III studies, having evaluated the efficacy and tolerance of canagliflozin, submitted in the context of the assessment of the INVOKANA proprietary medicinal products (canagliflozin alone):
  - in dual therapy with metformin in two studies, versus the metformin/placebo combination in study DIA3006, and the metformin/glimepiride (sulfonylurea) combination in study DIA3009,
  - in triple therapy with the metformin/sulfonylurea combination in two studies, versus metformin/sulfonylurea/sitagliptin triple therapy in DIA3015, metformin/sulfonylurea/placebo triple therapy in study DIA3002,
  - in combination with metformin and insulin in the intermediary analysis of substudy DIA3008

The results of the phase III studies, which were developed in the INVOKANA opinion of 5 November 2014, will be included in summary form in this document.

08.1 Efficacy

8.1.1 Bioequivalence studies

Bioequivalence was shown in the following two bioequivalence studies:
- Study DIA1051 for the fixed-dose combination of canagliflozin 50 mg and metformin 1000 mg twice daily versus separate administration of one tablet of canagliflozin 100 mg and two tablets of metformin 1000 mg per day;
- Study DIA1038 for the fixed-dose combination of canagliflozin 150 mg and metformin 1000 mg twice daily versus separate administration of one tablet of canagliflozin 300 mg and two tablets of metformin 1000 mg per day.

8.1.2 Summary of the results of the phase III studies

Five multicentre, randomised, controlled, double-blind studies, performed in patients with inadequately controlled type 2 diabetes, evaluated canagliflozin in combination with metformin, in dual therapy, or in triple therapy with other blood glucose lowering drugs.\(^5\)

The primary efficacy endpoint found in these studies was the change in HbA1c over the predetermined periods.

**Studies in dual therapy in combination with metformin**

Two studies had the primary objective of evaluating canagliflozin in combination with metformin, one versus placebo (study DIA3006) and the other versus a sulfonylurea, glimepiride (DIA3009).

**Study DIA3006** included 1284 patients with a mean age of 55 years with type 2 diabetes for nearly 7 years, and a mean HbA1c of 7.9% at baseline. These patients were randomised into four groups according to a 2:2:2:1 design (canagliflozin 100 mg, canagliflozin 300 mg, placebo, sitagliptin 100 mg), for a duration of 26 weeks. The sitagliptin group served as the active comparator for a secondary non-inferiority analysis evolving into a superiority study over a 52-week period. At 26 weeks, this study showed the superiority of canagliflozin 100 and 300 mg compared with placebo, in terms of change in HbA1c, with an intergroup difference with placebo of -0.6 (±0.1;
95% CI: [-0.8; -0.5]) for canagliflozin 100 mg and -0.8 (±0.1; 95% CI: [-0.9; -0.6]) for canagliflozin 300 mg.

The change in secondary endpoints at 26 weeks also favoured canagliflozin 100 and 300 mg compared with placebo, with 45.5 and 57.8% responders (HbA1c<7.0%) versus 29.8%, respectively, and an intergroup difference with placebo for weight of -2.5 kg (±0.3) and -2.9 kg (±0.3), respectively.

It should be noted that canagliflozin was non-inferior to sitagliptin 100 mg at 52 weeks with an intergroup difference in per protocol of 0.12% (±0.06; 95% CI: [0.01; 0.24]) for canagliflozin 100 mg and -0.03% (±0.06; 95% CI: [-0.15; 0.09]) for canagliflozin 300 mg, considering a non-inferiority margin of 0.30%. These results were confirmed by the mITT analysis. In the superiority analysis following the demonstration of non-inferiority, for the 300 mg dosage only, the upper limit of the confidence interval was slightly less than 0, which fulfilled the definition of superiority (-0.15; 95% CI [-0.27; -0.03]). This result should be interpreted with caution because of the high percentage of patients excluded (28% of patients in the canagliflozin 300 mg group and 35% from the sitagliptin 100 mg group) from the per-protocol analysis.

Study DIA3009 included 1452 patients with a mean age of 56 years with type 2 diabetes for nearly 7 years, and a mean HbA1c of 7.8% at baseline. These patients were randomised into three groups: canagliflozin 100 mg, canagliflozin 300 mg, glibenclamide.

