TABLES

TABLE 1 Summary of effects of pioglitazone and liraglutide on the liver, cardiovascular risk and type 2 diabetes, in patients with NAFLD / NASH

Drug	Licensed indications[i]	Liver effects	Diabetes effects	CVD effects	Consideration of potential adverse effects
Pioglitazone (PPAR-γ agonist)	T2DM[ii]	- NASH resolution in 47% of patients[44] -Improvement in fibrosis stage in patients with advanced fibrosis at baseline[44]	-Potent, durable HbA1c reduction[81] -Low risk of hypoglycaemia[81] -Improves insulin resistance[81]	-Decreases serum triglyceride concentration[81] -Decreases BP[81] -Increases HDL concentration[81] -Decreases risk of MI[51] and stroke[45,51]	-Weight gain (in ~3% compared to placebo)[44] -Decreased bone mineral deficiency[46] -Heart failure: no increased risk of heart failure in IRIS[51] trial but previous 2017 meta-analysis of 29 studies demonstrated thiazolidinediones significantly associated with heart failure (OR 1.59; 95% CI 1.34, 1.89; p < 0.00001). Lower limb oedema also more common in patients treated with pioglitazone in previous meta-analysis of pioglitazone patients with T2DM and NASH.[44] -Bladder cancer: the association between pioglitazone and bladder cancer has not been shown to be causative. However, previous history of bladder cancer is a listed contraindication.[47]
Liraglutide (*GLP-1 agonist)	1. T2DM[iii] 2. Adjunct in weight management[iv]	- NASH resolution in 39% of patients resolves NASH in up to 50%[59]	-Weight loss -HbA1c reduction	-Reduce MACE[58] -Reduce cardiovascular mortality[58] -Reduce all-cause mortality[58]	-Gastroparesis is a listed contraindication -Nausea and vomiting

i. In United Kingdom
ii. Alone or combined with metformin and/or a sulfonylurea, or with other antidiabetic drugs.
iii. Monotherapy (if metformin inappropriate) or combined with other antidiabetic drugs.
iv. In conjunction with dietary measures and increased physical activity in individuals with a body mass index (BMI) of 30 kg/m^2 or more, or in individuals with a BMI of 27 kg/m^2 or more in the presence of at least one weight-related co-morbidity.
* There is evidence that in addition to liraglutide, other GLP-1 agonists, such as semaglutide[60] and delaglutide[61], also cause reduction in hepatic fat, which suggests a GLP-1 agonist class effect.
Abbreviations: CI, 95% confidence interval; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; IRIS, Insulin Resistance Intervention after Stroke (trial); MACE, major cardiovascular events; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.