![HAS - Haute Autorité de Santé logo]

The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
23 April 2014

FORXIGA 10 mg, film-coated tablets
B/28 (CIP: 34 009 266 498-0 7)
B/30 (CIP: 34 009 266 499-7 5) – unit packaging

Applicant: ASTRAZENECA

INN	Dapagliflozin
ATC Code (2014)	A10BX09 (oral blood glucose lowering drug)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) for B/28 and B/30 only **Hospital use** (French Public Health Code L.5123 2) for B/30 only
Indications concerned	"Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: **Monotherapy** **When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.** **Add-on combination therapy** **In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations). "** *The company is not seeking to have this medicinal product included as monotherapy*

Actual Benefit	The actual benefit of FORXIGA is: - insufficient as monotherapy for reimbursement by National Health Insurance - moderate as dual therapy in combination with metformin or a sulfonylurea - insufficient as monotherapy for reimbursement by National Health Insurance - moderate as triple therapy in combination with insulin and metformin
Improvement in Actual Benefit	<u>In the monotherapy and dual therapy indications, in combination with insulin</u>: not applicable <u>In the dual therapy indications, in combination with metformin or a sulfonylurea and triple therapy, in combination with insulin and metformin:</u> Given the very modest glycaemic control observed compared with the placebo, doubts about the safety profile, particularly on an infectious, cardiovascular and carcinogenic level, and the difficulty in defining the therapeutic use, the Committee cannot recognise any improvement for FORXIGA. In addition, the Transparency Committee considers that FORXIGA does not provide any improvement in actual benefit (level V, non-existent) in the management of patients with type 2 diabetes in dual oral therapy, in combination with metformin or a sulfonylurea and in triple therapy, in combination with insulin and metformin.
Therapeutic use	In the absence of national and international recommendations concerning the class of gliflozins and given the available data, the Committee cannot define a precise therapeutic use for dapagliflozin. It leaves practitioners for whom the initial prescription is restricted (specialists in endocrinology, diabetes, metabolic diseases, internal medicine) the option of starting dapagliflozin treatment in line with the indications and precautions for use of its Marketing Authorisation, and the proposals for management recognised by the Committee.
Recommendations	-

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date (centralised procedure): 12 November 2012
Prescribing and dispensing conditions/special status	List I Initial annual prescription reserved for specialists in endocrinology, diabetes and metabolic disorders or internal medicine. Unrestricted renewal.

| ATC Classification | 2014;
A   Alimentary tract and metabolism
A10   Drugs used in diabetes
A10B   Blood glucose lowering drugs, excl. insulins
A10BX Other blood glucose lowering drugs, excl. insulins
A10BX09 dapagliflozin |

02 BACKGROUND

This is an application for inclusion of a new oral blood glucose lowering drug, dapagliflozin, in the management of patients with type 2 diabetes in dual therapy in combination with oral antidiabetic drugs (OADs), in dual therapy in combination with basal insulin and in triple therapy in combination with an OAD and basal insulin. The company is not seeking to have this medicinal product included as monotherapy.

Dapagliflozin is the 1st drug representing a new therapeutic category, the sodium-glucose co-transporter type 2 inhibitors (SGLT2). Dapagliflozin reduces the renal reabsorption of glucose and thereby promotes urinary excretion. It has the distinction of acting independently from the secretion and action of insulin.

03 THERAPEUTIC INDICATIONS

"Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations). "

04 DOSAGE

"Monotherapy and add-on combination therapy
The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose lowering medicinal products including insulin. When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulfonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

Special populations
Renal impairment
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m2 (see sections 4.4, 4.8, 5.1 and 5.2).
No dosage adjustment is indicated in patients with mild renal impairment.

Hepatic impairment
No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg (see sections 4.4 and 5.2).

Elderly patients (≥ 65 years)
In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 5.2). Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

Paediatric population
The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Method of administration
Forxiga can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole."

05   THERAPEUTIC NEED[1,2,3,4]

Objective of treatment in type 2 diabetes: 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 hyperglycaemic coma). The longer-term objective is the prevention of chronic microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, strokes and obliterating arteriopathy of the lower limbs) complications and reduction of mortality.

Glycaemic target: according to the HAS (2013) guidelines, it should be individualised depending on patient profile and can therefore evolve over time. Diabetes is progressive and treatment should be regularly re-assessed in all its components: hygiene and dietary measures, therapeutic education and drug treatment. Data from literature does not provide the opportunity of defining a lower limit for the HbA1c target. Once the target is achieved, the treatment will be adjusted on a case by-case basis. For most patients with type 2 diabetes, an HbA1c target ≤ 7% is recommended. The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.
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, an target ≤ 6.5% is recommended, subject to it being achieved by the implementation or reinforcement of hygiene 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 hygiene and dietary measures is a necessary prerequisite for glycaemic control medication.

Drug strategy:
According to recent HAS guidelines, as a general rule, the recommended strategy for introducing blood glucose lowering drugs is as follows:

- metformin **monotherapy**

Combinations recommended as dual therapy:
- If the glycaemic target is not achieved despite **metformin monotherapy**, the metformin + sulfonylurea combination is recommended monitoring weight gain 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),

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[1] NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.

[2] SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010.

[3] ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes). Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364-79.

[4] Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [Treatment strategy for glycaemic control of type 2 diabetes]. Recommandations de bonne pratique de la HAS [HAS Good practice guidelines]. January 2013.

- metformin + dipeptidyl peptidase-4 inhibitors/gliptins (if the occurrence of hypoglycaemia or the increase in weight are serious).

- If the glycaemic target is not achieved despite **sulfonylurea monotherapy** (metformin is not tolerated or contraindicated) 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.

The latest national and international guidelines do not formally cite the therapeutic use of sodium-glucose co-transporter type 2 inhibitors in the management of patients with type 2 diabetes.

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of the medicinal product assessed are medicinal products available and able to be prescribed at the same stage of therapeutic use and intended for the same population, on the date of the assessment.

06.1 Medicinal products

Dapagliflozin is the 1st drug representing a new therapeutic category of sodium-glucose co-transporter type 2 inhibitors. Consequently, there are no other medicines in the same therapeutic category.

The clinically relevant comparators are the proprietary medicinal products indicated in the **combination** treatment of type 2 diabetes:

- *In patients with type 2 diabetes who are not achieving adequate glycaemic control at maximum tolerated doses of oral **metformin**-based monotherapy combined with with hygiene and dietary measures:*
- sulfonylureas
- glinides

- intestinal alpha-glucosidase inhibitors
- gliptins
- GLP-1 analogues administered by injection:

- *In patients with type 2 diabetes with inadequate glycaemic control at maximum tolerated doses of oral **sulfonylurea**-based monotherapy, combined with hygiene and dietary measures and in whom metformin is contraindicated or not tolerated:*
- intestinal alpha-glucosidase inhibitors
- GLP-1 analogues administered by injection
- gliptins

- *In patients with type 2 diabetes with inadequate glycaemic control at maximum tolerated doses of **insulin alone or with blood glucose lowering treatment,** combined with hygiene and dietary measures:*
- metformin
- sulfonylureas
- intestinal alpha-glucosidase inhibitors
- gliptins
- GLP-1 analogues

The indications and the results of the TC assessments of all these different proprietary medicinal products are presented in the table in the appendix.

06.2 Other health technologies
Not applicable

▶ **Conclusion**
All the comparators listed are clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

FORXIGA was approved by the FDA in January 2014.

Country	Reimbursement		
	Date reimbursement started	Yes/No/Assessment in progress	Scope (indications) and special condition(s)
Germany	File submitted	Assessment in progress	All indications of the Marketing Authorisation
Italy	File submitted	In progress	All indications of the Marketing Authorisation
Belgium	File submitted	In progress	In combination with metformin/sulfonylurea
Denmark	December 2012	Yes	All indications of the Marketing Authorisation
UK	January 2013.	Yes	In combination with metformin/insulin
Sweden	June 2013	Yes	In combination with metformin/sulfonylurea/insulin
Netherlands	July 2013	Yes	In combination with metformin/insulin
Finland	August 2013	Yes	All indications of the Marketing Authorisation
Austria	August 2013	Yes	All indications of the Marketing Authorisation
Australia	August 2013	Yes	All indications of the Marketing Authorisation
Norway	September 2013	Yes	In combination with metformin/sulfonylurea
Spain	September 2013	Yes	All indications of the Marketing Authorisation

08 ANALYSIS OF AVAILABLE DATA

In support of its application for inclusion, the company has submitted all the clinical development studies for dapagliflozin comprising 11 phase III clinical studies including 7 pivotal studies and 4 support studies.

The <u>seven pivotal studies</u> are as follows:
- two studies in monotherapy in treatment-naive patients versus placebo (Studies MB102013[5] and MB102032 which are *off-label dosage*)
- four studies comparing dapagliflozin with placebo, in combination with one or more other blood glucose lowering drug(s):
    - one metformin add-on study (Study MB102014[6,7])
    - one glimepiride add-on study (Study D1690C00005[8])
    - one add-on to insulin study ± 1 or 2 oral antidiabetics-OAD (Study D1690C00006[9])
    - one pioglitazone add-on study (Study MB102030), *not retained by the Committee, as the pioglitazone-based proprietary medicinal products are no longer available in France*
- one glipizide-controlled, non-inferiority study, in combination with metformin (Study D1690C00004[10]).

The four <u>support studies</u> are:
- two studies comparing the initial dapagliflozin + metformin extended release (XR) combination with dapagliflozin alone and metformin XR alone in antidiabetic treatment-naive patients *(not retained by the Committee because dapagliflozin is not indicated in combination with metformin in naive patients and the XP form of metformin is not marketed in France)*
- one study comparing dapagliflozin with the placebo as an add-on to the pre-existing antidiabetic treatment in diabetics with moderate renal failure *(not retained because the use of dapaglifozin is not recommended in this patient type)*
- one study comparing dapagliflozin with a placebo, as an add-on to metformin, whose objective was to evaluate the effects on the reduction and composition of body weight (Study D1690C00012[11]).

<u>Two complementary</u> phase III <u>studies</u> were submitted during the Marketing Authorisation registration procedure. These are two studies comparing dapagliflozin with a placebo in combination with an OAD and/or insulin treatment in patients with type 2 diabetes with cardiovascular disease whether related or not to arterial hypertension (Studies D1690C00018 et D1690C00019).

Thus eight phase III studies (five pivotal combination studies including four versus placebo,

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[5] Ferrannini et al. Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise. Diabetes Care 33: 2217–2224, Oct 2010.

[6] Bailey et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double blind, placebo-controlled trial. Lancet June 2010.

