UNIVERSITY OF BIRMINGHAM

Literature search on the risk of hypoglycaemia in patients with type II diabetes treated with sulphonylureas with or without exenatide

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

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For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

Aggressive Research Intelligence Facility (ARIF)
West Midlands Health Technology Assessment Collaboration (WMHTAC)
Department of Public Health and Epidemiology
University of Birmingham
Birmingham
B15 2TT

arifservice@bham.ac.uk
0121 414 3166

1 Aims

The aims of this report were to address the following questions submitted by the Driver Medical Group:

1.1 Primary Questions

To determine

1) The risk of hypoglycaemic events in diabetic patients being treated with sulphonylureas (SFU)+ exenatide + any other treatment (including no treatment) except insulin.

2) The risk of hypoglycaemic events in diabetic patients being treated with SFUs + any other treatment (including no treatment) except exenatide or insulin.

Further details are given in the request submitted by the Drivers Medical Group (Appendix 1 – Details of Request)

2 Background

Background information is given in the documentation supplied by the Drivers Medical Group contained in Appendix 1 – Details of Request.

Hypoglycaemia is a frequent complication of the treatment of diabetes. Although more common in type I diabetes, it also occurs at a lower rate in type II diabetes. Acute hypoglycaemia refers to low blood glucose concentrations (below 50-60mg/dL or 3.0mmol/L). Manifestation of hypoglycaemia varies between individuals and within individuals across time and can impact on visual functions, cognitive functions and general orientation (e.g. slower reaction time, impaired co-ordination), which may in turn influence the ability of the individual to drive safely. In some severe cases it may lead to loss of consciousness. Unrecognised hypoglycaemia represents a significant driving hazard. Most episodes of mild-moderate hypoglycaemia can be self-treated by ingestion of glucose or carbohydrate; severe hypoglycaemia may require the assistance of another person and the administration of intravenous glucose or subcutaneous glucagons.[1]

The risk of severe hypoglycaemia in type II diabetes is thought to be nil with dietary treatment, and nil or very low with some oral drugs (alfa-glucosidase inhibitors, metformin, thiazolidinediones). Treatment with sulphonylureas (SFUs) is more likely to be associated with hypoglycaemic episodes.[1] The incidence of hypoglycaemia will vary between different types of SFUs, and is likely to be higher in individuals taking additional medication and in older individuals, particularly those with co-morbidities.[2,3]

Exenatide, an incretin mimetic, has recently been licensed for use in type II diabetes, in combination with metformin and/or SFUs. Trials have shown a small increased risk of hypoglycaemia associated with the use of exenatide with a SFU. This may be a potentially high-risk treatment for drivers holding Group 2 (LGV or PCV) licenses.[4]

The aim of this report is to identify the risks (incidence) of hypoglycaemia associated with the use of a) SFUs with exenatide with or without another treatment (not insulin) and b) SFUs with or without another treatment (not exenatide or insulin) in individuals with type II diabetes. Where possible the distinction between mild-moderate hypoglycaemia (self-treated) and severe hypoglycaemia (requiring assistance by another person) will be made.

3 Methods

Outline methods were submitted to the Drivers Medical Group by email and acceptance subsequently confirmed by email (Appendix 2 – Outline methods).

Briefly these were:

- To search for relevant reviews, ideally systematic reviews, reporting rates of hypoglycaemic events in patients with type II diabetes being treated with
    - a SFU + exenatide + any other treatment (including no treatment) except insulin *OR*
    - a SFU + any other treatment (including no treatment) except exenatide or insulin
- Where primary studies are required, to search for large randomised controlled trials (RCTs) or cohorts with long-term follow-up, ideally UK based
- To comment on methodological quality of the studies identified and on the likely accuracy of the reported outcomes

It should be noted that for a direct comparison of hypoglycaemia risk with the two treatment strategies of interest (SFUs with or without exenatide), results from randomised controlled trials are likely to be of most relevance; it will be difficult to compare hypoglycaemia risks across different studies, as there is likely to be substantial heterogeneity in terms of type of SFU, population characteristics and study design. It was beyond the scope of this report to conduct searches for primary studies reporting hypoglycaemic rates with individual drugs belonging to the class of SFUs; however, where relevant systematic reviews have addressed this question, we have reported the results. This report focuses on reporting rates of hypoglycaemic episodes and we did not search for studies assessing the likely consequences for driving outcomes resulting from hypoglycaemic events.

