Liraglutide for the treatment of type 2 diabetes:

A review of the Mixed Treatment Comparison (MTC) analysis provided by the manufacturer of liraglutide in response to the appraisal consultation document (ACD)

April 2010

Report by the NICE Decision Support Unit.

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NICE Decision Support Unit: Appraisal of the Mixed Treatment Comparison (MTC) analysis to inform the relative effectiveness of Liraglutide as part of triple therapy

The response document from Novo Nordisk states that their analysis "differs from the conventional mixed treatment comparisons in several ways" (Appendix 2 page 38) and goes on to describe three distinctions. I consider each of these in turn.

1) "The analyses are based on individual patient data" – The report does not state the implications of this statement. i.e. is this mentioned to imply a superior analysis (individual data meta-analyses have been described as the gold standard (1))? Or to justify the non standard approach to modelling they take (discussed below)?
2) "The analysis is used simply to recover different treatment information not available in the trials but available in the remainder." This statement is unclear. The remainder of what? Reading Higgins et al (2), which is what they later state they base their analysis on, I think this is related to assuming a random trial effect in the model (as well as the more conventional random treatment effects) which potentially allows for recovery of information across different contrasts for contrasts not actually studied in a trial.
3) "the outcomes of interest are continuous data". I don't consider the analysis of comparative continuous outcomes to be conceptually different from binary ones (which is what I infer the report to be contrasting them with – but this is not stated) and thus this does not concern me.

Their approach to analysis is said to be based upon Higgins et al (2001)(2), which, while predating the MTC name , does consider analyses including up to 3 different treatments, and which generalises to the full MTC model that has been used more recently. Therefore,*if* implemented correctly, the methodology used is sound however the model is quite a lot more complex than that of Higgins, and I am concerned how they define the alternative treatments in the analysis as described in detail below.

The MTC uses the 7 trials used in the initial submission (LEAD 1 – 6 & NN2211-1860). No consideration of further (non NN) trials is given. Page 6 of the "ERG comments on the Novo Nordisk responses to the ACED on liraglutide" (referred to subsequently as the ERG comments) outlines what further trials are available to include in the MTC network. It is impossible for me to predict the effect these excluded trials would have on the conclusion of the analysis. Best practice here would be to conduct a systematic literature search prior to the synthesis, but this would be a major undertaking.

Further, not all arms of the 7 trials included are included in the MTC analysis. No explanation for not including arms is given, although it would appear that it is the Liraglutide 0.6mg arms which have been dropped. This is presumably because this is not a licensed dose. Treatments do not have to be in the decision space (i.e. valid treatment options) to contribute to an MTC analysis (3), so a justification for dropping them would be welcome. However, as discussed next, this analysis diverges considerably from a typical MTC model which may have implications for this decision.

The analysis presented is potentially complex with several covariates being considered and potentially many different treatment option combinations. The following discussion is based around the assumption that the information provided in Tables 80 and 81 (pages 38 and 39) is correct. In

these tables the doses of Liraglutide are considered distinctly, but any variation in doses of all other drugs is not. Therefore if important dosing differences of the other drugs exist, and are of clinical importance (and the ERG comments document (page 3) highlights that the dose of rosiglitazone used in LEAD-1 (4mg) is less than the 8mg commonly used in the UK) then this may be a simplification of some concern (although other things concern me more as discussed below).

Figure 1 below sketches out the treatment arms used in the analysis from the seven trials (based on Table 81 in the report). An important point to note here is that the only replications of any treatment options are of the 1.2g + M and 1.8mg + M regimens which are in both trials LEAD2 and 1860. A network diagram (3) for these trials is presented in Figure 2.

