EXPLAINING THE DISPARITIES OF MARKET ACCESS FOR GLIFLOZINS IN FRANCE, SPAIN, GERMANY AND THE UNITED-KINGDOM

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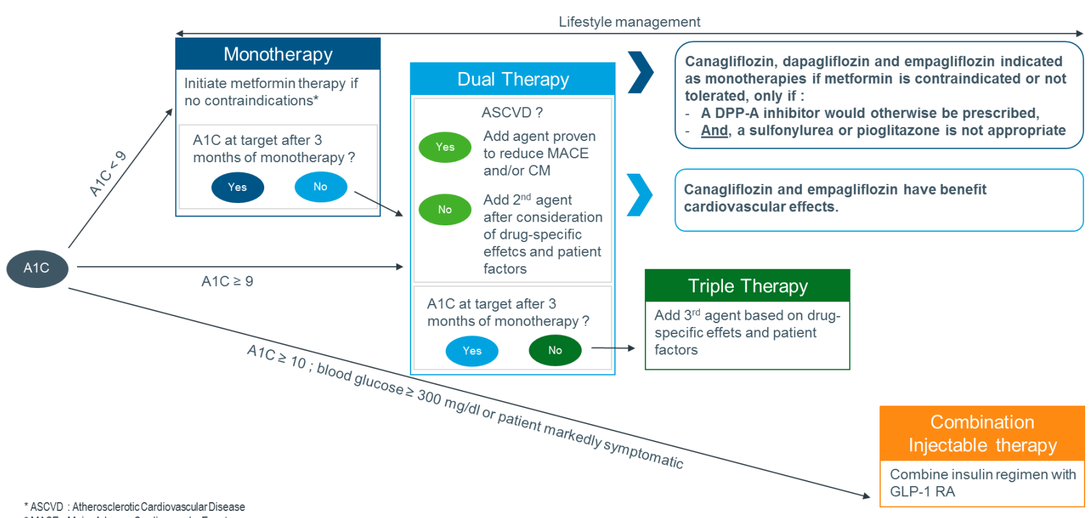
Background and Objectives

- The global prevalence of diabetes reached 8.5% in 2014[1].
- Gliflozins are SGLT2 inhibitors, a therapeutic class of drugs indicated the treatment of type 2 diabetes mellitus.
- Three products belonging to this class were granted marketing authorizations by the European Medicines Agency between 2012 and 2014: Invokana® (canagliflozin), Forxiga® (dapagliflozin), Jardiance® (empagliflozin).
- However these drugs presenting an innovative mechanism of action faced heterogenous market access outcomes on the European market.
- The purpose of this study is to understand the disparities of HTA outcomes for gliflozins in France, Spain, Germany and the United-Kingdom.

Methods

- To understand market access disparities, health technology assessments reports on gliflozins from HTA agencies in France, Germany, Spain and the United-Kingdom were compared.
- HTA-Accelerator™ platform was used to identify published evaluations of Invokana®, Forxiga®, and Jardiance®.
- The analysis was based on the type of evaluations, the submitted data, and the conclusions emerging from the assessments.

Treatment strategy in type 2 diabetes mellitus



* ASCVD : Atherosclerotic Cardiovascular Disease
* MACE : Major Adverse Cardiovascular Events
* Cardiovascular Mortality

Results[2]

Germany

Product	Agency	Type of evaluation	Date of decision	Agency Comments	HTA Outcome
Invokana	GBA	Original	04/09/2014	No added benefit demonstrated in any of the subgroups	Negative
Forxiga	GBA	Original	06/06/2013	No added benefit demonstrated for any of the subgroups, submitted studies did not comply recommended drug doses of market authorization	Negative
Jardiance	GBA	Original	05/02/2015	No added benefit demonstrated in any of the subgroups	Negative
Jardiance	GBA	Resubmission	01/09/2016	Increased risk of adverse events, no efficacy data for the target subgroup, study population being different from the target population	Positive with restrictions
Invokana	IQWIG	Original	16/06/2014	No added benefit for any of the subgroups, no suitable data against the appropriate comparator presented for the possible therapeutic indications	Positive with restrictions
Forxiga	IQWIG	Original	13/03/2013	Inappropriate comparator in the clinical study	Positive with restrictions
Forxiga	IQWIG	Resubmission	28/03/2018	Lack of hard outcomes, limited additional benefit to existing treatment	Positive with restrictions
Jardiance	IQWIG	Original	13/11/2014	Inappropriate comparator in the clinical study, no efficacy data for the target subgroup against the appropriate comparator	Positive with restrictions
Jardiance	IQWIG	Resubmission	30/05/2016	Inappropriate comparator in the clinical study, no efficacy data for the target subgroup against the appropriate comparator	Positive with restrictions

- In Germany the GBA regulates drugs reimbursement and restrictions. Its assessment was unfavorable with negative recommendation as no added benefit was demonstrated. It outlined that the study population was different from the target population and that the submitted studies did not comply with recommended doses.
- The IQWIG evaluates the effectiveness of drugs. It gave positive recommendation with restriction, mainly because it considered that the study comparator was inappropriate.