[7] Bailey et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo controlled 102-week trial. BMC Medicine Feb 2013

[8] Strojek et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24 week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism 13: 928-938, 2011.

[9] Wilding et al. Long-Term Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Receiving High Doses of Insulin. Ann Intern Med. 2012; 156: 405-415

[10] Nauck et al. Dapagliflozin Versus Glipizide as Add-on Therapy in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control With Metformin. Diabetes Care August 4, 2011.

[11] Jan Bolinder et al. Effects of Dapagliflozin on Body Weight, Total Fat Mass, and Regional Adipose Tissue Distribution in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin. J Clin Endocrinol Metab, March 2012, 97(3): 1020–1031

one versus active comparator, one support study and two complementary studies in a specific population) will be described.

Moreover, in all the studies, three dosages of dapagliflozin were tested: 2.5 mg/d, 5 mg/d and 10 mg/d. Only the results corresponding to the dosage of 10 mg/d, validated by the Marketing Authorisation, will be presented in this document.

We also have the results of an indirect comparison for the insulin add-on combination indication.

08.1 Efficacy

8.1.1 Placebo-controlled studies

8.1.1.1. In monotherapy (Study MB102013)

This phase III, randomised, double-blind study had the aim of evaluating the efficacy and safety, over 24 weeks, of dapagliflozin at the dosages of 2.5 mg/d, 5 mg/d and 10 mg/d, compared with a placebo, as monotherapy, in patients with type 2 diabetes with an HbA1c level of ≥ 7.0% and ≤ 10.0%, naive of all treatment and with insufficiently controlled hygiene and dietary measures.

The results of this study are presented. However, it should be noted that the inclusion of dapagliflozin10mg/j as monotherapy is not requested by the company.

The characteristics of the patients were similar in the two treatment groups at baseline. The majority of patients were aged under 65, with an average age of 50.6 years in the dapagliflozin 10 mg/d group (n=75) and 52.6 years in the placebo group (n=70). The average weight of patients was 94 kg in the dapagliflozin 10 mg/d group and 89 kg in the placebo group. Over 90% of patients were overweight (BMI ≥ 25kg/m^2), and 73% of patients in the dapagliflozin group and 64% of patients in the placebo group were obese (BMI ≥ 30 kg/m^2). The average duration of diabetes was just over 2 years in both groups, the average HbA1c level was 8.0% in the dapagliflozin group and 7.8% in the placebo group.

Results for the primary efficacy endpoint: *change in HbA1c level compared with the baseline value*
After 24 weeks of treatment, a statistically significant reduction in the HbA1c level was observed in the dapagliflozin 10 mg/d (-0.89%) as monotherapy group compared with the placebo group (-0.23%), i.e. a difference between the two groups of -0.66% (95% CI [-0.96; -0.36], p<0.0001).
Note: this study does not correspond with the population in the indication covered by the Marketing Authorisation. No patients with intolerance to metformin were included in the study. Indeed, the patients included were all treatment-naive.

8.1.1.2. As combination therapy

Table 1: presentation of studies

Studies	MB102014 Dapagliflozin + metformin	D1690C00005 Dapagliflozin + sulfonylurea	D1690C00006 Dapagliflozin + insulin
Principal study objective	To evaluate the efficacy and safety of dapagliflozin, in combination with metformin, compared with a placebo, in patients with type 2 diabetes, with insufficiently controlled treatment via metformin alone at a dosage of ≥ 1500 mg/day combined with hygiene and dietary measures.	To evaluate the efficacy and safety of dapagliflozin, in combination with a sulfonylurea, compared with a placebo, in patients with type 2 diabetes, with insufficiently controlled treatment via glimepiride alone at a dosage of 4 mg/day combined with hygiene and dietary measures.	To evaluate the efficacy and safety of dapagliflozin, compared with a placebo, in combination with insulin (± 1 or 2 OAD) in patients with type 2 diabetes, with insufficiently controlled treatment via insulin (± 1 or 2 OAD) combined with hygiene and dietary measures.
Study design	A phase III, double-blind, placebo-controlled study which had 1:1:1:1 randomisation, in combination with metformin. Extension phase with the main objective of evaluating safety.	A phase III, double-blind, placebo-controlled study which had 1:1:1:1 randomisation, in combination with glimepiride. Extension phase with the main objective of evaluating safety.	Phase III, double-blind placebo-controlled study, stratified according to intake or non-intake of OAD, in combination with insulin combined or not combined with one or two OAD. Extension phase with the main objective of evaluating safety.
Study duration:	24 weeks + extension of 78 weeks	24 weeks + extension of 24 weeks	24 weeks + extensions of 24 and 56 weeks
Main inclusion criteria	- Aged 18 to 77 years old - Type 2 diabetes with HbA1c ≥ 7.0% and ≤ 10.0% - Patients receiving antidiabetic treatment at a stable dose for at least 8 weeks before inclusion via metformin (dosage ≥ 1500 mg/d) - Body mass index (BMI) ≤ 45 kg/m^2	- Aged ≥ 18 - Type 2 diabetes with HbA1c ≥ 7.0% and ≤ 10.0% - Patients treated with a sulfonylurea at a dosage of ≥ ½ maximum recommended dose - BMI ≤ 45 kg/m^2	- Aged 18 to 80 years old - Type 2 diabetes with HbA1c ≥ 7.5% and ≤ 10.5% - Patients receiving antidiabetic treatment at an average stable dose for at least 8 weeks before inclusion via insulin ≥ 30 IU/d ± 1 or 2 OAD at a stable dose for at least 8 weeks before inclusion (metformin ≥ 1500 mg/d or maximum tolerated dose or other OAD at a dosage of ≥ ½ maximum recommended dose - BMI ≤ 45 kg/m^2
Main non-inclusion criteria	- Type 1 diabetes, insipid diabetes, diabetes induced by corticosteroids - Symptomatic poorly controlled diabetes (presence of symptoms such as pronounced polyuria and polydipsia associated with weight loss> 10% in the 3 months prior to inclusion in the studies and/or ketoacidosis) - Creatinine ≥ 1.5 mg/dl (133 µmol/l) for men and ≥ 1.4 mg/dl (124 µmol/l) for women - ASAT or ALAT > 3 times the upper limit of normal - Uncontrolled severe arterial hypertension (BP sys ≥ 180 mmHg and/or BP dia ≥ 110 mmHg) -A history of major cardiovascular disease in the 6 months prior to the study - Congestive heart failure (NYHA class III or IV) Active or unstable liver or kidney disease		
Treatment groups	- metformin + dapagliflozin 2.5 mg/d or 5mg/d or 10 mg/d - metformin + placebo	- glimepiride 4 mg + dapagliflozin 2.5 mg/d or 5 mg/d or 10 mg/d - glimepiride 4 mg + placebo	- insulin ± 1 or 2 OAD + dapagliflozin 2.5 mg/d or 5 mg/d or 10 mg/d - insulin ± 1 or 2 OAD + placebo
Primary efficacy endpoint	Average change in HbA1c level after 24 weeks compared with the baseline value		
Main secondary endpoints (in the order of hierarchical sequential	Change in fasting blood glucose since inclusion Change in weight since inclusion Proportion of patients achieving an HbA1c level < 7%		Change in fasting blood glucose since inclusion Change in weight since inclusion Change in the average daily dose of insulin

analysis)		since inclusion Percentage of patients with a reduction ≥ 10% of the average daily dose of insulin Proportion of patients achieving an HbA1c level < 7%
Calculation of the number of subjects required	136 patients needed to be included in each treatment group to detect a reduction in the average HbA1c levels of 0.5%, at Week 24 compared with the baseline value, with a standard deviation of 1.1% and a power of 90%	161 patients needed to be included in each treatment group to detect a reduction in the average HbA1c levels of 0.5%, at Week 24 compared with the baseline value, with a standard deviation of 1.2% with a power of 90%
Statistical analysis method	Concerning the primary efficacy endpoint: a method to control the risk of inflation of the alpha risk due to the multiple comparisons being implemented. Concerning the secondary endpoints: a hierarchical sequential statistical analysis planned for in the protocol was implemented independently for each dose of dapagliflozin so as to control the alpha risk.	

Results of the studies:

Study MB102014: dapagliflozin add-on to metformin
A total of 546 patients were randomised in the study, of whom 135 patients in the metformin + dapagliflozin 10 mg/d group and 137 patients in the metformin + placebo group.

The patient characteristics were similar in the two treatment groups at baseline. The average age was 52.7 years in the dapagliflozin 10 mg/d group and 53.7 years in the placebo group and almost 85% of patients were aged under 65 years. The average weight of patients was 86 kg in the dapagliflozin 10 mg/d group and 88 kg in the placebo group, over 9 patients in 10 were overweight (BMI ≥ 25kg/m2) and 56% and 58% respectively were obese (BMI ≥ 30kg/m2).
The average duration of diabetes was around 6 years in both groups. The average HbA1c level was 8.0% in the dapagliflozin 10 mg/d group and 8.1% in the placebo group.
The patients were treated with an average dose of metformin of 1800mg/d in each group.

24-week efficacy results, concerning:
The primary efficacy endpoint:
After 24 weeks of treatment, a statistically significant reduction in the HbA1c level was observed in the metformin + dapagliflozin 10 mg/d group (-0.84%) compared with the metformin + placebo group (-0.30%), i.e. a difference between the two groups of -0.54% (95% CI [0.74; -0.34], p<0.0001).
The HbA1c level decreased until Week 8 then the effect was maintained until Week 24 in the dapagliflozin group.

The main secondary endpoints (according to the order of hierarchical analysis):
After 24 weeks of treatment, a statistically significant difference in favour of the metformin + dapagliflozin 10 mg/d group compared with the metformin + placebo group was observed for all the main secondary endpoints:
-   Fasting blood glucose: -23.5 mg/dl in the dapagliflozin group versus -6.0mg/dl in the placebo group (difference between the two groups: -17.5 mg/dl, 95% CI [-25.0 ;-10.0], p<0.001),
-   Weight: -2.86 kg versus -0.89 kg (difference between the two groups: -1.97 kg, 95% CI [-2.63; -1.31], p<0.001),
-   Percentage of patients with an HbA1c level < 7%: 40.6% (58/132) versus 25.9% (33/134) (difference between the two groups: 14.7%, 95% CI [4.2; 25.3]; p=0.0062).

102-week efficacy results:
The patients who completed 24 weeks of treatment with or without rescue treatment (pioglitazone or acarbose) were eligible for an additional 78-week, double-blind follow-up phase. 95 patients in the dapagliflozin 10 mg/d group and 73 patients in the placebo group were involved.
At 102 weeks, the average HbA1c level had increased by 0.02% in the placebo group and decreased by 0.78% in the dapagliflozin group.