3.1 Searches

3.1.1 Existing Reviews.

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (Appendix 3 – Search strategies). The search strategy employed MeSH headings and text terms for ‘exenatide’ and ‘Byetta’ or terms relating to SFUs and a filter to identify reviews. MEDLINE,

EMBASE and the Cochrane Library were searched and reference lists of relevant identified reviews scanned for further relevant studies, including large UK based RCTs or cohort studies.

3.1.2 Primary Studies

No searches of the main electronic databases were required to specifically identify primary studies.

The UK Prospective Diabetes Database Study (UKPDS) database of publications[5] was searched. The UKPDS was a 20-year trial, which recruited 5,120 patients from 23 centres in the UK and has multiple reports associated with the study.

The detailed search strategies can be found in Appendix 3 – Search strategies. Searches were predominantly undertaken by an information specialist with additional searches by a research reviewer. Both interacted to ensure searches were conducted appropriately. An information specialist and a research reviewer scanned the search results for relevance based on information in the title and abstract. Articles that adhered to the following broad criteria were obtained in full for further scrutiny:

Design: Review or large UK based RCT or cohort study
Population: Patients with type II diabetes treated either with:
- a SFU with exenatide with any other treatment (not insulin) OR
- a SFU with any other treatment (not exenatide or insulin)

Outcome: Hypoglycaemic episodes (split by mild-moderate and severe where possible)
Exclusion: Patients treated with exenatide and insulin or patients treated with exenatide and metformin only

Full copy articles were assessed for their match to the questions being addressed (external validity) and the most informative articles (closest match to population [Section 1.1Primary Questions], longest follow-up) subjected to further scrutiny and reporting.

4 Results

4.1 SFUs with exenatide with other treatment (not insulin)

4.1.1 Reviews identified

The search strategy identified 147 references, which were scanned for relevance. Nineteen full copies were obtained for detailed consideration.[6-24]

Ten relevant reviews were identified. Of these, four were purely narrative (Barnett 2007[6], Bray 2006[9], Lam 2006[19], Stephens 2007[21]) with the remaining six reviews having at least some elements of systematic review methodology, e.g. details on the search strategy used (Amori 2007[23], Cvetkovic 2007[24], Iltz 2006[16], Mikhail 2006[20], Joy 2005[17], Yoo 2006[22]). The review by Amori 2007[23] had the most comprehensively reported

methodology and was considered to be a good quality systematic review. Of the remaining reviews, the study by Cvetkovic 2007[24] had the most comprehensive search strategy.

None of these reviews primarily addressed the issue of hypoglycaemic rates or adverse events, but related more generally to the effectiveness of exenatide (compared to placebo or insulin treatment), with patients receiving background treatment with SFUs and/or metformin. However, adverse events including hypoglycaemia were also reported. All reviews were scanned for included studies and were found in the main to refer to the same, relatively small body of evidence from RCTs. None of the reviews looked at evidence from cohort or other types of studies (other than open-label extensions of the relevant RCTs).

4.1.2 Primary studies identified

Given the small number of relevant RCTs identified from the reviews, we were able to study these directly. Five RCTs (Barnett 2007[7], Buse 2004[10], Heine 2005[15], Kendall 2005[18], Nauck 2007[25]) had a treatment arm with exenatide with a SFU (with or without another treatment-not insulin). One relevant study reporting on an open label extension of the Buse 2004[10] and Kendall 2005[18] trials was also identified (Riddle 2006[26]). We did not look at very small, early phase trials of exenatide (all n≤37). See Appendix 4 (section 6.4) for a list of excluded studies.

4.2 SFUs with other treatment (not exenatide or insulin)

4.2.1 Reviews identified

The search strategy identified 253 references, which were scanned for relevance. Thirteen full copies were obtained for detailed consideration.[2,3;27-37] One further review was identified through reference checking[38].

Of the 14 reviews considered, seven had as a focus hypoglycaemia (or more generally safety or adverse events) associated with SFUs (Salas 2002[37], Bolen 2007[28], Mukai 2007[36], Gangji 2007[31], DelPrato 2002[38], Holstein 2003[3], Harrower 2000[2]). Four of these (Salas 2002[37], Bolen 2007[28], Mukai 2007[36], Gangji 2007[31]) were systematic reviews and were looked at in detail. Three were purely narrative (DelPrato 2002[38], Holstein 2003[3], Harrower 2000[2]) and were not considered further.

