

# Why are GLP-1 receptor agonists in short supply?

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Concern has escalated during the spring and summer of 2022 as the Department of Health and Social Care (DHSC) issued notification that stocks of two once-weekly injected glucagon-like peptide-1 receptor agonists (GLP-1RAs) – semaglutide and dulaglutide – were dwindling.<sup>1,2</sup> Without restrictions of usage, the DHSC anticipates that UK supplies of these medicines can last only until early 2023. Has the success of these medicines caught prescribers and manufacturers by surprise, or have warnings of shortages passed unheeded?

Various suggestions have been offered on how to reduce the use of semaglutide and dulaglutide temporarily. The DHSC proposes a temporary halt to new initiations of patients earmarked to receive these medicines, and dose-titration times could be extended for existing recipients to delay full-dose usage. The Pharmaceutical Services Negotiating Committee points to the availability of other members of the GLP-1RA class.<sup>3</sup> However, increased demand for the other once-weekly GLP-1RA (exenatide) could also strain supplies, and switching to a once-daily injection of liraglutide may not be a comfortable manoeuvre for many patients. Similarly, transfer to oral semaglutide could be a challenge for patients and supplies. The problem has prompted a hasty consensus statement from the Primary Care Diabetes Society (PCDS), which provides a helpful table of dose equivalents if switching agents.<sup>4</sup>

Ironically, the shortage of GLP-1RAs coincides with further guidelines encouraging earlier and wider use of these agents in the glucose-lowering treatment algorithm for T2DM, especially for individuals who are overweight or obese and who have atherosclerotic cardiovascular disease.<sup>5,6</sup> Although the growth in demand for GLP-1RAs is an international issue, a cynic might observe that, in contrast to other guidelines, the latest NICE guidance (NG28, 2022 version) leaves GLP-1RAs at the foot of the treatment algorithm.<sup>7</sup> So if UK clinicians follow NICE guidance the shortage should have less impact than in some other countries. Whether the lowly positioning of GLP-1RAs by NICE in the treatment algorithm could have influenced procurement is another matter.

Manufacturers have previously flagged up the potential risk of a supply challenge for GLP-1RAs, and it is noted that the obesity indications for high doses of injected liraglutide (3mg/day) and semaglutide (2.4 mg/week) have received limited promotion, presumably to avoid diverting supplies away from diabetes. Production capacity cannot be expanded quickly since it relies on unique genetically modified cells, and the vaccination programme for Covid-19 has affected the availability of syringes. It may be expected that the recently approved dual incretin receptor agonist (GIP/GLP-1 receptor agonist) tirzepatide will be subject to similar supply pressures.

For the next few months, concerns about the use of a GLP-1RA may be changing from 'can we afford it' to 'can we get it', and while GLP-1RAs are the victims of their own success, it may be necessary to look to other glucose-lowering medications for temporary respite to maintain adequate glycaemic control.

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