Study D1690C00005: dapagliflozin in combination with glimepiride

A total of 596 patients were randomised in the study, of whom 151 patients in the glimepiride + dapagliflozin 10 mg/d group and 146 patients in the glimepiride + placebo group.

The patient characteristics were comparable between the treatment groups. At baseline, the average age was 58.9 years in the dapagliflozin group and 60.3 years in the placebo group and 75% and 63% of patients respectively were aged under 65 years. The average weight of patients was 81 kg in the two groups; over 80% of patients were overweight (BMI ≥ 25k g/m^2) and around 45% were obese (BMI ≥ 30 kg/m^2). Around 80% of patients had a history of cardiovascular disease.

The average duration of diabetes was over 7 years. The average HbA1c level was 8.1% in the dapagliflozin group and 8.2% in the placebo group.

Glimepiride was administered at a dosage of 4 mg/d. The dose of glimepiride could, at the investigator's discretion, be reduced in the event of occurrence of repeated hypoglycaemia. The average and median dosage of glimepiride was 4 mg/day.

24-week efficacy results, concerning:

The primary efficacy endpoint:

After 24 weeks of treatment, a statistically significant reduction in the HbA1c level was observed in the glimepiride + dapagliflozin group (0.82%) compared with the glimepiride + placebo group (-0.13%), i.e. a difference between the two groups of -0.68% (95% CI [-0.86; -0.51], p<0.0001).

The HbA1c level decreased until Week 12 of the treatment then stabilised until Week 24 in the dapagliflozin group.

The main secondary endpoints (in the order of hierarchical analysis):

After 24 weeks of treatment, a statistically significant difference in favour of the glimepiride + dapagliflozin group compared with the glimepiride alone group was observed for all the main secondary endpoints, in particular:

-   Fasting blood glucose: -28.5 mg/dl versus -2.0 mg/dl (difference between the two groups: -26.5 mg/dl, 95% CI [-33.5;-19.5], p<0.0001),
-   Weight: -2.26 kg in the dapagliflozin group versus -0.72 kg in the placebo group (difference between the two groups: -1.54 kg, 95% CI [-2.17; -0.92], p<0.0001),
-   Percentage of patients with an HbA1c level < 7%: 31.7% versus 13.0%, difference between the two groups: 18.7%, 95% CI [9.7; 27.6]; p<0.0001).

Results of the 48-week extension phase

The patients who completed 24 weeks of treatment with or without rescue treatment (metformin or pioglitazone or rosiglitazone) were eligible for an additional 24-week, double-blind follow-up phase.

At 48 weeks, the average HbA1c level had fallen by 0.04% in the placebo group (n=127) and 0.73% in the dapaglilozin group (n=133).

Study D1690C00006: dapagliflozin add-on to insulin

A total of 807 patients was randomised in the study, of whom 196 patients in the insulin ± OAD + dapagliflozin 10 mg/d group and 197 patients in the insulin ± OAD + placebo group.

At baseline, the patient characteristics were similar in the two treatment groups. The average age was 59.3 years in the dapagliflozin 10 mg/d group and 58.8 years in the placebo group and 75% of patients in the two groups were aged under 65 years. The average weight of patients was 94.5 kg in the two groups; 98% of patients in the dapagliflozin group and 94% of patients in the placebo group were overweight (BMI ≥ 25 kg/m^2) and 73% and 66% respectively were obese (BMI ≥ 30 kg/m^2).

The average duration of diabetes was around 14 years in the two groups. The average HbA1c level was 8.6% in the dapagliflozin group and 8.5% in the placebo group.

The patients were treated with insulin for around 6 years on average in the two groups. The average dose of insulin was 78 IU/day in the dapagliflozin group and 74 IU/day in the placebo group and 21% and 18% of patients respectively were treated with a dose of ≥ 100 IU/day.

The administration regimen for insulin was as follows:
- basal insulin: 16% of patients in the dapagliflozin group and 23% of patients in the placebo group;
- basal/bolus insulin regimen: 84% of patients in the dapagliflozin group and 77% of patients in the placebo group, administered alone in 34% and 31% of patients respectively or combined with basal insulin in 50% and 46% of patients respectively.

Half the patients in the two groups were treated with insulin alone, the other half with insulin + OAD. It was most often metformin alone (43% of patients in the dapagliflozin group and 40% in the placebo group) or metformin in combination with a sulfonylurea (4% and 7% of patients in the two groups, respectively).

24-week efficacy results, concerning:
The primary efficacy endpoint:
After 24 weeks of treatment, a statistically more significant reduction in the HbA1c level was observed in the dapagliflozin in combination with insulin ± OAD group (-0.90%) compared with the insulin alone ± OAD group (-0.3%), i.e. a difference between the two groups of 0.60%, 95% CI [-0.74; -0.45], p<0.0001.

A further analysis, specified in the protocol, on the reduction of HbA1c depending on the presence or absence of an OAD in combination with insulin, showed the following after 24 weeks of treatment:
- in the dapagliflozin in combination with insulin + OAD group: a significantly greater decrease in the HbA1c level compared with the insulin + OAD group: -0.94% versus -0.28%, (difference between the two groups): -0.66%, 95% CI [-0.86; -0.46]),
- in the dapagliflozin + insulin group: a significantly greater decrease in the HbA1c level compared with the insulin alone group: -0.86% versus -0.33%, (difference between the two groups): -0.53%, 95% CI [-0.74; -0.33])

The HbA1c level decreased until Week 12 of the treatment then stabilised until Week 24.

The main secondary endpoints:
After 24 weeks of treatment, a statistically significant difference in favour of the dapagliflozin in combination with insulin ± OAD group compared with the insulin alone ± OAD group was observed for all the main secondary endpoints, in particular:
- Fasting blood glucose: -21.7 mg/dl in the dapagliflozin group versus 3.3 mg/dl in the placebo group (difference between the two groups: -25.0 mg/dl, 95% CI [-34.3;-15.8], p<0.0001).
- Weight: -1.67 kg versus 0.02 kg (difference between the two groups: -1.68 kg, 95% CI [-2.19; -1.18], p<0.0001),

- Average insulin dose: -1.16 IU/day versus 5.08 IU/day (difference between the two groups: -6.23 IU/day, 95% CI [-8.84; -3.63] p<0.0001),
- Percentage of patients with a reduction of at least 10% of the average daily dose of insulin: 19.6% versus 11.0%, (difference between the two groups): 8.7%, 95% CI [1.6; 15.8]; p=0.0168),
- Significantly more patients achieved an HbA1c level < 7% in the dapagliflozin 10 mg/day plus insulin ± oral antidiabetic group than in the placebo plus insulin ± oral antidiabetic group: 21.5% versus 8.7%, (difference between the two groups): 12.8%, 95% CI [5.9; 19.8]; p=0.0003).

Results of the 104-week extension phases
The patients who completed 24 weeks of treatment were eligible for a long-term, double-blind follow-up with two extension phases, the 1st lasting 24 weeks followed by the 2nd lasting 56 weeks.
At the time of the analysis at 104 weeks, 142 patients in the dapagliflozin 10 mg/day group and 108 patients in the placebo group were undergoing a follow-up and receiving double-blind treatment.
The HbA1c level fell to 0.06% in the placebo group and 0.71% in the dapagliflozin group.
The HbA1c level decreased until Week 32 then increased until Week 104.

8.1.2 Active comparator-controlled studies

Study D1690C00004	
Principal study objective	To evaluate the efficacy and safety of the metformin + dapagliflozin combination compared with those of the metformin + glipizide combination in patients with type 2 diabetes with insufficiently controlled treatment via metformin alone at a dosage of ≥ 1500 mg/day combined with hygiene and dietary measures.
Method	Non-inferiority, randomised, double-blind study comparing dapagliflozin with glipizide, in combination with metformin.
Study duration:	52 weeks Extension with evaluation of safety at 52 weeks and 104 weeks
Inclusion criteria	• Aged ≥ 18 years old • Type 2 diabetes with HbA1c ≥ 6.5% and ≤ 10.0% • Patients receiving antidiabetic treatment at a stable metformin dose ≥ 1500 mg/day for at least 8 weeks before inclusion. The patients could also be treated with an antidiabetic as an add-on to metformin, provided that it is at a dose not exceeding half of the maximum authorised dose. • Fasting blood glucose ≤ 270 mg/dl • BMI ≤ 45 kg/m^2
Treatment groups	• Glipizide 5 mg/d or 10 mg/d or 20 mg/d + dapagliflozin 2.5 mg/d or 5 mg/d or 10 mg/d + • Glipizide 5 mg/d or 10 mg/d or 20 mg/d + metformin The doses of dapagliflozin and glipizide could be reduced when there is a justified medical reason (ex: recurrent hypoglycaemia).
Primary efficacy endpoint	Average change in HbA1c level after 52 weeks compared with the baseline value
Secondary endpoints:	• Change in fasting blood glucose since inclusion • Change in weight since inclusion • Percentage of patients who had at least one episode of hypoglycaemia • Percentage of patients achieving their glycaemic targets (HbA1c level < 7%)
Calculation of the number of subjects required	373 patients needed to be included to establish the non inferiority with a power of 90%, taking into account a standard deviation of 1.25% and an α risk=0.025
Statistical analysis	Non-inferiority was to be established if the upper limit of the 95% confidence interval of the difference in terms of change in the HbA1c level at 52 weeks observed between metformin + dapagliflozin and metformin + glipizide was lower than 0.35%.

Characteristics of the patients included:

A total of 814 patients were randomised in the study, of whom 406 patients in the dapagliflozin group and 408 in the glipizide group.

The patient characteristics were similar between the two treatment groups. The average age was 58 years and the majority of patients (73%) were aged under 65 years. The average weight of patients was 88 kg in the two treatment groups; 95% of patients in the dapagliflozin group and 91% of patients in the glipizide group were overweight (BMI ≥ 25 kg/m^2) and 57% and 55% respectively were obese (BMI ≥ 30 kg/m^2).

The average duration of diabetes was 6.3 years, the average HbA1c level 7.7% in the two treatment groups.

At the time of randomisation, around 45% of patients were receiving a dose of metformin of between 1500 and 2000 mg/d, 55% were receiving a dose ≥ 2000 mg/d and only one patient in each group received a dose < 1500 mg/d.

At baseline, 83.8% of patients in the glipizide group and 86.9% on dapagliflozin were receiving metformin at a dose > 1500 mg.

At the end of the dosage adaptation phase, 86.9% of patients in the dapagliflozin group were being treated with the dose of 10 mg/day and 72.5% of patients in the glipizide group with the dose of 20 mg/day. After this period, only 0.5% of patients treated with dapagliflozin 10 mg/day required a reduction in the dose of treatment, against 5.1% among those treated with glipizide.