4.2.2 Primary studies identified

Two of the five RCTs identified above (4.1.2) also had a treatment arm with a SFU (with or without another treatment-not exenatide or insulin).[10,18] Data on hypoglycaemia rates were extracted for these treatment arms in order to allow a direct comparison between rates for patients treated with and without exenatide. Additional relevant primary studies identified through reference checking and the UKPDS database were a UK cohort study[39] and two reports from UKPDS[40,41]. One additional UK cohort study identified by the Drivers Medical Group was also reviewed.[42]

4.3 Results: rates of hypoglycaemic episodes

4.3.1 SFUs with exenatide

Table 1 in Appendix 5 (section 6.5) reports the main population characteristics, length of study, treatment arms and reported rates of hypoglycaemic episodes in the five relevant RCTs.

The trials by Nauck 2007[25], Barnett 2007[7] and Heine 2005[15] all had well-described and adequate methods of randomisation and concealment. All were open-label trials, i.e. patients were aware of which treatment they were receiving. This may have implications for self-reported measures such as mild-moderate hypoglycaemic events, though less so for more objective measures such as severe hypoglycaemia where assistance by another person is required. In all three trials safety measurements were conducted for an ITT (intention-to-treat) population; however it is unclear how missing data was handled (around 80% of patients completed the trials), which may have implications for the accuracy of the reported hypoglycaemia rates. The trial by Barnett 2007[7] was a cross-over trial. There was no washout period between treatment periods, however a test for carry-over based on sequence effect was performed and no evidence of a carry-over effect from one treatment period to another was identified.

The trials by Buse 2004[10] and Kendall 2005[18] were described as randomised, and triple-blind (Buse 2004[10]) or double-blind (Kendall 2005[18]) respectively, but no further details were given. Blinded patients may be less likely to be biased in their reporting of mild-moderate hypoglycaemic events. In Buse 2004[10], hypoglycaemic events were measured in the evaluable population (68% of those randomised), in Kendall 2005[18], in the ITT population. Again, loss to follow-up may have implications for the accuracy of reported hypoglycaemia rates.

Trials were of 26 –52 week duration, with between 62 and 282 patients in the relevant (exenatide) treatment arms. All patients had type II diabetes, were on average in their mid to late 50's and were using a SFU with or without metformin. The dose of exenatide was either 5 or 10 μg b.i.d. All trial protocols advocated a progressive 50% decrease in SFU usage if hypoglycaemic episodes occurred. Two trials (Heine 2005[15] and Nauck 2007[25]) excluded patients if they had more than three hypoglycaemic episodes within six months prior to screening. All defined severe hypoglycaemia as the patient requiring assistance from another person, except the trial by Nauck 2007[25], which stated that the severity (mild, moderate or severe) was assessed by the investigator.

Episodes of hypoglycaemia were variably reported as incidence, episodes/person-year or number of patients with a hypoglycaemic episode.

Episodes/patient-year were 4.1 (Barnett 2007[7], mild-moderate hypoglycaemia), 7.3 (Heine 2005[15], includes 4 patients with a severe hypoglycaemic episode) and 4.7 (Nauck 2007[25], mild-moderate hypoglycaemia). These all related to a dose of 10 μg b.i.d of exenatide (starting with a 4-week run-in period of 5 μg b.i.d of exenatide).

Incidences were 30% (Barnett 2007[7], mild-moderate hypoglycaemia), 14% and 36% (Buse 2004[10], 5 and 10μg doses respectively), 19.2% and 27.8% (Kendall 2005[18], 5 and 10μg doses respectively) and 17% (Nauck 2007[25], mild-moderate nocturnal hypoglycaemia only). The definition of incidence (particularly with respect to time-frame and how patients with repeated incidences were counted) was not clearly stated for Barnett 2007[7], Buse 2004[10] or Kendall 2005[18]. Nauck 2007[25] stated that the incidence referred to the number of patients experiencing at least one episode of nocturnal hypoglycaemia.

No episodes of severe hypoglycaemia occurred in the trials by Barnett 2007[7], Buse 2004[10] or Nauck 2007[25] . Heine 2005[15] reported that 4/282 patients experienced a severe episode and Kendall 2005[18] reported one case of severe hypoglycaemia (486 patients in total).