United-Kingdom

Product	Agency	Type of evaluation	Date of decision	Agency Comments	HTA Outcome
Jardiance	AWMSG	Original	11/01/2016	Good safety and tolerability, non-inferior or similar efficacy as existing treatment	Positive
Forxiga	SMC	Original	07/12/2012	Cost-effectiveness against sulfonylurea not demonstrated, therefore dapagliflozin is only recommended when the use of a sulfonylurea is inappropriate	Positive with restrictions
Forxiga	SMC	Resubmission	07/02/2014	Not recommended to use as monotherapy	Positive with restrictions
Invokana	SMC	Original	09/05/2014	Not recommended to use as monotherapy	Positive with restrictions
Forxiga	SMC	Resubmission	06/06/2014	Clinical efficacy and cost-effectiveness were demonstrated	Positive with restrictions
Jardiance	SMC	Original	05/09/2014	Not recommended to use as monotherapy as the company's submission did not include evidence of cost-effectiveness in this setting	Positive with restrictions
Forxiga	NICE	Original	25/06/2013	Not recommended to use as monotherapy	Positive with restrictions
Invokana	NICE	Original	20/06/2014	Not recommended to use as monotherapy, no data against the appropriate comparator	Positive with restrictions
Invokana Forxiga Jardiance	NICE	Resubmission	25/05/2016	Recommended as monotherapy in adults when metformin is contraindicated, and when pioglitazone or sulfonylureas are not appropriate	Positive
Forxiga	NICE	Original	07/10/2016	Recommended in triple therapy with metformin and a sulfonylurea	Positive

- In the UK, the SMC issued a positive recommendation with restrictions, as gliflozins were not recommended in monotherapy.
- The NICE had the same evaluation, but in 2016, gliflozins were recommended in a multiple drug assessment to be used in monotherapy for some patients.
- The AWMSG considered that Jardiance® presented good safety and tolerability.

Spain

Product	Agency	Type of evaluation	Date of decision	Agency Comments	HTA Outcome
Invokana	AEMPS	Resubmission	10/03/2016	Gliflozins are considered an alternative treatment in patients with a renal glomerular filtration > 60 mL/min	Positive
Invokana	AEMPS	Original	22/06/2017		Positive
Invokana	AEMPS	Resubmission	26/06/2015		Positive
Jardiance	AEMPS	Resubmission	10/03/2016		Positive
Jardiance	AEMPS	Original	08/06/2017		Positive
Jardiance	AEMPS	Resubmission	23/06/2015		Positive

- In Spain, the AEMPS is responsible for the registration of pharmaceutical products
- The evaluation of gliflozins resulted in a positive outcome, as they were considered an alternative treatment in patients with renal glomerular filtration above 60 mL/min.

France

Product	Agency	Type of evaluation	Date of decision	Agency Comments	HTA Outcome
Forxiga	HAS	Original	23/04/2014	Modest benefit on glycemic control, doubts on safety profile, difficulty in defining a place in the therapeutic strategy, study not corresponding to the population in the indication	Positive with restrictions
Invokana	HAS	Original	05/11/2014	Demonstration of non-inferiority versus active comparator, no data on long term follow-up	Positive with restrictions
Jardiance	HAS	Original	17/12/2014	Study versus placebo whereas active comparators are available, modest efficacy results, lack of hard outcomes	Positive with restrictions
Forxiga	HAS	Resubmission	07/10/2015	Modest efficacy and tolerance profile, absence of relevant clinical data	Positive with restrictions
Jardiance	HAS	Resubmission	19/10/2016	Lack of hard outcomes, no efficacy data for the target subgroup, no data against the appropriate comparator	Positive with restrictions

- In France, a favorable advice from HAS was granted with restrictions. The HAS criticized the design of the clinical trials that did not use the appropriate comparator, and used non-inferiority endpoints.
- Jardiance® is the only gliflozin which went through cost-effectiveness assessment by the HAS as its expected yearly turnover was above €20 million. This pharmacoeconomic evaluation has not been published.

Positive | Positive with restrictions | Negative

Conclusion

- **This analysis outlines that gliflozins have been assessed differently by these four European HTA agencies. Whereas HAS and GBA are looking at clinical benefit, NICE is considering economic impact as well. Then it is not surprising that a favorable recommendation from the NICE has been issued, knowing the price of these drugs.**
- **Although this new class of drug presents an innovative mechanism of action, considering the clinical assessment, the submitted data did not demonstrate their interest in the therapeutic strategy, and overall the European agencies considered that the benefit with gliflozins was modest on glycemic control.**
- **This raises the question of the relevance of a collaborative HTA pathway throughout Europe. Indeed, the EUnetHTA initiative could bring equal added value to healthcare systems and citizens at the European, national and regional level.**

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GBA : Gemeinsamer Bundesausschuss ; IQWIG : Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen ; AWMSG : All Wales Medicines Strategy Group ; SMC : Scottish Medicines Consortium ; NICE : National Institute for Health and Care Excellence ; AEMPS : Agencia Española de Medicamentos y Productos Sanitarios ; HAS : Haute Autorité de Santé