Changes to the ERG report

Page 2

The phrase

“Given the absence of head-to-head trials between dapagliflozin and active comparators, the submission relies on network meta-analysis (NMA)”

has been replaced by

“Given the absence of head-to-head trials comparing dapagliflozin with other relevant comparators, the submission relies on network meta-analysis (NMA)”

Page 19

The phrase

”In April 2012, the CHMP issued a recommendation that dapagliflozin should be approved”

has been replaced by

“Marketing authorisation was granted in November 2012”

Page 22

The phrase

“Furthermore, no systematic searching was undertaken after May 2011”

has been replaced by

“Furthermore, in the main submission, there is no evidence that systematic searching was undertaken after May 2011”

Page 44

The phrase

“No up-to-date searches were performed and only studies involving some kinds of triple therapy were included”

has been replaced by

“Trials since 2009 that resulted in oral antidiabetic drugs getting a triple therapy license were added (saxagliptin and linagliptin)”

Page 104

The paragraph entitled ‘Conclusions of the cost effectiveness section’ has been deleted.

Page 107

The phrase

“It may be most cost effective to try a safe cheap drug first and check whether there is a sufficient response before trying a new more expensive drug, regardless of the estimated cost effectiveness of the direct pairwise comparison”

has been replaced by

“It may be most cost effective to try a cheap drug with a known safety record first and check whether there is a sufficient response before trying a new more expensive drug, regardless of the estimated cost effectiveness of the direct pairwise comparison”

”

Safety

- The incidence of genital and urinary tract infections was reported to be higher after administration of dapagliflozin 10 mg compared with placebo (but infections were not serious and of mild intensity);
- The manufacturer reported that in a meta-analysis of 14 Phase 2 and Phase 3 clinical trials, dapagliflozin was not associated with an increased risk of cardiovascular events (using a composite outcome of cardiovascular death, MI, and stroke). No further details of this meta-analysis were, however, provided;
- The overall rate of all cancers was similar between dapagliflozin and placebo/comparators but the total number of clinical trials which contributed to these rates was not given;
- The rates of bladder, prostate, and breast cancer were higher in the dapagliflozin group compared with placebo/comparators (with wide confidence intervals for the incidence rate ratios);
- There is a concern that the rates of bladder and breast cancer within the dapagliflozin programme are higher than those expected in the general T2DM population
- The potential risk of cancer required further investigations

In summary, dapagliflozin is a clinically effective drug which improves glycaemic control and provides benefits in terms of weight changes and systolic blood pressure. With the current available evidence, no firm conclusions can be drawn on the risk of cancer after dapagliflozin administration.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

While most aspects of the manufacturer's review were robust and conducted to acceptable standards there were some areas of concern:

- The main short-coming was the absence of RCTs against active comparators, and in particular against the DPP-4 inhibitors, which the ERG regards as the key comparators;
- One trial against a sulphonylurea was included, but given the very low cost of SUs and their known safety record, the ERG would expect SUs to be tried before dapaglifozin, a much more expensive drug with only short-term safety data. So, SUs would be precursors not comparators;
- Given the absence of head-to-head trials comparing dapagliflozin with other relevant comparators, the submission relies on network meta-analysis (NMA);

3 DEFINITION OF THE DECISION PROBLEM

3.1 Population

The manufacturer's submission states that dapagliflozin is indicated as a second or third drug treatment in adults over 18 years old with type 2 diabetes (T2DM) whose glycaemic control, with metformin or insulin, with or without a second oral agent, and together with diet and exercise, is not satisfactory.

The definition of the population is in line with the final scope of this appraisal and the license indications.

3.2 Intervention

The technology submitted is a highly potent, selective and reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2) - dapagliflozin - that is given at a dose of 10 mg once daily at any time during the day, with or without food. In the current submission there is no proposed dose adjustment based on renal function. Nevertheless, the manufacturer states that dapagliflozin is indicated in patients with mild renal impairment and not recommended in patients with moderate to severe renal impairment (defined as creatinine clearance <60 mL/min or estimated glomerular filtration rate <60 mL/min/1.73 m^2). Monitoring of renal function is recommended i) prior to initiation of dapagliflozin and at least yearly thereafter, and ii) prior to initiation of concomitant medications that may potentially reduce renal function. Due to the fact that dapagliflozin causes an increase in the urinary volume excretion, it is not recommended in patients receiving loop diuretics or those who are volume depleted.

The method of administration, monitoring and side-effects are those described in the summary of product characteristics.

There are currently no approved SGLT2 inhibitors for the management of T2DM. If approved, dapagliflozin will be a first-in-class therapy. Marketing authorisation was granted in November 2012.