Figure 1 Treatment regimens used in the trial arms used in the MTC analysis

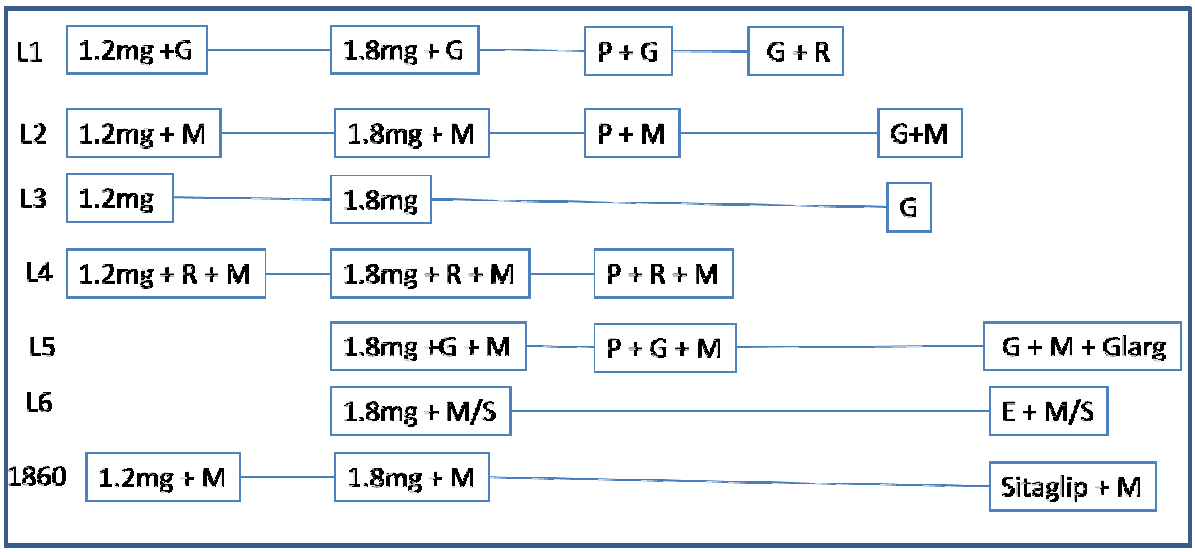
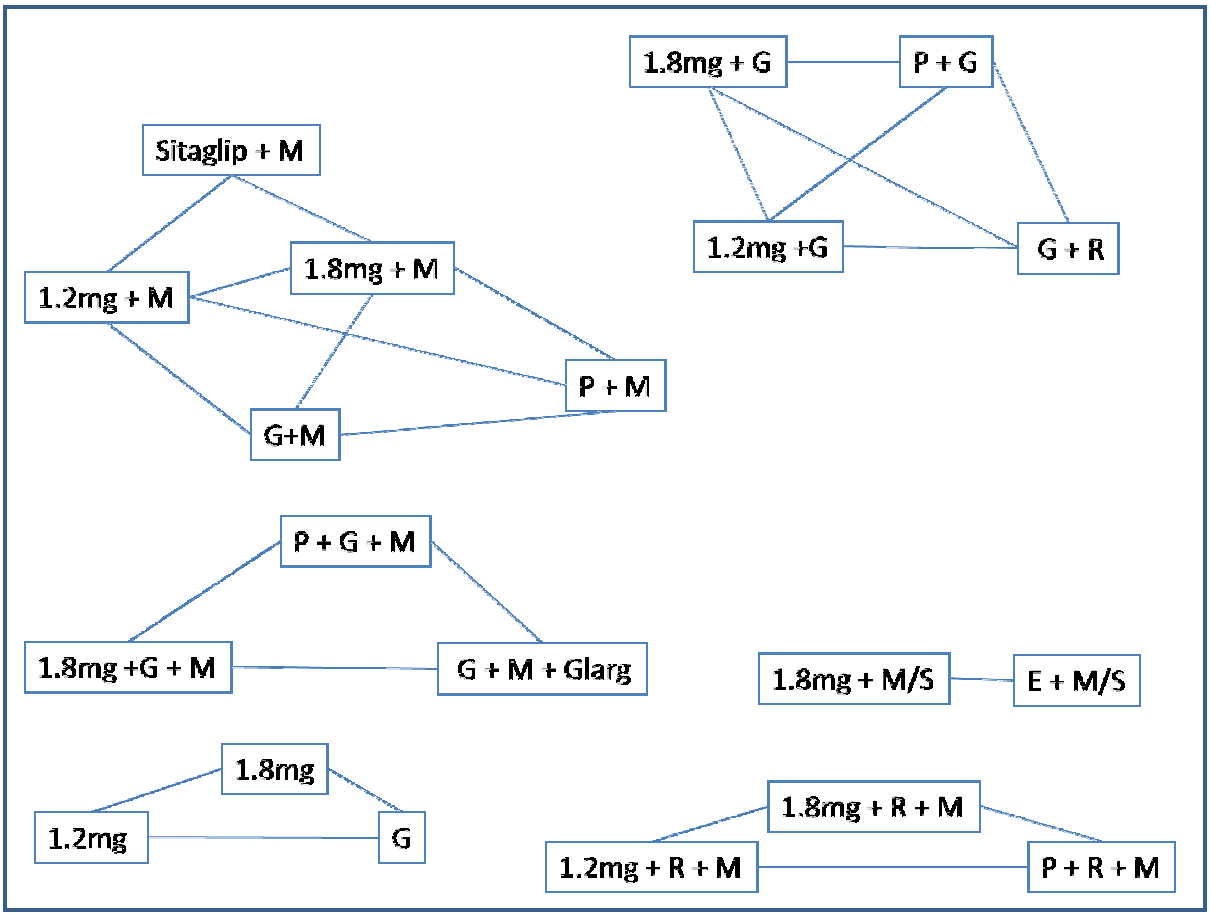