Efficacy result for the primary efficacy endpoint:

Table 2: change in the HbA1c level at 52 weeks (PP, LOCF ANALYSIS)

	metformin in combination with	
	dapagliflozin	glipizide
HbA1c level (%)		
n/N randomised	360/406	353/408
Initial mean (SD)	7.71 (0.87)	7.74 (0.89)
Mean in week 52 (SD)	7.16 (0.76)	7.18 (1.08)
Change compared to the initial state		
Adjusted mean (SE)	-0.55 (0.04)	-0.56 (0.04)
95% CI	[-0.64; -0.47]	[-0.64; -0.47]
Difference in relation to glipizide		
Adjusted mean (SE)	**0.00 (0.06)**	
95% CI	[-0.12; 0.12]	

n: number of per-protocol patients, SD = Standard deviation of the mean, SE = standard error of the mean, PP

After 52 weeks of treatment, in the per protocol population, as the upper limit of the 95% CI was lower than the predefined non inferiority threshold (0.35%), the metformin + dapagliflozin combination was shown to be non-inferior to the metformin + sulfonylurea (glipizide) combination. This result was confirmed in the ITT population.

The evaluation profile of HbA1c over the 52 weeks was different between the two treatment groups:
- in patients treated with metformin + dapagliflozin, the reduction in the HbA1c level was mainly observed during the first 12 weeks of treatment, then the HbA1c level continued to gradually decrease until the 52nd week,
- in patients in the metformin + glipizide group, a reduction up to the 18th week was observed then an increase continued until the 52nd week.

In terms of the main secondary endpoints (according to the order of hierarchical analysis)
After 52 weeks of treatment, a statistically significant difference in favour of the metformin + dapagliflozin group compared with the metformin + glipizide group was observed for all these endpoints:

- Weight: -3.22 kg versus 1.44 kg (difference between the two groups: -4.65 kg, 95% CI [-5.14; -4.17], p<0.0001),
- Percentage of patients with at least one episode of hypoglycaemia: 3.5% versus 40.8%,

(difference between the two groups): -37.2%, 95% CI [-42.3; -32.2]; p<0.0001).
There was no difference between the groups in terms of a change in fasting blood glucose and % of patients achieving their therapeutic objective.

104-week efficacy results
The patients who completed 52 weeks of treatment were eligible for an additional 52-week, double-blind follow-up phase.
The average HbA1c level had fallen by 0.32% in the metformin + dapagliflozin group (n=228) and 0.14% in the metformin + glipizide group (n=204).

208-week efficacy results
The patients who completed 104 weeks of treatment were eligible for a 2nd additional 104-week, double-blind, follow up phase.
The HbA1c level fell by 0.10% in the metformin + dapagliflozin group (n=161) and increased by 0.20% in the metformin + glipizide group (n=141).

8.1.3 Studies in a particular population

	Studies D1690C00018 and D1690C00019
Principal study objective	To evaluate the efficacy of dapagliflozin versus placebo, in combination with one or two OAD and/or insulin in patients with type 2 diabetes with cardiovascular disease and arterial hypertension, insufficiently controlled with treatment in current practice combined with hygiene and dietary measures.
Method	Randomised, double-blind, phase III, placebo-controlled studies Moreover, in order to balance the risk of subsequent cardiovascular events between treatment groups, the randomisation was also stratified according to the duration of the most recent cardiovascular event justifying inclusion in the study. A total of eight strata were formed for the purpose of randomisation for each combination of these three stratification factors (the antidiabetic treatments (Yes and No), the duration of the most recent cardiovascular event and age (< 65 years and ≥ 65 years), and for each of these strata, the patients had to be randomised (1:1) and assigned to one of the two groups (dapagliflozin or placebo).
Study duration:	24 weeks Long-term 28-week follow-up phase
Inclusion criteria	• ≥ 45 years for men and ≥ 50 years for women • Type 2 diabetes with HbA1c ≥ 7.0% and ≤ 10.0% • Patient receiving one or two OAD (metformin, pioglitazone, sulfonylurea, gliptine) alone or in combination with insulin • Patient with cardiovascular disease defined by: o a history of coronary disease: myocardial infarction, or coronary revascularisation or coronary stenosis > 50%, or abnormal stress test consistent with ischaemia or with a history of myocardial infarction o or a history of stroke or transitory ischaemic attack, o or a history of peripheral arterial disease treated with revascularisation. • In Study D1690C00018, the patients also had to have arterial hypertension, not treated or treated with one or more antihypertensive agents
Treatment groups	• dapagliflozin 10 mg/day + OAD ± insulin • placebo + OAD ± insulin The antidiabetic and antihypertensive treatments had to be administered without interruption for, respectively, at least 12 and 8 weeks before randomisation and at stable doses for, respectively, 8 and 4 weeks before randomisation.
Primary efficacy endpoint	Co-primary efficacy endpoints: - Change in HbA1c level after 24 weeks compared with the initial value - % of patients verifying a composite endpoint defined by the combination of the following three items: o Absolute reduction in HbA1c level of at least 0.5 % compared with the initial value o Relative reduction in weight of at least 3% compared with the initial value o Absolute reduction in systolic blood pressure of at least 3 mmHg compared

	with the initial value
	These two main objectives had to be demonstrated in the total population and in each subgroup defined according to age (< 65 years and ≥ 65 years).
Calculation of the number of subjects required	181 subjects in each age group (stratification by age of patient: < 65 years and ≥ 65 years) to detect a difference of % of patients verifying the composite endpoint of 15% between the dapagliflozin 10 mg/day group and the placebo group, with a power of 90%
	Study D1690C00018: Number of subjects required: (ITT population) •dapagliflozin 10 mg/day + OAD ± insulin: 455 subjects including 192 subjects aged at least 65 years •placebo + OAD ± insulin: 459 subjects including 196 subjects aged at least 65 years
	Study D1690C00019: Number of subjects required: (ITT population) •dapagliflozin 10 mg/day + OAD ± insulin: 480 subjects including 227 subjects aged at least 65 years •placebo + OAD ± insulin: 482 subjects including 224 subjects aged at least 65 years
Statistical analysis	A method of adjustment of the alpha risk because of multiple comparisons (two primary efficacy endpoints, analysed in subgroups) was implemented.[12]

Patient characteristics in the study
> Study D1690C00018:

A total of 922 patients were randomised in the study, of whom 460 patients in the dapagliflozin 10 mg/day group and 462 in the placebo group.
> Study D1690C00019:

A total of 965 patients were randomised in the study, of whom 482 patients in the dapagliflozin 10 mg/day group and 483 in the placebo group.

The patient characteristics were comparable in the two studies and in the different treatment groups. The patients were aged 63-64 years on average and 42% to 47% of patients were 65 or over. The average weight of patients was 93-94 kg in the two studies, over 9 patients in 10 were overweight (BMI ≥ 25 kg/m^2) and 65% to 69% were obese (BMI ≥ 30 kg/m^2). The average duration of diabetes was 12 to 13 years, the average HbA1c level was 8.1% and the average fasting blood glucose was around 160 mg/dl.

The antidiabetic treatments received by the patients at the time of their inclusion differed in the two studies: the patients in Study D1690C00019 received an OAD treatment without insulin less often (40% versus 48%) and more often insulin in combination with the OAD treatment (41% versus 35%) compared with the patients in Study D1690C00018.
The most prescribed OAD was metformin in 35 to 40% of cases following the study. Metformin was prescribed in combination with another OAD for 33% to 40% of patients included, among whom 30% did not receive insulin.
The most common cardiovascular disease was CHD (75% and 77% of patients respectively from Studies D1690C00018 and D1690C00019). A history of stroke or transient ischaemic attack was the 2nd most observed cardiovascular disease (21% and 20% of patients respectively from Studies D1690C00018 and D1690C00019). These cardiovascular diseases existed for more than a year in 82% and 85% of patients respectively. Finally, 13% of patients in Study D1690C00018 and 16% of patients in Study D1690C00019 had cardiac failure.

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[12] A hierarchical sequential statistical analysis on the two primary endpoints, initially specified in the protocol, was implemented in the total population then in the age subgroups in order to guarantee an α significance level of 5%. Each test on the total population was conducted with an α significance level of 0.025 (bilateral) using a Bonferroni correction. If the significance of the efficacy endpoint was proven in the total population, an additional Bonferroni correction was applied in order for each comparison of primary endpoints in each of the age strata to be carried out with an α significance level of 0.0125 (bilateral).

In Study D1690C00019, all patients had hypertension (in line with the inclusion criteria) and 96% of them were receiving antihypertensive treatment. Arterial hypertension was diagnosed for at least 3 years in around 90% of patients and well-controlled (mean systolic arterial pressure: 135 mmHg and mean diastolic arterial pressure: 78 mmHg).

In Study D1690C00018, although arterial hypertension was not an inclusion criterion, over 93% of patients had hypertension and 99% of them were receiving antihypertensive treatment. Arterial hypertension was diagnosed for at least 3 years in around 87% of patients and well-controlled (mean systolic arterial pressure: 133 mmHg and mean diastolic arterial pressure: 77 mmHg).

Overall, in each study, the populations of the two subgroups linked to age were no different from the overall population. However, certain patient characteristics were considerably different between the two age strata.[13]

Efficacy results on the co-primary efficacy endpoints:

After 24 weeks of treatment, a significantly greater reduction in the HbA1c level was observed in the dapagliflozin in combination with an OAD ± insulin group (which included at least one bout of dual therapy in 2/3 of patients) compared with the OAD ± insulin treatment:

- *Study D1690C00018:* -0.38% versus 0.08%, (difference between the two groups: -0.46%, 95% CI [-0.56; -0.37]; p<0.0001). Comparable results were observed in the two age strata[14]
- *Study D1690C00019:* -0.33% versus 0.07%, (difference between the two groups: -0.40%, 95% CI [-0.50; -0.30]; p<0.0001). Comparable results were observed in the two age strata.[15]

After 24 weeks of treatment, dapagliflozin in combination with an OAD ± insulin treatment allowed patients to achieve the composite endpoint (in % of responder patients) in a significantly greater number compared with the OAD ± insulin treatment:

- *Study D1690C00018:* 11.7% (52/444) versus 0.9% (4/451) (difference between the two groups: 9.9%, 95% CI [7.0; 12.9]; p<0.0001). Comparable results were observed in the two age strata[16]
- *Study D1690C00019:* 10.0% (47/468) versus 1.9% (9/469) (difference between the two groups: 7.0%, 95% CI [4.3; 9.8]; p<0.0001). Comparable results were observed in the two age strata.[17]

The HbA1c level decreased until Week 8 then increased until Week 24.