This study showed the non-inferiority of canagliflozin 100 and 300 mg at 52 weeks compared with glimepiride, in terms of change in HbA1c, with an intergroup difference with the glimepiride group of -0.01 (±0.05; 95% CI: [-0.11; 0.09]) for canagliflozin 100 mg and -0.12 (±0.05; 95% CI: [-0.22; -0.02]) for canagliflozin 300 mg, respecting the upper limit of non-inferiority for the 95% confidence interval set at 0.30.

The change in secondary endpoints at 52 weeks also favoured canagliflozin 100 and 300 mg compared with glimepiride, with 5.6% and 4.9% of patients with hypoglycaemia versus 34.2%, respectively, and an intergroup difference with glimepiride for weight of -5.2 kg (±0.3) and -5.7 kg (±0.3), respectively. The percentage of responder patients was part of the exploratory criteria and was 53.6% and 60.1% in the canagliflozin 100 and 300 mg groups and 55.8% in the glimepiride group.

Overall, these studies showed the superiority of canagliflozin 100 and 300 mg in combination with metformin at sufficient doses compared with placebo, and the non-inferiority of both doses compared with glimepiride (sulfonylurea), setting a non-inferiority limit of 0.30% in accordance with the guidelines. Non-inferiority compared with sitagliptin 100 mg was demonstrated a second time. In both studies, the decrease in HbA1c between baseline and week 26 or 52 was 0.8 to 0.9% for canagliflozin, from a moderately high mean baseline HbA1c value (7.8%).

The difference in percentage of responder patients compared with placebo was 15.7% and 28% for the 100 mg and 300 mg dosages, respectively, at week 26; in the second study, this percentage was not very different from that of glimepiride. The weight change should be interpreted in light of the mechanism of action of canagliflozin, as the weight change is accompanied by fluid loss.6

**Studies in triple therapy in combination with metformin/sulfonylurea**

Two studies had the primary objective of evaluating canagliflozin in combination with metformin/sulfonylurea, one versus placebo (study DIA3002) and the other versus a gliptin, sitagliptin (DIA3015).

Study DIA3002 included 469 patients with a mean age of 56 years with type 2 diabetes for nearly 10 years, and a mean HbA1c of 8.1% at baseline. These patients were randomised into three groups: canagliflozin 100 mg, canagliflozin 300 mg, placebo.

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At 26 weeks, this study showed the superiority of canagliflozin 100 and 300 mg compared with placebo, in terms of change in HbA1c, with an intergroup difference with placebo of -0.7 (±0.1; 95% CI: [-0.9;-0.5]) for canagliflozin 100 mg and -0.9 (±0.1; 95% CI: [-1.1;-0.7]) for canagliflozin 300 mg.

The change in secondary endpoints at 26 weeks also favoured canagliflozin 100 and 300 mg compared with placebo, with 43.2 and 56.6% responders versus 18%, respectively, and an intergroup difference with placebo for weight of -1.4 kg (±0.4) and -2.0 kg (±0.4), respectively.

**Study DIA3015** included 756 patients with a mean age of 57 years with type 2 diabetes for nearly 7 years, and a mean HbA1c of 8.1% at baseline. About 33% of patients left the study, primarily due to failure to achieve blood glucose targets during the study. These patients were randomised into two groups: canagliflozin 300 mg, sitagliptin 100 mg.

This study showed the non-inferiority of canagliflozin 300 mg compared with sitagliptin 100 mg at week 52, in terms of change in HbA1c level, with an intergroup difference compared with sitagliptin of -0.21 in per protocol (95% CI [-0.34;-0.08]). These results were confirmed by the modified mITT analysis. In the superiority analysis following the demonstration of non-inferiority, the upper limit of the confidence interval was less than 0, which fulfilled the definition of superiority (-0.37; 95% CI [-0.50;-0.25]). This result should be interpreted with caution because of the high percentage of patients excluded (34% of patients in the canagliflozin 300 mg group and 45% from the sitagliptin 100 mg group) from the per-protocol analysis.

In terms of secondary endpoints, this study showed the superiority of canagliflozin at week 52 compared with sitagliptin 100 mg

The change in secondary endpoints at 52 weeks also favoured canagliflozin 300 mg compared with sitagliptin, with an intergroup difference with sitagliptin for weight of -2.8 kg (±0.3). The percentage of responder patients was part of the exploratory criteria and was 45.6% in the canagliflozin 300 mg group and 35.3% in the sitagliptin group.