Two trials (Buse 2004[10] and Kendall 2005[18]) also reported hypoglycaemia incidences in a SFU treatment arm (with or without metformin, no insulin or exenatide). These were 3% (Buse 2004[10], mild-moderate hypoglycaemia) and 12.6% (Kendall 2005[18], mild-moderate hypoglycaemia). Both these incidences are lower than the respective incidences reported for the exenatide treatment arms. There were no cases of severe hypoglycaemia.

The study by Riddle 2006[26] reports on an open-label extension of the Buse 2004[10]and Kendall 2005[18] trials (combined data). Of 733 patients originally in the exenatide arms, 518 entered open label extension and 222 completed; data reported here refer to an ITT population of 401. All patients in the open label extension received 10μg exenatide b.i.d. (after four weeks on 5μg exenatide b.i.d.); a proportion of these would have previously been in the 5μg exenatide b.i.d treatment arms of the RCTs. The incidence of hypoglycaemia varied between 8-15% between week 30 and 82 (reported for 10 week intervals, see Table 2). There was no definition of incidence; it was for example unclear how patients with more than one event in the same time-frame were counted. There were four (of 401) cases of severe hypoglycaemia (defined as requiring the assistance of another person) and a 0.5% withdrawal rate due to hypoglycaemia during open-label period.

There are limitations to this analysis, which may have implications for the accuracy of the data reported. Patients self-selected to continue with the open label study and there was large loss to follow-up over time. There was no control group, so we are unable to compare these rates to those in patients on SFUs only.

Table 2 Incidence of hypoglycaemia in open-label extensions of exenatide trials

	Placebo controlled trials week 0-30			Open-label uncontrolled extensions weeks 30-82				
Week	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-82
Incidence hypoglycaemia (%)	14	12	6	15	8	10	11	14

Adapted from table 2 in Riddle 2006[26]

Comments & Conclusions

- The relatively limited evidence for rates of hypoglycaemia in patients taking exenatide (with an SFU) is based on five (26-52 week) RCTs with a total of 1339 patients in the relevant exenatide treatment arms.
- Hypoglycaemic episodes per patient-year ranged from 4.1 to 7.3; incidence of hypoglycaemia between 14% and 30% (it should be noted that 30% is based on a relatively small sub-group of patients (n=62) only); confidence intervals were not reported.
- Severe hypoglycaemic episodes were observed in one and four patients (two trials respectively) or not at all (three trials).
- Where reported (two trials) incidence of hypoglycaemia was higher in those patients taking a higher dose of exenatide; comparisons within an RCT are likely to provide the best evidence on differences between doses, it should be noted however that confidence intervals are not reported and the studies were not specifically powered to detect a difference between hypoglycaemia rates with different dosages.
- Pooled data from open-label extensions (up to 82 weeks) of two trials found incidences of between 8% and 15% (exenatide arm only).
- Where there was a comparison arm consisting of patients taking a SFU (two trials), incidences (3% and 12.6%) were lower than in those patients taking an SFU with exenatide; within-RCT comparisons are likely to provide the best evidence on differences in rates between the treatment arms for the patient groups studies; confidence intervals were however not reported.
- Comparisons across trials are hampered by the use of different outcome measures (episodes per patient-year, incidence, number of patients with an event) and likely heterogeneity between patients for example in terms of previous medication or background medication used (e.g. different types of SFU, SFU with or without metformin).
- Hypoglycaemia is primarily a self-reported measure and estimates may vary depending on the method and/or frequency of reporting, again hampering comparisons across different trials.
- “Incidence” was not usually defined and it was not always clear which time-frame this applied to or how repeat episodes were dealt with.
- All studies had some loss to follow-up, particularly the longer open-label extensions, which is likely to impact on the accuracy of the reported rates; sensitivity analyses were not performed.
- Hypoglycaemia and loss to follow-up have been found to be associated, which may lead to an underestimation of absolute rates and may change the differential effect between groups.[31]
- Doses of SFU could be reduced in response to hypoglycaemic events (with the aim of reducing the frequency), so it is possible that the frequency of hypoglycaemic events is higher at the beginning of the treatment periods; no reduction over time was seen in the open label extensions, however, the high loss to follow-up may reduce the accuracy of this data.
- The trials were conducted either in the US or were multi-national; applicability of these results to a UK population only are therefore unclear.
- In two trials patients were not eligible if they had experienced more than three episodes of severe hypoglycaemia within six months before screening; it is unclear whether trial populations are representative of all patients who could be eligible for this type of treatment.
- Large, long-term cohort studies with good follow-up in a UK population would be required for more accurate information on risk of hypoglycaemia.