08.2 Safety/Adverse effects

8.2.1 SPC data

"In a pre-specified pooled analysis of 12 placebo-controlled studies, 1193 patients were treated with dapagliflozin 10 mg and 1393 with placebo.

The overall incidence of adverse events (short-term treatment) in patients treated with dapagliflozin 10 mg was similar to the placebo. Few adverse events caused treatment discontinuation and were controlled in all the groups in the study. The most frequently reported adverse events which led to treatment discontinuation in patients treated with dapagliflozin 10 mg were: an increase in creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), vertigo (0.2%), and rash (0.2%).

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[13] In patients under 65, cardiovascular disease, type 2 diabetes and arterial hypertension were diagnosed for less time than in those over 65. The patients under 65 were receiving oral antidiabetic treatment in combination with insulin more often, while the over 65s were receiving treatment with insulin alone more often.

[14] Under 65 years of age: -0.40% versus 0.02%, (difference between the two groups): -0.42%, 95% CI [-0.54; -0.29]; p<0.0001).
65 years and older: -0.37% versus 0.16%, (difference between the two groups: -0.53%, 95% CI [-0.67; -0.39]; p<0.0001).

[15] Under 65 years of age: -0.40% versus 0.06%, (difference between the two groups: -0.46%, 95% CI [-0.60; -0.32]; p<0.0001).
65 years and older: -0.27% versus 0.07% (difference between the two groups: -0.34%, 95% CI [-0.47; -0.21]; p<0.0001).

[16] Under 65 years of age: 11.2% versus 0.4% (difference between the two groups: 10.0%, 95% CI [6.2; 13.7]; p<0.0001).
65 years and older: 12.4% versus 1.6% (difference between the two groups: 9.9%, 95% CI [5.1; 14.7]; p<0.0001),

[17] Under 65 years of age: 10.9% versus 1.6%, (difference between the two groups: 7.8%, 95% CI [4.0; 11.5]; p<0.0001),
65 years and older: 9.1% versus 2.3% (difference between the two groups: 6.2%, 95% CI [2.1; 10.3]; p=0.0023).

A patient receiving dapagliflozin had a hepatic adverse event with a diagnosis of drug-induced hepatitis and/or autoimmune hepatitis.

The most commonly reported adverse effect was hypoglycaemia, which depended on the initial treatment used in each study. The frequency of minor episodes of hyperglycaemia was similar between treatment groups, including the placebo, with the exception of studies with add-on sulfonylureas (SU) and add-on with insulin. A greater rate of hypoglycaemia was observed in the therapeutic combination with the sulfonylureas and the insulin combination.

Hypoglycaemia
The frequency of hypoglycaemia depended on the type of background therapy used in each study. For the studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia proved to be similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, the major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulfonylureas and insulin therapies had higher rates of hypoglycaemia (see section 4.5).
In an add-on to glimepiride study, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0%) than in the patients who received the placebo plus glimepiride (2.1%). In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of the group of patients treated with dapagliflozin 10 mg and insulin, at Weeks 24 and 104 respectively and in 0.5% of the group of patients treated with placebo plus insulin at Weeks 24 and 104. In Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of patients who received dapagliflozin 10 mg and insulin and in 34.0% and 41.6% of the patients receiving placebo plus insulin.

Volume depletion
Effects associated with volume depletion (including cases of dehydration, hypovolaemia or hypotension) were reported in 0.8% and 0.4% of patients who received dapagliflozin 10 mg and placebo, respectively. Serious reactions occurred in < 0.2% of patients, and were evenly distributed between patients treated with dapagliflozin 10 mg and placebo (see section 4.4).

Use in patients at risk of volume depletion, hypotension and/or electrolyte imbalance
Because of its mechanism of action, dapagliflozin increases diuresis, combined with a moderate decrease in blood pressure (see section 5.1), which could be more pronounced in patients with very high blood glucose levels.
Use of dapagliflozin is not recommended in patients receiving loop diuretics (see section 4.5) or who have volume depletion, for example, because of an acute condition (such as gastrointestinal disease).
Particular attention should be given to patients in whom a decrease in blood pressure induced by dapagliflozin may represent a risk, like patients with known cardiovascular disease, patients on antihypertensive treatment with a history of hypotension or elderly patients.
For the patients receiving dapagliflozin, in the event of intercurrent conditions possibly causing volume depletion, close monitoring of the hydration status (for example: clinical exam, blood pressure measurement, biological tests including haematocrit) and electrolytes is recommended. A temporary interruption of treatment with dapagliflozin is recommended in patients who develop volume depletion until the depletion is corrected (see section 4.8).

Vulvovaginitis, balanitis and related genital infections
Cases of vulvovaginitis, balanitis and related genital infections were reported in 4.8% and 0.9% of patients who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and patients responded to an initial course of standard treatment and rarely discontinued the dapagliflozin treatment. These infections were more frequent in females (6.9% and 1.5% for dapagliflozin and placebo, respectively), and patients with a prior history were more likely to have a recurring infection.

Urinary tract infections

Urinary tract infections were more frquently reported in patients who received dapagliflozin 10 mg compared to placebo (4.3% versus 3.7%, respectively; see section 4.4). Most infections were mild to moderate, and patients responded to an initial course of standard treatment and rarely resulted in discontinuation on from dapaglifolzin treatment. These infections were more frequent in females, and patients with a prior history were more likely to have a recurrent infection.

Parathyroid hormone (PTH)
Small increases in serum PTH levels were observed with increases being larger in patients with higher baseline PTH concentrations. Bone densitometry in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of one year.

Malignant tumours
During clinical trials, the overall proportion of patients with malignant or unspecified tumours was similar between the patients treated with dapagliflozin (1.47%) and those treated with placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in the animal data (see section 5.3). When considering the cases of tumours occurring in different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (for example, blood and lymphatic system, ovaries, renal tubules), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any organ system. Considering the lack of tumour cases in the non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with, it will be further investigated in post authorisation studies.[18]

Elderly patients (≥ 65 years)
In patients ≥ 65 years, adverse effects linked to renal impairment or failure were reported in 2.5% of patients treated with dapagliflozin and 1.1% of patients treated with placebo (see section 4.4). The most commonly reported adverse effect linked to renal function was elevated creatinine. The majority of these effects were transient and reversible. In patients ≥ 65 years, the most commonly reported adverse effects linked to volume depletion, such as hypotension, were observed in 1.5% and 0.4% of dapaglifozin-treated patients and placebo-treated patients, respectively (see section 4.4). "

8.2.2 Study data

Overall, the number of patients who had had at least one adverse event was 61.5% (734/1193) in the dapagliflozin 10 mg group and 56.9% in the placebo group (792/1393).
This event led to discontinuation of treatment in 38 patients on dapagliflozin and 35 under placebo. It was considered as linked to the treatment for 18.1% of patients in the dapagliflozin group and 13.3% of patients in the placebo group.
The long-term safety analysis did not identify a specific or new signal compared with the shorter evaluation periods.

A phase III, randomised, double-blind placebo-controlled study lasting 24 weeks evaluated the effect of dapagliflozin as an add-on to metformin, in terms of the change in body weight (primary efficacy endpoint) in patients with type 2 diabetes insufficiently controlled by treatment with metformin alone at a dosage ≥ 1500 mg/day combined with hygiene and dietary measures.
At baseline, the average age of patients was 61 years and the majority of patients (68%) were aged under 65 years. The average weight was 91 kg, 99% of patients were overweight (BMI ≥ 25 kg/m^2) and 67% were obese (BMI ≥ 30 kg/m^2). The average duration of diabetes was 5.8 years and the average HbA1c level was 7.2%. The average dose of metformin was around 2000mg/d in the two treatment groups, 45% of patients were treated with a dose of metformin of between 1500 and 2000 mg/d and 55% with a dose of 2000mg/d or more.

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[18] These include one of the objectives of the RMP

After 24 weeks of treatment, a statistically significant reduction in weight was observed in the metformin + dapagliflozin 10 mg/d (2.96%) compared with the metformin + placebo group (-0.88 kg), i.e. a difference between the two groups of -2.08 kg (95% CI [-2.84; -1.31], p<0.0001).

A meta-analysis of specified cardiovascular events was performed on the basis of 19 studies including 8682 patients in total (5498 in the dapagliflozin group and 3184 in the comparator group). In all these patients, almost 70% had arterial hypertension at baseline, almost 35% a history of cardiovascular disease other than hypertension, and around 5% congestive heart disease.
The primary composite endpoint was the time to onset of the first cardiovascular event among the following: cardiovascular death, myocardial infarction, stroke or hospitalisation for unstable angina pectoris, and the secondary composite endpoint was the time to onset of the first event among the events of the primary endpoint to which were added unplanned coronary revascularisation and hospitalisation for heart failure.
No difference was revealed.

8.2.3 Pharmacovigilance data (1st PSUR - period from 5 October 2012 to 4 April 2013)

Exposure to dapagliflozin was estimated to have affected 8850 patients by 31 March 2013 (beyond clinical studies). This estimation was carried out from data collected by Cegedim Strategic Data and IMS in several different European countries and available on the data of the PSUR.

In this first report, on the basis of clinical and post-marketing data, the conclusions were as follows:
- no new information on the potential or identified risks, considerable or not, was shown during this period.
- A new assessment of the risk/benefit ratio of dapagliflozin was carried out on this reference period. This indicates that the patients treated with dapagliflozin 10 mg/d, according to the pre-defined age subgroups (< 65 years and ≥ 65 years) presented significant improvements in HbA1c levels and other clinical benefits, compared with the placebo. On dapagliflozin 10 mg/d, compared with the placebo, a significant improvement in weight was observed in the two subgroups and a significant reduction in systolic blood pressure was observed in the subgroup of patients under 65 years.
- Genital and urinary infections were generally mild to moderate, responding easily to conventional medical treatment and not requiring any treatment discontinuation. These infections were not associated with more serious or severe medical events, such as pyelonephritis or septicaemia.
- Data from post-marketing surveillance is still limited, but did not indicate a new safety signal.