Overall, these studies showed the superiority of canagliflozin in combination with metformin and a sulfonylurea (glimepiride) compared with placebo, as well as, for the 300 mg dosage only, the non-inferiority, setting a non-inferiority limit of 0.30% in accordance with the guidelines, and this superiority compared with sitagliptin 100 mg. It should be noted that a third of patients were excluded from the non-inferiority study, primarily due to failure to achieve the blood glucose targets established; this fact could cause an attrition bias. It is unfortunate that the 100 mg dosage was not evaluated. The change in HbA1c with canagliflozin in triple therapy, compared with baseline, was 0.8% for the 100 mg dose and 1% for the 300 mg dose (at week 26 and week 52), from an HbA1c value of 8.1%.

The difference in percentage of responder patients compared with placebo was 25.2% and 38.6% for the 100 mg and 300 mg dosages, respectively, at week 26; in study DIA3015, this difference was +10% compared with sitagliptin.
**Study in combination with insulin and metformin**

The efficacy of canagliflozin versus placebo, in combination with insulin, was evaluated in a substudy of safety study DIA3008 performed in patients with cardiovascular risk. The efficacy was evaluated in a subpopulation on insulin ≥ 30 IU/d and metformin ≥ 2000 mg/d (n=432). These patients had a mean HbA1c level of 8.2% at baseline. The intergroup difference with placebo was -0.7 (±0.1) and -0.8 (±0.1) respectively for the 100 and 300 mg doses of canagliflozin (p<0.001).

**08.2 Safety/Adverse effects**

**8.2.1 Review of the findings in the opinion of 3 September 2014 for canagliflozin (INVOKANA)**

"Between 60 and 77% of adverse events were found in the clinical studies provided. Most were of mild to moderate intensity. The most frequently reported treatment-related adverse events were hypoglycaemia, vulvovaginal mycotic infections, urinary tract infections, and frequent urination/polyuria. Adverse events related to volume depletion were found (1.2% for canagliflozin 100 mg and 1.3% for the 300 mg dose): arterial and orthostatic hypotension, feeling of vertigo, dehydration, syncope. These events were more common in specific populations (subjects 55 to 80 years of age, moderate renal impairment). An increase in LDL-cholesterol was found in the clinical studies."

**8.2.2 SPC data**

The SPC presents the adverse effects related to canagliflozin found in clinical studies, as well as the adverse effects related to metformin from clinical study data and post-marketing data. For canagliflozin, common adverse effects were gastrointestinal disorders (constipation, thirst, nausea), dyslipidaemia, and increased haematocrit. Uncommon adverse effects were neurological disorders (postural vertigo, syncope), vascular disorders (arterial and orthostatic hypotension), metabolic disorders (dehydration), skin disorders (rash and urticaria), and increased creatinaemia, uraemia, kalaemia, and phosphataemia. For metformin, very common adverse effects were gastrointestinal symptoms (nausea, vomiting, abdominal pain, loss of appetite). Common adverse effects were taste disorders. Very rare adverse effects included lactic acidosis, vitamin B12 deficiencies, skin disorders (erythema, pruritus, urticaria), and liver function disorders and hepatitis.
08.3 Summary & discussion

The application for inclusion of VOKANAMET is based on the data from two bioequivalence studies and five multicentre, randomised, controlled, double-blind studies, performed in patients with type 2 diabetes not adequately controlled by metformin.

The bioequivalence between the fixed-dose combination and the separate administration of each of the active ingredients was established.

The efficacy of the free combination of canagliflozin 100 or 300 mg/d and metformin 2000 mg/d in patients initially treated by metformin alone was evaluated in two studies in terms of reduction in HbA1c compared with placebo, and by a study of non-inferiority to glimepiride. This combination was also evaluated in triple therapy, only for the 300 mg dose, in combination with a sulfonylurea, in two studies in which canagliflozin was compared with placebo and with sitagliptin (non-inferiority study). The 100 mg dose was not evaluated for this triple therapy. Data for the combination of canagliflozin with insulin and metformin in triple therapy come from a subpopulation of a study done in patients with cardiovascular risk.

The findings from the evaluation on the efficacy/adverse effects ratio of INVOKANA (canagliflozin) based on these phase III studies are as follows:7

"The efficacy/adverse effects ratio is:
- Substantial in dual therapy with metformin and in triple therapy with metformin/sulfonylurea, considering the amount of effect or HbA1c provided in the clinical studies, similar to other recommended oral blood glucose lowering drugs.
- Moderate in triple therapy with metformin and insulin, considering the methodological weaknesses."