Figure 2 Network diagram for treatment regimens in the MTC analysis



Note that for a standard MTC analysis the network needs to be connected. (4) That is to say, all treatment options being considered need to be connected by a line (which implies a randomised comparison). In Figure 2, 6 distinct "islands" exist, implying the network is not connected. Therefore, in order for the analysis presented to be valid, some further assumptions must be made (and those assumptions may or may not be valid).

The original report does not discuss this issue explicitly, but SAS code is provided for the model they fit. It is still difficult to understand exactly what model has been fitted (an equation and full explanation of variable definitions would be very welcome at this point!). Specifically, it states ggtrea2x = randomised treatment and I have received clarification that this is coded as the columns of Table 81 of the NN document.

This implies that combinations of drugs were not modelled distinctly; rather all combinations given in each of the columns of Table 81 are considered the same. For example, for the Liraglutide 1.2 mg column, 1.2mg, 1.2mg +G, 1.2mg + M , 1.2mg + R + M treatment arms are all coded as the same treatment (even though these include mono, dual and triple therapy options). This implies that 1.2 mg of Liraglutide has the same relative effect irrespective of the combination it is applied to etc. (Once this is done the network essentially becomes connected with nodes for each of the columns in Table 81.)

It is understandable why such an approach to modelling has been taken with so many potential treatment options, but the modelling makes stronger assumptions than a standard MTC analysis (although these are not stated). The ERG comments document (page 5) considers the comparability of the patients in the different trials by examining baseline characteristics. This suggests baseline Hba1c values are broadly similar across trials although this report suggests there is a suggestion that the impact of liragulutide on Hba1c is diminished when used as triple compared to dual therapy. It may be valuable to elicit expert clinical opinion on how reasonable this assumption is.

The model also appears to include adjustment for several covariate effects including previous treatment and baseline HbA1c although the implications of including these are not discussed. (The ECG comments document outlines the differences in prior treatment regimes in the included trials (page 6).)

Conclusion

The MTC presented does not use all available relevant trial data and it makes strong assumptions about the equal effectiveness of interventions when used in different combinations. However, these two issues do not necessarily imply the analysis is invalid (i.e. the treatment effects estimated could be unbiased). It is difficult to assess the impact of the limited network without running an analysis of the "full" network (and this is beyond the scope of the work requested). Regarding the impact of the assumptions regarding equal effectiveness of interventions used in different combinations, since an analysis relaxing this assumption is not possible (i.e. the network becomes disconnected as discussed above) this is also difficult to assess which is why seeking expert clinical opinion is recommended.

References

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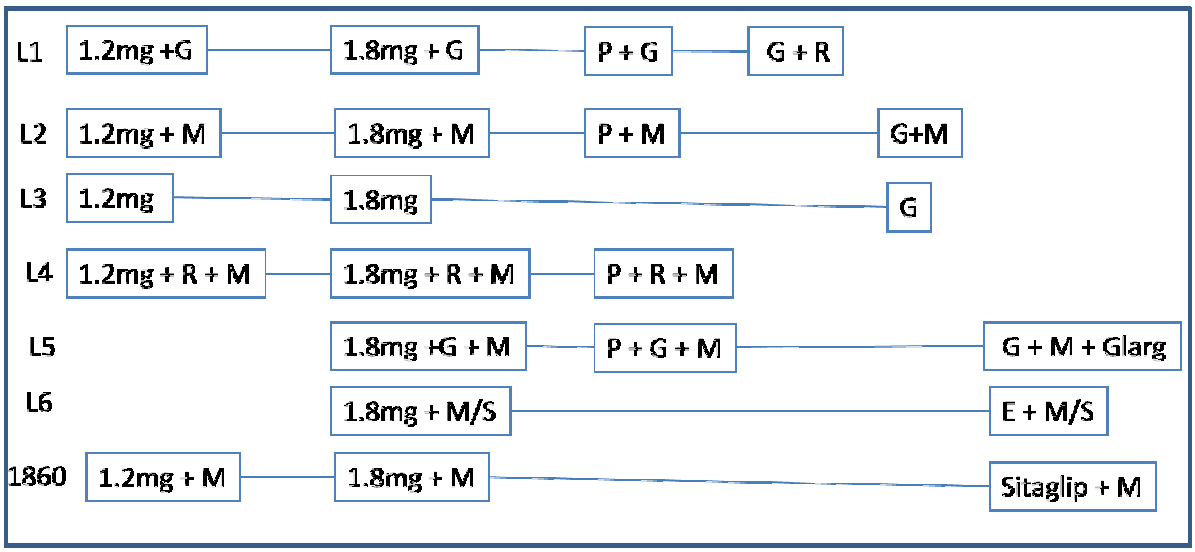