8.2.4 The risk management plan (RMP)

The RMP includes:
- a programme of pharmaco-epidemiological studies over a period extending to 2023 with intermediary analyses in order to estimate, in patients treated with dapagliflozin, and compare with patients treated with other antidiabetics, the following:
  - o the incidence of accident and emergency consultations and hospitalisations linked to severe complications in urinary tract infections (MB102103)
  - o the incidence of hospitalisations linked to acute renal failure (MB102110)
  - o the incidence of hospitalisations linked to acute hepatic failure (MB102104)
  - o the incidence of occurrence of breast or bladder cancer (MB102118).
- a programme of clinical studies (in the course of the analysis or planned):
  - o two studies in patients with type 2 diabetes with a history of cardiovascular disease, including patients with NYHA III class heart failure and elderly patients aged 65 years and older (D1690C00018 and D1690C00019).
  - o a study evaluating the effect of dapagliflozin on the occurrence of major cardiovascular events (deaths from cardiovascular disease, myocardial infarction and cerebral ischaemic accidents) in patients with type two diabetes with a history

of cardiovascular disease or at least two cardiovascular risk factors associated with diabetes (D1693C00001)
- a useability study aiming to evaluate off-label prescriptions of dapagliflozin and with the main objective of describing the characteristics of European patients receiving a prescription of dapagliflozin according to age, sex, dose of dapagliflozin, country, certain associated co-morbidities and certain associated concomitant treatments.

The following adverse events will be monitored as part of the RMP as they were:
- identified during pre-clinical or clinical development (bone metabolism)
- understood on the basis of the mechanism of action of dapagliflozin (genital infections, urinary tract infections, renal tolerance, volume depletion, increase of haematocrit and haemoglobin)
- identified in diabetic patients and/or during their treatment (cardiovascular tolerance, hypoglycaemia)
- unexpected (tumours).

A causal relationship between breast, bladder and prostate cancers and dapagliflozin seems unlikely. However, these cancers were identified as a potential risk of dapagliflozin and will be monitored as part of the RMP.

08.3 Other data: indirect comparison in the indication in combination with insulin

The clinical development of dapagliflozin 10 mg/day provided a particular opportunity to generate data from an indirect comparison in combination with insulin versus placebo. An indirect comparison of dapagliflozin 10 mg/day compared with other therapeutic classes has thus been carried out in the treatment of patients with type 2 diabetes with uncontrolled blood glucose on insulin (with or without combined OAD).
The objective of this indirect comparison was to determine the relative efficacy and safety of dapagliflozin 10 mg/day compared with other therapeutic categories, in particular GLP-1 analogues and dipeptidyl peptidase-4 inhibitors (iDPP-4 or gliptins) in patients with type 2 diabetes with uncontrolled blood glucose on insulin (with or without combined OAD).

Method
A systematic literature review of the randomised clinical trials available on the MEDLINE, EMBASE and CENTRAL databases and those of the main diabetology congresses for all the molecules of the two therapeutic categories relevant in the indication in combination with insulin: gliptins, GLP-1 analogues. The indirect comparison used the Bucher method and Bayesian network meta-analyses.
The endpoints were:
- efficacy endpoints: average change from the initial state of the HbA1c level, weight and percentage of patients who experienced at least one episode of hypoglycaemia
- safety endpoints: percentage of patients who experienced a serious adverse event, percentage of patients who experienced an adverse event resulting in treatment discontinuation.
A sensitivity analysis was performed.

Results
The systematic review provided an opportunity to identify six relevant trials with a 24-week follow-up (four trials with glitpins and one trial with a GLP-1 analogue, lixisenatide), and a 7th trial on exenatide with a 30-week follow-up. The inclusion criteria in these trials were similar. The patients had an average age ranging from 57 to 60.4 years and their diabetes lasted from 11.8 to 14.2 years. For six trials, the insulin dose remained stable during the follow-up, but it was able to be altered in the 7th trial on exenatide to maintain the blood glucose level.

No difference was observed in terms of a change in HbA1c level (primary efficacy endpoint of all the studies) between dapagliflozin and GLP-1 analogues or glitpins.

As regards the other exploratory criteria, no difference was observed in terms of a change in weight between dapagliflozin and GLP-1 analogues, and glitpins in terms of hypoglycaemia, and serious adverse events, and adverse events resulting in treatment discontinuation.

Remarks:
- in this indirect comparison, all the available alternatives were taken into consideration;
- a systematic and exhaustive search was performed;
- there are differences between the studies selected for the indirect comparison in terms of duration of treatment, primary efficacy endpoint, and previous treatments;
- The exchangeability assumption has not been discussed (the interaction factors have not been assessed), neither has the comparability of the studies in terms of effect size;
- the Bayesian method of analysis used is not validated at the statistical level (it is not known whether the *priors* were informative or not, independence of the results compared with the priors has not been verified).

09   SUMMARY & DISCUSSION

The efficacy and safety of dapagliflozin at a dosage of 10 mg/day were evaluated in type 2 diabetes, particularly in eight phase III studies (five pivotal studies in combination with metformin, or a sulfonylurea or insulin including four versus placebo, one versus active comparator; one support study whose objective was to evaluate the effect on the reduction in weight and two additional studies in a specific population).

As monotherapy
A phase III, randomised, double-blind, placebo-controlled study included 145 patients with type 2 diabetes for just over 2 years, naive of all treatment and insufficiently controlled by hygiene and dietary measures, aged on average 52 years, mostly obese with an average HbA1c level of 8.0% in the dapagliflozin group and 7.8% in the placebo group.
After 24 weeks of treatment, a statistically significant reduction in the HbA1c level was observed in the dapagliflozin 10 mg/d (-0.89%) as monotherapy group compared with the placebo group (-0.23%), i.e. a difference between the two groups of -0.66% (95% CI [-0.96; -0.36], $p < 0.0001$).
This study does not correspond with the population in the indication covered by the Marketing Authorisation. No patients with intolerance to metformin were included in the study.

As dual therapy in combination with metformin
A phase III, randomised, double-blind study evaluated the efficacy and safety of dapagliflozin, in combination with metformin, compared with placebo in 546 patients with type 2 diabetes for around 6 years, aged on average 52.7 years in the dapagliflozin 10 mg/d group (n=135) and 53.7 years in the placebo group with almost 85% of patients aged under 65 years, mostly overweight or obese, with an average HbA1c level of 8.0% and insufficiently controlled by treatment with metformin alone at an average dose of 1800mg/d combined with hygiene and dietary measures.

As regards the primary endpoint, after 24 weeks of treatment, a statistically significant reduction in the HbA1c level was observed in the metformin + dapagliflozin 10 mg/d group (-0.84%) compared with the metformin + placebo group (-0.30%), i.e. a difference between the two groups of -0.54% (95% CI [-0.74; -0.34], $p < 0.0001$).

As regards the secondary endpoints, after 24 weeks of treatment, a statistically significant difference in favour of the metformin + dapagliflozin 10 mg/d group compared with the metformin + placebo group was observed for all the main secondary endpoints (difference between the two groups in terms of change in fasting blood glucose of -17.5 mg/dl, 95% CI [-25.0; -10.0], $p < 0.001$; difference between the two groups in terms of weight: -1.97 kg, 95% CI [-2.63; -1.31], $p < 0.001$); percentage of patients who achieved an HbA1c level < 7%: 40.6% (58/132) versus 25.9% (33/134).

As dual therapy in combination with a sulfonylurea

- **Placebo-controlled study in combination with glimepiride**

A phase III, randomised, double-blind study evaluated the efficacy and safety of dapagliflozin, in combination with a sulfonylurea (glimepiride), compared with placebo in 596 patients with type 2 diabetes for over 7 years, aged on average 59 years in the dapagliflozin 10 mg/d group (n=151) and 60 years in the placebo group (n=146), mostly overweight or obese, with an average HbA1c level of 8.1% and insufficiently controlled by treatment with glimepiride at an average dose of 4 mg/d combined with hygiene and dietary measures. Around 80% of patients had a history of cardiovascular disease.

As regards the primary endpoint, after 24 weeks of treatment, a statistically significant reduction in the HbA1c level was observed in the glimepiride + dapagliflozin group (-0.82%) compared with the glimepiride + placebo group (-0.13%), i.e. a difference between the two groups of -0.68% (95% CI [-0.86; -0.51], p<0.0001).

As regards the secondary endpoints, after 24 weeks of treatment, a statistically significant difference in favour of the glimepiride + dapagliflozin 10 mg/d group compared with the glimepiride + placebo group was observed for all the main secondary endpoints (difference between the two groups in terms of change in fasting blood glucose of -26.5 mg/dl, 95% CI [-33.5; -19.5], p<0.0001; difference between the two groups in terms of weight: -1.54 kg, 95% CI [-2.17; -0.92], p<0.0001; percentage of patients who achieved an HbA1c level < 7%: 31.7% versus 13.0%).

- **Glipizide-controlled study add-on to metformin**

A randomised, non-inferiority study, in a double-blind 52-week procedure, compared dapagliflozin at a dosage of 10 mg/d with a sulfonylurea, glipizide administered for 72.5% at a dosage of 20 mg/d, as dual therapy as an add-on to metformin, in 814 patients with type 2 diabetes. At baseline, the patients were aged on average 58 years and mostly overweight or obese. The duration of diabetes was on average 6.3 years, the average level of HbA1c was 7.7% and 83.8% of patients in the glipizide group, and 86.9% on dapagliflozin, received metformin at a dosage of > 1500 mg.

After 52 weeks of treatment, in the per protocol population, the difference between dapagliflozin and glipizide in terms of the reduction in the HbA1c level (primary efficacy endpoint) was 0 ± 0.06% 95% CI [-0.12; 0.12]. As the upper limit of the confidence interval of this difference is less than the fixed threshold (0.35%), the non-inferiority of dapagliflozin compared with glipizide has been demonstrated. The same result was seen in the analysis of the ITT population.
The evolution profile of HbA1c over the course of 52 weeks was different between the two treatment groups:
- in patients treated with metformin + dapagliflozin, the reduction in the HbA1c level was mainly observed during the first 12 weeks of treatment, then the HbA1c level continued to decrease gradually until the 52nd week,
- in patients in the metformin + glipizide group, a reduction until the 18th week was observed then an increase continued until the 52nd week.

After 52 weeks of treatment, a statistically significant difference in favour of the metformin + dapagliflozin group compared with the metformin + glipizide group was observed for the secondary endpoints change in weight (difference between the two groups: -4.65 kg, 95% CI [-5.14; -4.17], p<0.0001) and % of patients with at least one episode of hypoglycaemia: (difference between the two groups: -37.2%, 95% CI [-42.3; -32.2]; p<0.0001).
There was no difference between the groups in terms of a change in fasting blood glucose and % of patients achieving their therapeutic objective (27% in the dapagliflozin group and 32% in the glipizide group).

As dual therapy in combination with insulin and as triple therapy in combination with insulin and metformin

A phase III, randomised, double-blind study evaluated the efficacy and safety of dapagliflozin 10 mg/d, compared with placebo, in combination with insulin (± 1 or 2 OAD) in 807 patients with

type 2 diabetes for around 14 years, with an average HbA1c level of 8.5%, aged on average 59 years, mostly overweight or obese, insufficiently controlled with insulin treatment (± 1 or 2 OAD) combined with hygiene and dietary measures. Half the patients in the two groups were treated with insulin alone, the other half with insulin + OAD. It was most often metformin alone (43% of patients in the dapagliflozin group and 40% in the placebo group).