As no phase III study has been conducted on the fixed-dose combination, it is difficult to judge the value of a fixed-dose combination compared with these medicines administered separately. Therefore, this fixed-dose combination would be reserved only for patients treated with a maximum dosage of 1000 mg of metformin administered twice per day. According to these guidelines, the use of metformin requires that a patient remain on monotherapy with the possibility of increasing the doses to 2000 to 3000 mg per day in case of inadequate glycaemic control and good tolerance, before combining with another oral blood glucose lowering drug.

In terms of safety, this fixed-dose combination particularly exposes [patients] to adverse events from canagliflozin and metformin. For canagliflozin, the most frequently reported treatment-related adverse events were hypoglycaemia, vulvovaginal mycotic infections, urinary tract infections, and frequent urination/polyuria. Adverse events related to volume depletion were found: arterial and orthostatic hypotension, feeling of vertigo, dehydration, syncope. These events were more common in specific populations (patients 55 to 80 years of age or with moderate renal impairment). For metformin, the most frequently reported adverse events were gastrointestinal disorders and taste disorders.

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7 Transparency Committee Opinion of 5 November 2014 for the INVOKANA proprietary medicinal products (canagliflozin).
08.4 Planned studies

The study schedule concerns the development of canagliflozin, and the risk management plan:
- continuation of study DIA3008 evaluating the safety of canagliflozin on major cardiac events in patients with inadequately controlled type 2 diabetes and cardiovascular risk (planned end in 2018),
- safety study DIA4003 on renal function in adult patients with inadequately controlled type 2 diabetes and cardiovascular risk (planned end 2018).

09 THERAPEUTIC USE

The objective of treatment in type 2 diabetes is to reduce morbidity and mortality, in particular using the correct glycaemic control. According to the 2013 HAS guidelines, the glycaemic target of type 2 diabetes patients should be defined for each patient based on comorbidities and life expectancy: the target HbA1c varies from 6.5% to 8%. A target HbA1c less than or equal to 7% is recommended for most patients. The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.

According to HAS guidelines, if the glycaemic target is not achieved despite the implementation of lifestyle and dietary measures, monotherapy should be initiated with metformin as first-line treatment or, in case of contraindications, sulfonylureas (for contraindications for both substances, repaglinide or alpha-glucosidase inhibitors are recommended).

Dual therapy with metformin
If the glycaemic target is not achieved with monotherapy, dual therapy is recommended, combining metformin and sulfonylureas as first-line treatment, monitoring weight and the occurrence of hypoglycaemia. In case of intolerance or contraindication for sulfonylureas, metformin can be combined with alpha-glucosidase inhibitors, DPP-4 inhibitors/gliptin, and repaglinide. According to the opinion of 3 September 2014, canagliflozin is a supplemental therapeutic means in dual therapy in combination with metformin, among the oral blood glucose lowering drugs available in case of intolerance or contraindication for sulfonylureas.

Triple therapy with oral blood glucose lowering drugs
If the glycaemic target is not achieved despite dual therapy with metformin + sulfonylurea, an alpha-glucosidase inhibitor or a gliptin may be added. According to the opinion of 3 September 2014, canagliflozin is a supplemental therapeutic means in triple therapy in combination with metformin and a sulfonylurea, among the recommended oral blood glucose lowering drugs available.

In combination with insulin
The benefit of maintaining oral blood glucose lowering drugs should be assessed depending on the expected benefits for each of the substances. Thus, as applicable, metformin or sulfonylureas (after dosage adjustment) can be continued. According to the opinion of 3 September 2014,
canagliflozin is only an alternative in triple therapy with insulin and metformin.

VOKANAMET is the fixed-dose combination of canagliflozin 50 or 150 mg and metformin 1000 mg, to be taken twice daily.

The VOKANAMET proprietary medicinal products are a supplemental therapeutic means:
- in patients not adequately controlled on their maximally tolerated doses of metformin alone; remember that the use of metformin requires that a patient remain on monotherapy with the possibility of increasing the doses to 2000 to 3000 mg per day in case of inadequate glycaemic control and good tolerance, before combining with another oral blood glucose lowering drug;
- in patients not adequately controlled on their maximally tolerated doses of metformin in combination with a sulfonylurea or an insulin.

It is preferable to perform a titration of individual tablets to achieve the optimal dose of treatments before using the fixed-dose combination.