3.3 Comparators

The manufacturer states that the main comparators for dapagliflozin used as a second line treatment option (add-on to metformin) are: sulphonylureas (SUs), thiazolidinediones (TZDs - now only pioglitazone) and dipeptidyl peptidase-4 inhibitors (DPP-4). The main comparators for dapagliflozin used as a third line treatment option (add-on to insulin) are: TZDs and DPP-4 inhibitors. NICE Clinical Guideline 87 recommends pioglitazone with insulin in patients

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Description of manufacturer's search strategies and critique

Overall the sources searched for this submission were appropriate although the electronic searches lacked sensitivity. Furthermore, in the main submission, there is no evidence that systematic searching was undertaken after May 2011. However, four studies (including three of the five main dapagliflozin RCTs considered by the manufacturer) were published after this date and it is unclear which methods were used to identify these additional papers. There were no literature searches undertaken for additional information on adverse events from case series studies therefore the evidence-base for evaluation of adverse events might be incomplete. A detailed critique of the manufacturer's search strategies is given in Appendix 1.

A recent systematic review of SDGLT2 drugs was identified which did not identify any additional trials that met the inclusion criteria for this assessment.[20]

4.1.2 Inclusion criteria

The inclusion criteria used in the systematic review of clinical effectiveness are tabulated in Table 1.

RCTs involving metformin as a comparator in the insulin add-on NMA were also excluded at this stage. The manufacturer maintained that as metformin is not a comparator of interest in the UK for the insulin add-on indication since it would usually be used in combination with insulin, before dapagliflozin.

4.3.3 Triple therapy

This part of the submission was presented as an addendum. The data come from a subset of patients from two RCTs which included participants who were at high risk of cardiovascular events. The report was conducted in a shorter time frame than for the original submission. Therefore, the manufacturer recommends caution in interpreting the results of dapagliflozin in triple therapy.

Four studies were selected by the manufacturer. One was an ongoing trial of dapagliflozin used in combination with metformin and SU, which is not expected to report results until late 2013. Of the remaining three studies, one (Study 10) focused on patients who had failed to reach glycaemic control following metformin and DPP-4, and was not considered further; the remaining two studies (Studies 18 and 19) enrolled patients who were being treated with metformin and SU at baseline. It is worth noting that all patients suffered from prior cardiovascular disease and therefore could differ from those recruited in other dapagliflozin studies.

The manufacturer's results appear to come mainly from simple pooling of the results of the triple therapy patients from Studies 18 and 19, but the methods of the presented analyses are not particularly clear.

Instead of conducting a new NMA including all evidence from all appropriate comparators, the manufacturer referred to a Canadian report.[19] The literature search for this report only included studies up to 2009.

Overall, the ERG considers the methodology of the triple therapy review as less robust as that of the main submission. It is worth noting, however, that this was submitted as an addendum to the main submission following a request by NICE. The manufacturer did not initially intend to provide findings of the use of dapagliflozin in the triple therapy setting as an important triple therapy RCT is currently ongoing. Trials since 2009 that resulted in oral antidiabetic drugs getting a triple therapy license were added (saxagliptin and linagliptin). The two dapagliflozin studies that were included were subsets of larger studies and only included patients with cardiovascular disease that were older and might be expected to have poorer outcome than

The input values have been reasonably well explored within the manufacturer sensitivity analyses, and in particular the HRQoL impact of weight changes. Changes to HRQoL impact and the average cost per severe hypoglycaemic event would result in proportionate changes to the total costs, total QALYs, net costs and net QALYs reported above.

safety). However, given the non-insulin-dependent mechanism of action, there may be a particular place for the SGLT2 inhibitors in long-standing T2DM where beta-cell capacity has declined to the point where drugs whose effect is in whole or in part through stimulating insulin secretion (SUs, GLP-1 analogues, DPP 4 inhibitors), have lost effectiveness.

Summary of cost-effectiveness issues

There is no obvious justification presented for the revision to the cohesive set of risk equations of the UKPDS 68 and the introduction of other risk equations. This may have tended to downplay the role of HbA1c and increase the role of SBP within the DCEM.

The implementation of the UKPDS 68 risk evolution equations and some of the UKPDS 68 event risk equations does not appear to be in line with a literal reading of the UKPDS 68. Initial treatment effects upon some of the risk factors in the first year are maintained for the patient lifetime. This also applies to the differences in patient weights estimated between the treatment sequences that arise from any initial weight gains in the first year.

The ERG views the estimates of the direct HRQoL impacts from weight changes as too large given the results of other published studies and previous NICE assessments. The ERG would also be interested in whether the study these are drawn from collected data on UTIs and GIs, and whether any exploration of the impacts of these upon HRQoL was conducted.

The modelling of a common prior line of dual therapy within the consideration of the triple therapy comparisons is peculiar. The manufacturer justification for this lacks credibility.

Pairwise comparisons are undertaken but this may be a poor guide to the optimal sequence of treatments. It may be most cost effective to try a cheap drug with a known safety record first and check whether there is a sufficient response before trying a new more expensive drug, regardless of the estimated cost effectiveness of the direct pairwise comparison. There may also be some concerns around the treatment sequences which have been modelled, and the assumption that once having started dapagliflozin patients will be willing to discontinue treatment with dapagliflozin when going onto insulin therapy.

The HbA1c therapy switching values that are applied within the base case modelling are quite far above the 7.5% of the NICE guideline. The manufacturer does undertake sensitivity analyses around this. The scenario analyses that apply switching values more in line with the NICE guideline, coupled with other changes including some patients having prevalent events at baseline and applying the direct