After 24 weeks of treatment, a significantly greater reduction in the HbA1c level was observed in the insulin ± OAD + dapagliflozin group (0.90%) compared with the insulin ± ADO + placebo group (-0.3%), i.e. a difference between the two groups of -0.60% (95% CI [-0.74; -0.45], p<0.0001).
A further analysis, specified in the protocol, on the reduction of HbA1c depending on the presence or absence of an OAD in combination with insulin, showed the following after 24 weeks of treatment:
- in the dapagliflozin in combination with insulin + OAD group: a significantly greater decrease in the HbA1c level compared with the insulin + OAD group: -0.94% versus -0.28%, (difference between the two groups: -0.66%, 95% CI [-0.86; -0.46]), *triple therapy indication in combination with insulin + metformin*
- in the dapagliflozin + insulin group: a significantly greater decrease in the HbA1c level compared with the insulin alone group: -0.86% versus -0.33%, (difference between the two groups: -0.53%, 95% CI [-0.74; -0.33]), *dual therapy indication in combination with metformin*

After 24 weeks of treatment, a statistically significant difference in favour of the dapagliflozin in combination with insulin ± OAD group compared with the insulin alone ± OAD group was observed for all the main secondary endpoints (fasting blood glucose: difference between the two groups: -25.0 mg/dl, 95% CI [-34.3; -15.8], p<0.0001; weight: difference between the two groups: -1.68 kg, 95% CI [-2.19; -1.18], p<0.0001); % of patients who achieved an HbA1c level < 7%**:** 21.5% in the insulin ± OAD + dapagliflozin group and 8.7% in the insulin ± OAD + placebo group).

Two phase III, randomised, double-blind studies had the aim of evaluating the efficacy of dapagliflozin versus placebo, in combination with one or two OAD (metformin most often) and/or insulin (prescribed in around 40% of cases) in a total of 1887 patients with type 2 diabetes for 12 to 13 years, with an HbA1c level at baseline of 8.1%, aged on average 63-64 years, mostly overweight or obese, with cardiovascular disease, the most common being coronary disease, and arterial hypertension. This study evaluated two co-primary efficacy endpoints (change in the HbA1c level at 24 weeks compared with the initial value, % of patients verifying a composite endpoint defined by the combination of the following three items: absolute reduction in the HbA1c level of at least 0.5% compared with the initial value, reduction relating to weight of at least 3% compared with the initial value, absolute reduction of systolic blood pressure of at least 3 mmHg compared with the initial value.
After 24 weeks of treatment,
- a significantly greater reduction in the HbA1c level was observed in the dapagliflozin in combination with an OAD ± insulin group (which included at least one bout of dual therapy in 2/3 of patients) compared with the OAD ± insulin treatment:
    o -0.38% versus 0.08% in one study (difference between the two groups: -0.46%, 95% CI [-0.56; -0.37]; p<0.0001).
    o -0.33% versus 0.07% in the second study (difference between the two groups: -0.40%, 95% CI [-0.50; -0.30]; p<0.0001).
- dapagliflozin in combination with OAD ± insulin treatment allowed patients to achieve the composite endpoint (in % of responder patients) in a significantly greater number compared with the OAD ± insulin treatment:
    o 11.7% (52/444) versus 0.9% (4/451) in one study (difference between the two groups: 9.9%, 95% CI [7.0; 12.9]; p<0.0001).
    o 10.0% (47/468) versus 1.9% (9/469) in the other study (difference between the two groups: 7.0%, 95% CI [4.3; 9.8]; p<0.0001).
Comparable results were observed in the two age strata (< 65 years, > 65 years).

The development dates of dapagliflozin, gliptins and GLP-1 analogues would not have allowed direct comparison with these treatments.

The company has thus provided the results of an indirect comparison between dapagliflozin and incretins (gliptins and GLP-1 analogues) for the indication in combination with insulin. No conclusions can be drawn from this indirect comparison seeking to prioritise the treatments.

Overall, the effect of dapagliflozin in terms of reducing the HbA1c level is very modest (it varied depending on the studies from -0.55% to -0.68%) and close to the clinical relevance threshold of -0.5%.

There is just one study versus active comparator (non-inferiority study).

There is no direct comparison and satisfactory efficacy profile versus recommended dual or triple therapies.

The dual therapy indication in combination with insulin was evaluated in 50% of patients in the study, the triple therapy indication in combination with insulin + metformin in around 45% of patients.

In this study, a comparison group with an optimised insulin therapy regimen would have been useful in determining the benefit of adding dapagliflozin.

The percentage of responder patients (achieving the objective of HbA1c level < 7%) when it was evaluated varied from 20% to 40% in the dapagliflozin group and from 10% to 25% in the placebo group.

The results of the two studies carried out in the specific populations of patients with arterial hypertension are not sufficient to draw conclusions in terms of morbidity in view of the intermediary and non-clinical co-primary efficacy endpoints.

There are no morbidity and mortality data but a study is under way.

The adverse events most commonly observed on dapagliflozin compared with placebo were hypoglycaemia, infections (genital and urinary) and volume depletion, an effect which leads to a precaution for use[19] particularly in patients under antihypertensive treatment or with a cardiovascular disease which more or less corresponds to all diabetic patients.

A reduction in weight of around 1.5 kg to 2 kg was observed on dapagliflozin compared with placebo, in the studies. In this glipizide-controlled, non-inferiority study, this reduction is around 4.65 kg. These differences are not relevant on the clinical level, the majority of patients included in all the studies being overweight or obese.

No study (apart from the glipizide-controlled, non-inferiority study) has included patients at risk of cardiovascular disease.

No difference was shown between dapagliflozin and the comparator treatments in the studies (placebo or active treatment) in a meta analysis which evaluated cardiovascular events in 8682 patients.

The following adverse events will be followed as part of the RMP: bone metabolism, genital infections, urinary tract infections, renal tolerance, volume depletion, increased hematocrit and haemoglobin, cardiovascular tolerance, hypoglycaemia, tumours.

A causal relationship between breast, bladder and prostate cancers and dapagliflozin seems unlikely. However, these cancers were identified as a potential risk of dapagliflozin and will also be monitored as part of the RMP.

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[19] The SPC specifies the precautions for use in patients at risk of volume depletion, hypotension and/or electrolyte imbalance Indeed, because of its mechanism of action, dapagliflozin increases diuresis, combined with a moderate decrease in blood pressure, which could be more pronounced in patients with very high blood glucose levels. Use of dapagliflozin is not recommended in patients receiving loop diuretics or who have volume depletion (for example, because of an acute condition (such as gastrointestinal disease). Particular attention should be given to patients in whom a decrease in blood pressure induced by dapagliflozin may represent a risk, like patients with known cardiovascular disease, patients on antihypertensive treatment with a history of hypotension or elderly patients.

010 PLANNED STUDIES

Ongoing studies are those organised as part of the RMP.

011 THE MEDICINE'S THERAPEUTIC USE

In the absence of national and international recommendations concerning the class of gliflozins and given the available data, the Committee cannot define a precise therapeutic use for dapagliflozin.

It leaves practitioners for whom the initial prescription is restricted (specialists in endocrinology, diabetes, metabolic diseases, internal medicine) the option of starting dapagliflozin in line with the indications and precautions for use of its Marketing Authorisation, and the proposals for management recognised by the Committee.

See section 012.1

012 TRANSPARENCY COMMITTEE conclusions

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

012.1 Actual benefit

◗ Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.

◗ FORXIGA is used in the context of treatment for hyperglycaemia.

◗ It is intended as curative treatment;

◗ **Efficacy/adverse effects ratio:**

In monotherapy

In this indication, the efficacy of FORXIGA versus placebo is modest in terms of the reduction in HbA1c level (-0.66%) in view of the reduction observed with comparators, such as metformin and sulfonylureas (roughly -1 to -1.5%), and a positive impact furthermore in terms of morbidity and mortality.[20]

There are no data against an active comparator, particularly sulfonylureas.

According to the wording of the Marketing Authorisation indication, FORXIGA would be for patients who are intolerant to metformin. However, in the study conducted by the firm, there were no patients included who had been pre-treated with metformin.

For these reasons, the efficacy/adverse effects ratio for FORXIGA, as monotherapy, cannot be qualified.

In dual therapy in combination with insulin

In view of:

- the absence of clinical practice guidelines on this dual therapy and the fact that the only antidiabetics recommended in combination with insulin and used in practice are metformin and the sulfonylureas (in certain situations),

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[20] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998, 352, 854-65.

- the absence of any study comparing the combination insulin + dapagliflozin versus insulin + metformin or versus insulin + sulfonylurea which could have quantified the benefit and contribution of this dual therapy,
- the long-term risks particularly in relation to cardiac, infectious and carcinogenic adverse events, which are poorly defined,
the efficacy/adverse effects ratio for FORXIGA, in dual therapy in addition to insulin, cannot be quantified.

As dual therapy in combination with metformin or a sulfonylurea and triple therapy in combination with insulin and metformin
The meta-analyses and systematic reviews[21] relating to dapagliflozin found similar results to those of the clinical studies, to be precise a difference versus placebo in terms of reduction in the HbA1c level of 0.66% and in terms of weight of 2 kg. These differences, versus placebo, are very modest. They have limits in terms of clinical relevance given the profile of patients included and in view of the low percentage of responder patients.
The efficacy/adverse effects ratio is therefore modest in view of the effect size observed in terms of change in HbA1c level and long-term risks concerning in particular cardiovascular, infectious and carcinogenic adverse effects which not very well-known.

◗ **Therapeutic use:**

In monotherapy
Given the available data, FORXIGA cannot be recommended as monotherapy. There are treatment alternatives to this proprietary medicinal product in the management of diabetic patients with an intolerance (or contraindication) to metformin, that is to say, predominantly sulfonylureas and insulin in patients with moderate renal impairment, and insulin in patients with severe renal impairment. In the event of failure of properly conducted monotherapy using drugs that have proven to be effective, a change to dual therapy can be considered.

In dual therapy in combination with insulin
In view of the available data, the proprietary medicinal product FORXIGA cannot be recommended as dual therapy in combination with insulin. In fact, when initiating insulin treatment, metformin is the reference treatment to combine with it. In a systematic review[22] which included 23 trials, a total of 2117 patients, and evaluated metformin in combination with insulin versus insulin alone, the combination of insulin + metformin was associated, by comparison with insulin alone, with a greater reduction in HbA1c level (difference between groups of -0.60% 95%CI [0.89; 0.31] p<0.001). According to the guidelines[23,24], when insulin therapy is started to maintain or improve glycaemic control, the following dual therapies, insulin + metformin or insulin + sulfonylurea, are the validated combinations.