Remember that due to the diuretic action of canagliflozin, caution is recommended in patients for whom a decrease in blood pressure could present a risk: patients with cardiovascular disease, mild or moderate renal impairment, on antihypertensive treatment with a history of hypotension, on diuretics, or patients 65 years and older.

Diabetes is progressive and treatment should be regularly re-assessed in all its components: lifestyle and dietary measures, therapeutic education and drug treatment.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
- These proprietary medicinal products are used in the context of symptomatic treatment of blood glucose in type 2 diabetes.
- The efficacy/adverse effects ratio is:
  - substantial when it is used alone in patients not adequately controlled on their maximally tolerated doses of metformin alone, and in combination with a sulfonylurea,
  - moderate in combination with insulin, considering the methodological weaknesses of the studies on canagliflozin alone.
- VOKANAMET is a supplemental therapeutic means in type 2 diabetes not adequately controlled:
  - in patients not adequately controlled on their maximally tolerated doses of metformin alone,
  - in combination with a sulfonylurea or an insulin, as part of a triple therapy,
  - as a replacement of a free combination of canagliflozin and metformin.
- There are treatment alternatives to this proprietary medicinal product.

Public health benefit:
Because of its high prevalence, which is constantly increasing, and the associated microvascular and macrovascular complications, the public health burden of type 2 diabetes is substantial. The public health burden in the subpopulation of patients with each of the indications for VOKANAMET is considered to be moderate.
Improving the treatment of patients with type 2 diabetes is a public health need which is an established priority (Objective 55 of the Law of 9 August 2004 on public health policy, National plan to improve the quality of life of individuals with chronic diseases 2007-2011). Access to effective treatments which are well tolerated in type 2 diabetes patients is a public health need. In view of the results of the clinical studies performed in all the indications, no additional impact on glycaemic control is expected from the proprietary medicinal product VOKANAMET. Moreover, the available data do not make it possible to estimate the impact of VOKANAMET on morbidity and mortality and quality of life in patients with type 2 diabetes compared with currently available treatments.
In addition, it is not certain that it will be possible to transpose the experimental data into clinical practice because of uncertainties about the long-term effect of this treatment including its effect on glycaemic control.
In the current state of knowledge, the proprietary medicinal product VOKANAMET is unable to offer any response to the identified public health need.
It is therefore not expected that the proprietary medicinal product VOKANAMET will impact public health in any of the Marketing Authorisation indications.
Taking account of these points, the Committee considers that the actual benefit of VOKANAMET is:
- substantial in patients not adequately controlled on their maximally tolerated doses of metformin alone, or in combination with a sulfonylurea;
- moderate in patients on their maximally tolerated doses of metformin along with insulin, when these do not provide adequate glycaemic control;
- substantial as replacement of the free combination of canagliflozin and metformin, at the same doses.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

Taking into account the lack of clinical benefit shown by the fixed-dose combination compared with the free combination of metformin and canagliflozin or other oral blood glucose lowering drugs, the Committee considers that the VOKANAMET proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the treatment of patients with type 2 diabetes, whose treatment includes free association of canagliflozin and metformin, or as part of a triple therapy in patients not adequately controlled on their maximally tolerated doses of metformin in combination with a sulfonylurea or an insulin.

010.3 Target population

The target population of VOKANAMET is patients with type 2 diabetes treated with canagliflozin and metformin or not adequately controlled on the maximum dose of metformin in combination with a sulfonylurea or insulin.

It is, at most, equal to the target population of INVOKANA, which is 282,078 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