4.3.2 SFUs without exenatide

Review findings

Four reviews[28,31;36,37] with systematic review methodology components were identified (see Table 3, Appendix 5, section 6.5 for details).

The review by Bolen 2007[28] was a well-conducted systematic review, in that it had a comprehensive search strategy (though limited to English language studies) and well-documented study selection criteria, data extraction, quality assessment and data synthesis process. It was focused on efficacy and safety (including hypoglycaemia) of oral medications for type II diabetes in general rather than SFUs only. Second-generation SFUs only were included. The review included 167 RCTs and observational studies reporting adverse events, however, it is unclear how many of these included data on hypoglycaemia in SFU users. A wide range of hypoglycaemia risk in second-generation SFU users was reported (0-36%). Results from UKPDS were reported separately with annual rates of minor and major hypoglycaemia of 17.5% and 2.5% respectively (glibenclamide group). These UKPDS results are not consistent with those reported in Table 4 (primary studies), possibly due to multiple publications of trial results at different time-points. Absolute risks/incidences of hypoglycaemia for different types of SFUs were not reported. A meta-analysis of RCTs comparing different SFUs or combinations of SFUs with other drugs found that: hypoglycaemic episodes were more frequent in patients receiving SFUs (particularly glyburide) compared to metformin or thiazolidinediones; glyburide and glibenclamide were associated with slightly higher risk of hypoglycaemia compared to other SFUs; and the incidence of hypoglycaemia was higher with combinations that included SFUs compared to metformin or SFU monotherapy (full results in Table 3). No distinction was made in this analysis between different severities of hyopglycaemia.

Gangji 2007[31] was also a well-conducted systematic review, though again limited to English language studies. It had a narrower focus than Bolen 2007 and included RCTs comparing glyburide with another SFU or insulin or meglitinides. Twelve relevant RCTs were included. Patients experiencing at least one hypoglycaemic episode (any severity) were between 3% and 29% (glyburide, 12 studies), 2%-7% (glicazide, two studies), 11%-12% (Glimiperide, two studies), 0%-12% (chlorpropamide, three studies) and 1% (glipizide, one study). The time-period for these episodes occurring was not stated. Meta-analysis showed that glyburide consistently caused more hypoglycaemia than other SFUs. In two included RCTs that reported major hypoglycaemia there were greater numbers of hypoglycaemic events in patients treated with glyburide compared to other SFUs. Length and loss to follow-up of individual RCTs are not reported, making it difficult to assess what implications this might have for accuracy of results.

The systematic review by Mukai 2007[36] was also well conducted, though it was not stated that any of the review processes were performed in duplicate. The search strategy was slightly less comprehensive than that of Bolen and Gangji and was limited to English and Japanese language studies. The focus was on RCTs comparing a SFU with a SFU+ another treatment (biguanides, α-glucosidase inhibitors or thiozolidinediones). Six RCTs were identified, which reported an incidence of 0%-4.2% of patients with a hypoglycaemic episode with SFU alone. The time-period for these episodes occurring was not stated. Meta-analysis found consistently fewer hypoglycaemic episodes for patients treated with SFU alone compared to

SFU with another treatment. Length and loss to follow-up of individual RCTs are not reported, making it difficult to assess what implications this might have for accuracy of results. No distinction was made between mild-moderate or severe hypoglycaemia.

Salas 2002[37] was a less well-conducted systematic review albeit with a comprehensive search strategy (with no language restrictions) and documented study selection and data synthesis process. There were however no details on data extraction or quality assessment and processes were not performed in duplicate. Reporting of results is part narrative and part tabular and poorly structured. The number of relevant studies identified is not stated and study design is not always specified for included studies. The review reports results from Van Staa 1997 and UKPDS (see primary studies section); results for UKPDS (based on four reports) are not consistent with those extracted from the publications directly. Again, this may be due to multiple publications reporting results in slightly different formats or for different time-points. An incidence of hypoglycaemia for glimepiride of between 0.9% and 14.2% was reported (based on six studies); for glibenclamide 31.5%, 23 events in 13 patients over 12 months and 110 complaints of hypoglycaemia in nine patients over 15 months (based on three studies respectively); for glipizide 11/204 patients or 11/143 patients (two studies). Differences in the way hypoglycaemic events were reported (incidence, events or number of patients) makes comparisons between types of SFU difficult. No distinction was made between mild-moderate or severe hypoglycaemia.

