Dapagliflozin use in type 1 diabetes: industry, business and ethics

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Abstract

We provide a summary on the unprecedented withdrawal of dapagliflozin's license in Type 1 diabetes by AstraZeneca. We also provide a summary from a national survey of 52 sites in the United Kingdom, with 70% respondents reporting clinically significant benefits following dapagliflozin use in type 1 diabetes. We describe some of the challenges faced by clinicians supporting people with type 1 diabetes using dapagliflozin. This withdrawal, which was solely for commercial reasons and not due to adverse safety events, raises important considerations about ethics and transparency required from the pharmaceutical industry. It also strongly highlights the need for consultation from key stakeholders including clinicians and patient groups prior to such decisions.

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On Monday 14th February, 2022 BBC Radio 4, complementing a report in the *British Medical Journal (BMJ)*, provided coverage of the circumstances surrounding the withdrawal of the licence for the use of dapaglifozin in Type 1 diabetes (T1D). This licence withdrawal was based solely on the commercial considerations of the manufacturer, AstraZeneca.[1] It would be very easy to scroll away from this soundbite and move on to the next, but it triggered a series of thoughts and discussions amongst healthcare professionals that relate to this issue and ethical practices in industry. To some of our system leaders this was a minor situation and followed a very logical commercial decision that was accepted as the norm in industry practice; that, in itself, is concerning to some.

To remind ourselves of the sequence of events, recent evidence from trials of the sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors) such as dapagliflozin, empagliflozin and sotagliflozin demonstrated them to be a promising adjunct to insulin in the management of T1D.[2-5] These medications offered the potential of glycaemic improvements and weight loss when added to insulin. Furthermore, following the beneficial impact on cardiovascular and renal outcomes in type 2 diabetes (T2D), many considered that these agents could offer similar benefits to those with T1D.[6-9]

However, despite the investments in the development pipeline and the positive results from trials, some companies abandoned these projects prior to launch, partly because regulatory approval was not obtained in the US. In the UK and Europe however, AstraZeneca acquired a licence for the use of dapagliflozin in T1D, which in 2019 proved to be the only treatment licensed for T1D since the discovery of insulin 100 years ago.[10] It promptly received endorsement from the National Institute for Health and Care Excellence (NICE) following their technology appraisal, with carefully worded guidance to support its prescription in clinical practice.[11] Research evaluations have provided further reassurance, identifying careful patient selection and risk mitigation protocols involving ketone monitoring to reduce potential ketosis-related adverse events.[12] Its licence approval just before the COVID-19 pandemic and a professional statement suggesting that its initiation should be avoided meant that the number of people receiving this may have been smaller than predicted.[13] However, as the pandemic situation and capacity amongst healthcare professionals improved, the SGLT2 inhibitors provided a useful way of managing a niche but increasing group of people with insulin resistance or raised body mass index (BMI) on a background of T1D.

What then followed was unprecedented. On 25th October 2021, AstraZeneca announced the withdrawal of dapagliflozin's T1D licence.[14] It was stated that this was because the licence for T1D required the drug to have a 'black triangle' placed to highlight additional monitoring by the MHRA (Medicines and Healthcare products Regulatory Agency). There were concerns that this might discourage prescription of the drug in the T2D setting, which is the main business of the company.[1] The situation here is unusual in that the licence has been withdrawn solely for commercial reasons and not due to any adverse safety signal or new data.[15] This is despite the drug having a plethora of positive data, with no major safety concerns and with potential major benefits confirmed by a number of research trials.[12] Moreover, the way in which this decision was made and communicated demonstrates that better stakeholder engagement by industry is

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Key messages

- Trials demonstrated that with careful patient selection and risk mitigation protocols, SGLT2 inhibitors were promising as adjuncts to insulin with potential metabolic benefits in T1D
- A recent national survey highlights specialist clinicians are cautious and do prioritize safety, however report clinically significant benefits in people with T1D prescribed dapagliflozin.
- The issue raises important considerations about the ethics and transparency required from the pharmaceutical industry to deliver both purpose and profit

needed with healthcare professionals and those living with the condition. To date, very little effort has been made to understand those affected and how to support them. Other options such as rebranding a T1D version of thedrug under a different name to avoid the confusion of the black triangle affecting dapagliflozin's prescriptions in T2D were apparently not considered.

Following this announcement, the ABCD conducted a national survey in December 2021 relating to dapagliflozin's use in T1D. Some 52 sites responded to this snapshot survey. The number of patients with T1D receiving SGLT2 medication at each site was small, with most specialists offering it to only 1-5 patients. The majority of specialists initiated this drug for its weight reduction and/or glycaemic benefits and 63% of them undertook this prescription in a cautious and selective manner, given the safety concerns around the potential for diabetic ketoacidosis. In this survey 70% reported clinically significant benefits, with 30% noting weight reduction, 38% improved glycaemic control, 24% observed reduction in glucose variability and 8% noting other benefits.

What can clinicians do next? At present healthcare professionals, who believe in doing the right thing, are having to develop guidance and practices to support the off-label use of these medications. This requires additional work, and some risk taking by healthcare professionals. Careful documented discussions with patients would be required, and this may not be supported by other stakeholder professionals involved in ongoing community prescribing. In essence, the removal of licencing for use in T1D is likely to impact strongly the initiation of new prescriptions and to reduce the number of people who could benefit in this setting unless a solution to support its use is found.

The issue raises important considerations about the ethics and transparency required from the pharmaceutical industry to deliver both purpose and profit. This recent decision is concerning as it highlights that industry decisions may be dominated by commercial priorities, with little consultation from stakeholders.

Conflict of interest HN is JDRF UK Director of Policy and Communications (staff role). All other authors declare no related conflicts of interest.

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