### APPENDIX

<table>
<thead>
<tr>
<th>INN</th>
<th>Name (Company)</th>
<th>Date of opinion</th>
<th>Actual Benefit</th>
<th>Improvement in Actual Benefit</th>
<th>Reimbursement</th>
</tr>
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<tbody>
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<tr>
<td></td>
<td>Metformin and its generics</td>
<td>GLUCOPHAGE (Merck Santé)</td>
<td>21 July 2010 (RI)</td>
<td>Substantial</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td><strong>Biguanide</strong></td>
<td></td>
<td></td>
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<td></td>
<td>Sulfonylureas and their generics</td>
<td>GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)</td>
<td>5 September 2012 (RI)</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Insulin secretagogues</strong></td>
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<tr>
<td></td>
<td>Sulfonylureas and their generics</td>
<td>GLUCOPHAGE (Merck Santé) DIASTABOL (Sanofi Aventis)</td>
<td>5 September 2012 (RI)</td>
<td>Substantial</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td><strong>Alpha-glucosidase inhibitors (acarbose, miglitol)</strong></td>
<td>GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)</td>
<td>5 September 2012 (RI)</td>
<td>Substantial</td>
</tr>
<tr>
<td></td>
<td>Repaglinide</td>
<td>NOVONORM (Novo Nordisk)</td>
<td>21 July 2010 (RI)</td>
<td>Substantial</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td><strong>Injectable incretin mimetic or GLP-1 analogues (not indicated as monotherapy)</strong></td>
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<td></td>
<td>Exenatide</td>
<td>BYETTA (Bristol-Myers Squibb)</td>
<td>28 February 2007</td>
<td>Substantial as dual therapy in combination with metformin or a sulfonylurea</td>
<td>-</td>
</tr>
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<td></td>
<td></td>
<td><strong>Being assessed as dual therapy with insulin and as triple therapy with insulin + metformin</strong></td>
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<td></td>
<td>Liraglutide</td>
<td>VICTOZA (Novo Nordisk)</td>
<td>2 December 2009</td>
<td>Substantial as dual therapy in combination with metformin or a sulfonylurea</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide</td>
<td>LYXUMIA (Sanofi Aventis)</td>
<td></td>
<td>Still being assessed by the TC</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Gliptins</strong></td>
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<tr>
<td></td>
<td>Sitagliptin and its fixed-dose combinations with metformin</td>
<td>JANUVIA 100 mg/XELEVIA 100 mg (MSD, Pierre Fabre)</td>
<td>18 July 2012</td>
<td>Insufficient as monotherapy</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 June 2007</td>
<td>Substantial as dual therapy in combination with metformin</td>
<td>IV</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>24 June 2009</td>
<td>Low as dual therapy in combination with a sulfonylurea</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 July 2012</td>
<td>Insufficient as dual therapy in combination with insulin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 July 2012</td>
<td>Substantial as triple therapy in combination with insulin and metformin</td>
<td>V</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin and its fixed-dose combinations with metformin</td>
<td>GALVUS/JALRA (Novartis Pharma)</td>
<td>21 Nov. 2012</td>
<td>Insufficient as monotherapy</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 December 2008</td>
<td>Substantial as dual therapy in combination with metformin or a sulfonylurea</td>
<td>V</td>
</tr>
</tbody>
</table>

14 On 20 September 2012, vildagliptin-based proprietary medicinal products received a favourable opinion from the CHMP in the following extension of indication: “in combination with insulin, with or without metformin, when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.”
<table>
<thead>
<tr>
<th>INN</th>
<th>Name (Company)</th>
<th>Date of opinion</th>
<th>Actual Benefit</th>
<th>Improvement in Actual Benefit</th>
<th>Reimbursement</th>
</tr>
</thead>
</table>
| Saxagliptin and its fixed-dose combination with metformin | ONGLYZA (Bristol-Myers Squibb)
| 2 December 2009                  | Substantial as dual therapy in combination with metformin or a sulfonylurea | V                             | Yes                          |               |
|                                   | 15 May 2013                            | Insufficient as dual therapy in combination with insulin     | V                             |                              | No            |
|                                   | 15 May 2013                            | Low as triple therapy in combination with insulin and metformin | V                             | Yes                          |               |
| Linagliptin and its fixed-dose combination | TRAJENTA (Boehringer Ingelheim)
| 20 June 2012                     | Insufficient as monotherapy                                  | -                             |                              | No            |
|                                   | 20 March 2013                          | Substantial as dual therapy in combination with metformin    | V                             | No                           |               |
|                                   |                                       | Insufficient as dual therapy in combination with insulin      | V                             |                              |               |
|                                   |                                       | Substantial as triple therapy in combination with insulin and metformin | V                             |                              |               |
| Sodium-glucose cotransporter type 2 inhibitors | Dapagliflozin FORXIGA
| 23 April 2014                    | Insufficient as monotherapy                                  |                              | V                             | No            |
|                                   |                                        | Moderate as dual therapy in combination with metformin        |                              | No                           |               |
|                                   |                                        | Insufficient as dual therapy in combination with insulin      |                              |                              |               |
|                                   |                                        | Moderate as triple therapy in combination with insulin and metformin |                              |                              |               |