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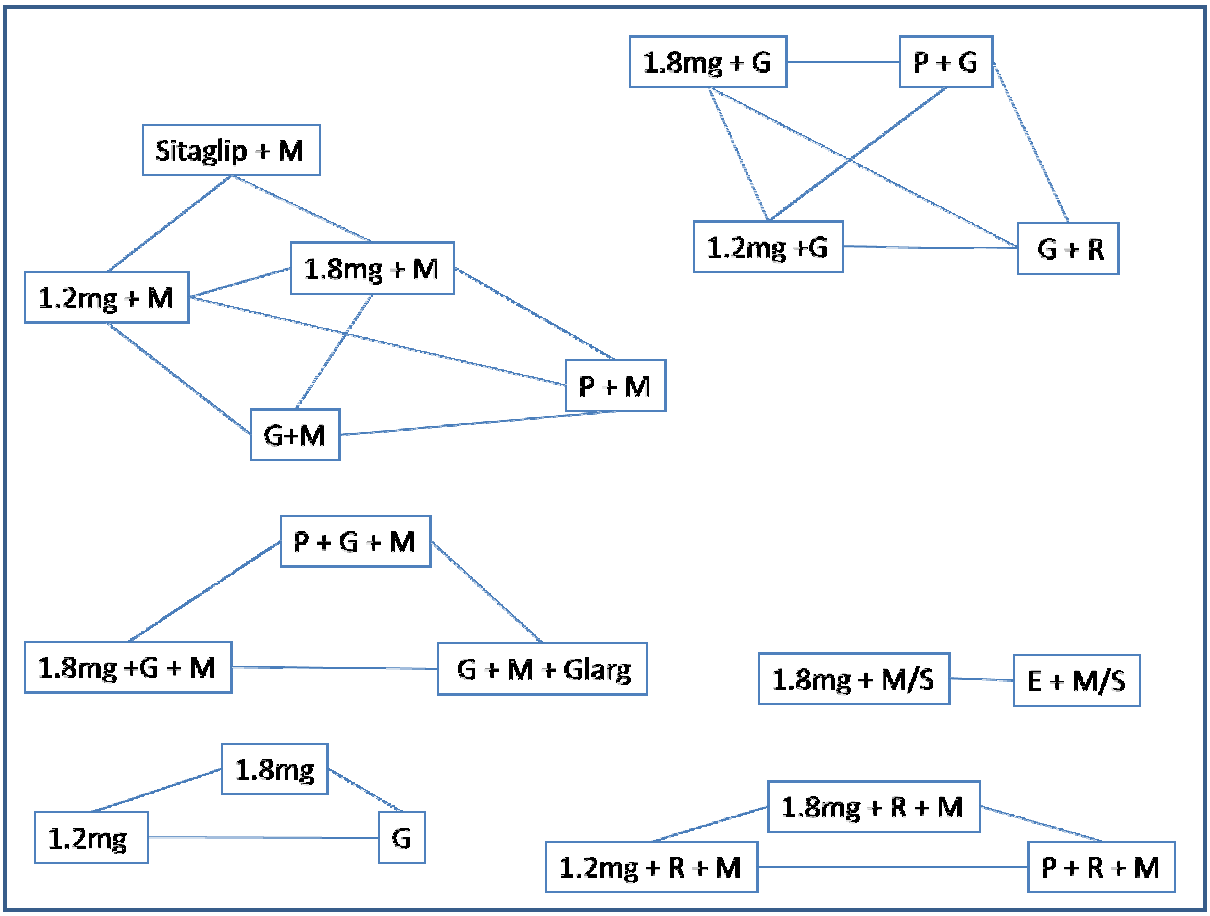

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