As dual therapy, in combination with metformin or a sulfonylurea and triple therapy, in combination with insulin and metformin
FORXIGA is a treatment able to be used as dual therapy in combination with metformin or a sulphonylurea and as triple therapy after the failure of the insulin/metformin combination.
It is an additional means of treatment for the management of patients with type 2 diabetes.
Alternative medicinal products exist.

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[21] D. Vasilakou and al. Sodium-Glucose Cotransporter 2 inhibitors for type 2 diabetes. A systematic review and meta-analysis. Annals of Internal Medicine 2013; 159: 262-274
[22] Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ. 2012 Apr 19; 344: e1771. doi: 10.1136/bmj.e1771.
[23] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al.* Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia 2009; 52(1): 17-30.*
[24] Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. http://www.sign.ac.uk/pdf/sign116.pdf.

◗ **Public health benefit:**
The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the associated microvascular and macrovascular complications. The public health burden in the sub-population of patients with each of the indications for FORXIGA is also considered to be moderate.

Improvement in the treatment of type 2 diabetics is a public health need which comes within the framework of established priorities.[25] 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 FORXIGA. Moreover, the available data do not make it possible to estimate the impact of FORXIGA on morbidity and mortality and quality of life of 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 FORXIGA is unable to offer any response to the identified public health need.

It is therefore not expected that the proprietary medicinal product FORXIGA will impact public health in all the Marketing Authorisation indications.

Consequently, the Committee considers that the actual benefit of FORXIGA is:
- **insufficient as monotherapy for reimbursement by National Health Insurance**
- **moderate as dual therapy in combination with metformin or a sulphonylurea**
- **insufficient as monotherapy as an add-on to insulin for reimbursement by National Health Insurance**
- **moderate as triple therapy in combination with insulin and metformin**

012.2   Improvement in actual benefit (IAB)

➢ In the indications as monotherapy and dual therapy, in combination with insulin: not applicable

➢ In the indications as dual therapy, in combination with metformin or a sulfonylurea and triple therapy, in combination with insulin and metformin:

Given the very modest glycaemic control observed compared with the placebo, doubts about the safety profile, particularly on an infectious, cardiovascular and carcinogenic level, and the difficulty in defining the therapeutic use, the Committee cannot recognise any improvement for FORXIGA.

In addition, the Transparency Committee considers that FORXIGA does not provide any improvement in actual benefit (level V, non-existent) in the management of type 2 diabetes patients in dual oral therapy, in combination with metformin or a sulfonylurea and as triple therapy, in combination with insulin and metformin.

013 TARGET POPULATION

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[25] Objective 55 of the Law of 9 August 2004 relating to public health policy: Reducing the frequency and severity of the complications of diabetes and particularly cardiovascular complications, a national improvement plan for the quality of life of persons with from chronic diseases 2007-2011.

The Bulletin Epidémiologique Hebdomadaire [Weekly Epidemiological Bulletin] has published an update to French data on the prevalence of diabetes from the database of the national health insurance cross schemes information system (Sniiram) for the period 2006-2009. In 2009, the prevalence of diabetes treated was estimated to be 4.4%, and the population of diabetic patients treated increased to 2.9 million patients.[26] Between 2006 and 2009, the average annual growth rate (AAGR) increased to 4.7%. Assuming a constant AAGR after 2009, the diabetic population (type 1 and 2) treated in France should reach around 3.5 million patients in 2013.

The ENTRED 2007-2010 (Echantillon National Témoin Représentatif des personnes Diabétiques [The French 'Representative National Control Sample of the Diabetic Population') study estimated the proportion of patients with type 2 diabetes to be 91.9%,[27] i.e. around **3.20 million patients in 2013**.

The target population of FORXIGA was estimated according to the indications requested in the reimbursement and admitted by the Committee.

Estimation of the target population of dapagliflozin 10 mg/day as dual therapy (combination with metformin or a sulfonylurea)

If the glycaemic target is not reached despite treatment with metformin (in the event of intolerance or contraindication to sulfonylureas) or sulfonylurea (metformin is not tolerated or is contraindicated), and if the deviation from the target is lower than 1 % HbA1c, the FORXIGA + metformin or sulfonylurea combination may be proposed. In the cases where another OAD in combination with metformin or a sulfonylurea did not allow the glycaemic target to be reached, FORXIGA may be proposed as an alternative.

In the ENTRED study, 42% of patients were treated with oral monotherapy. Moreover, according to the distribution of the available HbA1c level, 26% of patients with type 2 diabetes in the sample had an HbA1c between 7% and 8%.

According to the opinions delivered by the Transparency Committee, the proportion of patients who are intolerant or contraindicated to metformin is estimated to be 20%. No data is available concerning the proportion of patients who are intolerant or contraindicted to sulfonylureas. In contrast, in 2006, HAS estimated the proportion of patients prone to severe hypoglycaemia on sulfonylureas to be around 8%.

Table: Target population of FORXIGA corresponding to the dual therapy indication

Populations considered	Numbers	Sources
Patients with type 2 diabetes	3.20 million	ENTRED
Patients treated with oral monotherapy (42%)	1.34 million	
Patients intolerant or contraindicated to SU (8%) **_Or_** Patients intolerant or contraindicated to metformin (20%)	376,300	HAS
Sub-population with an HbA1c between 7% and 8% (26%)	97,800	ENTRED
Target population of FORXIGA in patients not controlled in monotherapy	**97,800**	

The target population of FORXIGA corresponding to the indication as dual oral therapy is therefore estimated to be around **97,800 patients**.

Estimation of the target population of dapagliflozin 10 mg/day as triple therapy (insulin + metformin combination)

Table: Target population of FORXIGA corresponding to the indication as triple therapy

Populations	Numbers	Comments	Sources

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[26] Ricci P, Blotière PO, Weill A et al. Diabète traité: quelles évolutions entre 2000 et 2009 en France? BEH 2010; 42-43: 425-31.
[27] Echantillon National Témoin Représentatif des personnes Diabétiques (ENTRED) 2007-2010 [The French 'Representative national sample of the Diabetic Population' (ENTRED) 2007-2010 Diaporama] Available at: www.invs.sante.fr/surveillance/diabete/entred_2007_2010/resultats_metropole_principaux.htm.

	considered	considered		
Patients treated with insulin in 2007 (23% of T2D patients in 2007)	358,000			HAS
- of which insulin alone (39.0%) **- of which insulin + OAD (61.0%)**	139,620 218,380	14.1% of T2D patients are treated with insulin, of which 5.5% with insulin alone		ECODIA 2 study
<u>**Sub-population on insulin + OAD**</u> - 51.5% with HbA1c > 7%	218,380 112,465			ECODIA 2 study
Total target population in this indication	**112,465 patients**			

The target population of Forxiga corresponding to the indication in combination with insulin is therefore estimated to be around **<u>113,000 patients</u>**.

Overall, the target population of FORXIGA would be about 210,800 patients.

014 TRANSPARENCY COMMITTEE RECOMMENDATIONS

> <u>In the indications as monotherapy and dual therapy, in combination with with insulin</u>:

The Committee does not recommend inclusion of the proprietary medicinal product FORXIGA 10 mg on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use.

> <u>In the indications as dual therapy, in combination with metformin or a sulfonylurea and as triple therapy, in combination with insulin and metformin</u>:

The Transparency Committee recommends inclusion of the proprietary medicinal product FORXIGA 10 mg on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation.

◗ **Packaging**
Appropriate for the prescribing conditions.

◗ **Reimbursement rate**
30%

Appendix:

INN	Name (Company)	Date of opinion	Actual Benefit	Improvement in Actual Benefit	Reimbursement
Biguanide					
Metformin and its generics	GLUCOPHAGE (Merck Santé)	21 July 2010 (RI)	Substantial		Yes
Insulin secretagogues					
Sulfonylureas and their generics			Substantial		Yes
Alpha-glucosidase inhibitors (acarbose, miglitol)	GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)	5 September 2012 (RI)	Substantial		Yes
Repaglinide	NOVONORM (Novo Nordisk)	21 July 2010 (RI)	Substantial		Yes
Injectable incretin mimetic or GLP-1 analogues (not indicated as monotherapy)					
Exenatide	BYETTA (Bristol-Myers Squibb)	28 February 2007	substantial as dual therapy in combination with metformin or a sulfonylurea	No IAB	Yes
			Being assessed as dual therapy with insulin and as triple therapy with insulin + metformin		
Liraglutide	VICTOZA (Novo Nordisk)	2 December 2009	substantial as dual therapy in combination with metformin or a sulfonylurea	IAB IV	Yes
Lixisenatide	LYXUMIA (Sanofi Aventis)		*Still being assessed by the TC*		
Gliptins					
Sitagliptin and its fixed combinations with metformin	JANUVIA 100 mg/XELEVIA 100 mg (MSD, Pierre Fabre)	18 July 2012	Insufficient as monotherapy	Not applicable	
		6 June 2007	Substantial as dual therapy in combination with metformin	IAB IV	Yes
		24 June 2009	low as dual therapy in combination with a sulfonylurea	IAB V	Yes
		18 July 2012	Insufficient as dual therapy in combination with insulin	Not applicable	No
		18 July 2012	Substantial as triple therapy in combination with insulin and metformin	IAB V	Yes
Vildagliptin and its fixed-dose combinations with metformin	GALVUS/JALRA (Novartis Pharma)[28]	21 November 2012	Insufficient as monotherapy	Not applicable	
		10 December 2008	Substantial as dual therapy in combination with metformin or a sulfonylurea	IAB V	Yes
Saxagliptin and its fixed combination with metformin	ONGLYZA (Bristol-Myers Squibb)[29]	2 December 2009	Substantial as dual therapy in combination with metformin or a sulfonylurea	IAB V	Yes
		15 May 2013	Insufficient as dual therapy in combination with insulin	Not applicable	No
			Low as triple therapy in combination with insulin and metformin	IAB V	Yes
Linagliptin and its fixed-dose combination	TRAJENTA (Boehringer Ingelheim)[30]	20 June 2012	Insufficient as monotherapy	Not applicable	No
			Substantial as dual therapy in combination with metformin	IAB V	
		20 March 2013	Insufficient as dual therapy	Not	

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[28] 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. "
[29] Not indicated as monotherapy
[30] Not indicated as dual therapy in combination with a sulfonylurea

| | | | in combination with insulin | applicable | |
| | | | Substantial as triple therapy in combination with insulin and metformin | IAB V | |