

## The EMA and Glucagon-Like Peptide-1 Agonists: A Wake-Up Call

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## 1. Abstract

The European Medicines Authority (EMA) is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU and the European economic Area (EEA). On July 11<sup>th</sup>, 2023, it issued a press release stating that PRAC (The EMA's safety committee) was reviewing data on the *potential* risk of suicidal thoughts and thoughts of self-harm with medicines known as GLP-1 receptor agonists, including Ozempic (semaglutide), Saxenda (liraglutide) and Wegovy (semaglutide). This was in response to reports by the Icelandic Medicines Authority of patients on liraglutide and semaglutide experiencing suicidal tendencies and thoughts of self-harm. Such reported signals are rightly taken very seriously by the EMA. However, looking at Ozempic, one is stricken by the EU's Medicine's Authority lack of publicly highlighting warnings in view of three burning issues. Firstly, the rampant, rarely seen meteoric use of the drug, which is becoming a seeming status symbol for use in weight loss and is openly promulgated as such by media and movie moguls as such. Secondly, the fact that the use of Ozempic in weight-loss is off-label. And thirdly, thirdly the *established* number of *still-increasing*, serious complications which carry serious health risks and even a risk to life in the face of this orgiastic misuse of a GLP-1 receptor agonist.

## 2. The European Medicines Agency

The European Medicines Agency (EMA) does an invaluable job of safeguarding and promoting both human and animal health by constantly evaluating medical products within the European Union (EU) and the European Economic Area (EEA). The Agency has had its fair share of criticism regarding its stipulated mission statement. Some of these attacks include the quality of its clinical trial reports (e.g. Barbui et al 2011) [1], its closeness to the industry (e.g. Grattini 2016) [2], the protection of drug company profits above patient welfare by withholding access to the data (e.g. Tzsche et al.,) [3]. However much criticised, the Agency is indispensable and has repeatedly obtained European Court re-affirmation of its purported standing. Thus, in *PTC Therapeutics International v EMA* [4] and *MSD Animal Health Innovation v EMA* [5], the European Court has unambiguously upheld the EMA's approach to transparency, confirming the right of citizens for access to clinical study and toxicology reports submitted to the EMA for the purpose of the granting of a marketing authorisation for human and veterinary medicinal products.

## 3. Glucagon-Like Peptide 1 (GLP-1) Agonists

Glucagon-like-peptide 1 (GLP-1) is a gut-derived peptide hormone which lowers blood glucose through the stimulation of insulin secretion from the pancreas. Its action is mimicked by these synthetic

agonists and this class of medications are utilized in the treatment of type 2 diabetes mellitus and obesity. Examples of these drugs include Ozempic (semaglutide), Saxenda (liraglutide) and Wegovy (semaglutide). While liraglutide (Saxenda) is indicated for physician-oriented weight-loss programmes, semaglutide (Ozempic) is indicated as part of Type II diabetes mellitus. Ozempic is not intended for weight loss and any such use is, off-label.

Ozempic has been cleared for use in type 2 diabetes mellitus, period. The EMA *specifically* states that Ozempic should be used in the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, either as monotherapy when metformin is considered inappropriate due to intolerance or contraindications or in addition to other medicinal products. Semaglutide as Wegovy is approved for weight loss but not as Ozempic, although semaglutide is present in both products, albeit in different doses.

#### 4. A Game Changer'

According to the EMA, -liraglutide and semaglutide are extremely widely used and to-date (11/07/2023) there are over 20 million patient-years [6], defining one patient-year as the equivalent of one patient taking a medicine for one year. Ozempic is Novo-Nordisk leading drug and its sales growth for 2023 is forecasted at 23% with sales of \$12.5bn [7]. The surge in the sales of the GLP-1 drugs is the topic of conversation in every (healthcare) trade organization today, the product being repeatedly referred to as a game changer. We speak here of a stock market game changer with long-term ripple effects across equities and economy [8]. The *off-label* use of Ozempic for weight loss has even led to a shortage in the medication for what it was intended for, namely type -2 diabetes mellitus management. This phenomenon is worldwide. For example, in Australia, Novo Nordisk has advised that very limited new supplies of Ozempic 0.25/0.5mg would be available before the end of 2023 and there would be intermittent supply of all strengths of Ozempic for the rest of 2023 and throughout 2024<sup>1</sup>. In view of this shortage the FDA has warned against the use of fraudulent and unapproved products including compounded varieties [9]. Such a warning would not have been out of place if also issued by the EMA as fraudulent and unapproved variants of Ozempic in the thirst for a miracle weight-losing drug are also riding the wave within the European Union and the European Economic Area. And among the one powerful catalysts in this worrying process is the media. In British Columbia, the Health Ministry is officially investigating the relationship between the almost 10 per cent use of Ozempic prescriptions for weight loss and the contributory influence of social media on the matter [10].

#### 5. Potentially Fatal Side-Effects

The use of pharmacological agents on an off-line basis is well known in the medical world, in circumstances some of which are more justifiable than other. However, the phenomenon needs to

be re-visited when applied to a drug, the off-label use of which constitutes up to about 10% of consumption, and which has proven and potentially devastating and even fatal side-effects. We live in a culture where patient autonomy seems to be extra-polated to prescribing all that the patient wants and demands. This is questionable at best and at times, outright unethical and potentially illegal. For although patients, dreaming of dramatic weight loss may put up with abdominal pain, constipation, diarrhoea, nausea and vomiting, the situation may be different if any of the major potential side-effects supervene. These include hypoglycaemia, acute gallbladder disease, acute renal damage, anaphylaxis, retinopathy, thyroid tumours and pancreatitis. The reportage of potentially serious complications is a work in progress. Thus, on 28 September 2023, the FDA reported 2 deaths from ileus and warned about potential Ozempic-induced paralytic ileus. 2 Another 2023 publication, warns of potential life-threatening stomach content regurgitation and pulmonary aspiration in cases of surgery in the presence of Ozempic [11]. The drug works by decreasing appetite both through suppression of the brain's hunger centres as well as by slowing gastric emptying. It is the latter effect which is considered as posing a surgical threat, especially, but not only, in emergency cases where possibly a sufficiently long period of starvation may not have been observed in a patient on Ozempic.

#### 6. Conclusion

In accordance with its self-declared transparency, the EMA was correct in recently revealing the Icelandic Drug Authority signals relating to self-harm and stating that an investigation was to be launched. If the connection is confirmed, then, obviously a new major potential complication is added to Ozempic official complications. This is particularly important especially when considering the increased risk of depression, suicidal ideation and suicidal attempts in diabetics [12], as well as the high rates of suicide ideation and/or behaviour in the severely obese [13].

However, we also firmly believe that the occasion of the Icelandic signal reportage is an opportune occasion to wake up, see the elephant in the room and respond accordingly. In an age which is hell-bent on physique, the off-label use of a "miracle weight-reducing drug" fostered by the media, screen personalities and certain medical practitioners, (particularly in certain specialties e.g. plastic surgery) is not easy to control. Yet, the EMA is uniquely poised to issue the right directives to medical practitioners as well as suitable press-releases to the general public concerning the current distorted status quo of Ozempic. This applies both to its irrational and increasing off-label use as well as to its complications, the list of which does not seem to be complete. The EMA must clearly warn the public that drugs are licensed for use in specific situations and carry certain potential serious and possibly fatal complication risks. The present indiscriminate abuse of Ozempic must be curtailed by a multi-front approach and it is one where the powerful EMA honouring its stated mission statement, must take the lead.

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