Primary study findings

For results from the two trials comparing a SFU+ exenatide arm to a SFU only treatment arm, see section 4.3.1.

Four reports[39-42] of UK based cohorts or RCTs reporting hypoglycaemia rates in SFU users were identified (see Table 4, Appendix 5, section 6.5). Two of these reports refer to UKPDS (UKPDS 33 1998[40] and Wright 2006[41]).

UKPDS was a large 20-year trial starting in 1977 and enrolling >5000 patients. There are multiple reports of trial results, here we have identified two reports that appear to best report hypoglycaemic episodes. Results are based on n=1234 (10 year follow-up) and n=1687 (6 year follow-up) patients respectively randomised to a SFU (chlorpropamide or glibenclamide). The trial had an appropriate method of randomisation and concealment. It was open label, which may have an effect on self-reporting of hypoglycaemia rates. Results are reported for both ITT and assigned treatment populations (UKPDS33 1998[40]) or assigned treatment population only (Wright 2006[41]). It is unclear how missing data was handled for the ITT analysis. There was a difference between the two reports in how severity of hypoglycaemia was defined.

UKPDS 33 1998[40] found an incidence of 16% and 1.0% (any and severe episode respectively, chlorpropamide) and of 21% and 1.4% (any and severe episode respectively, glibenclamide) for an ITT population and an incidence of 11% and 0.4% (any and severe episode respectively, chlorpropamide) and of 17.7% and 0.6% (any and severe episode respectively, glibenclamide) for an assigned treatment population.

Incidence was defined as the mean proportion of patients per year with an episode, over a 10-year period. 28% of patients were still on their allocated therapy at 10 years.

Wright 2006[41] found, over six years, the annual proportion of patients reporting at least one hypoglycaemic episode was 7.9% (95% CI 5.1, 11.9; allocated therapy population) for grades I-IV of hypoglycaemia and of 1.2 (95% CI 0.4, 3.4; allocated therapy population) for grades II-IV of hypoglycaemia (see Table 4 for definitions of severity). No distinction was made in Wright 2006[41] regarding different types of SFU. It is unclear why there is such a discrepancy between the two reports for any hypoglycaemic event (7.9%, Wright 2006[41] and 11% and 17.7%, UKPDS 33 1998[40]) unless there is a difference in the definition of incidence or assigned treatment population, or there is an increase in hypoglycaemic episodes after six years. Incidence of severe hypoglycaemia cannot be compared as the definitions differ.

The other two relevant studies are a relatively small (n=108) UK based prospective cohort (UK Hypoglycaemia Study Group 2007[42]) with a follow-up of 9-12 months and a large retrospective UK cohort based on a study population of n=33,243 (Van Staa 1997[39]).

The prospective cohort[42] reports mean episodes/person-year (95% CI) of 1.92 (1.2, 2.6) for mild-moderate hypoglycaemia and 0.1 (0.0, 0.4) for severe. There was little loss to follow-up. No details on the type(s) of SFU were provided. The retrospective cohort[39] reports an annual risk of hypoglycaemia (=number of cases divided by number of therapy years) of 1.8% overall (glibenclamide 1.6%, glicazide 1.7%, tolbutamide 0.7% and chlorpropamide 1.3%). This is based on reports made by GPs after a patient visit and is thus more likely to be representative of more severe cases (mild cases are less likely to trigger a visit or report to the GP) and cannot be compared to prospective data results.

Comments & conclusions

- A very wide range of hypoglycaemic risk is reported across different studies (0-36%)
- Hypoglycaemic risk is likely to depend amongst other factors on the type of SFU, whether the SFU is used alone or in combination, patients characteristics (age, co-morbidities), previous medication, study design (prospective, retrospective, length of study, amount of loss to follow-up, method of data collection) and it would thus not be appropriate to attempt to combine risks from different studies into a single risk of hypoglycaemia for (any) SFU users
- It is difficult to compare results across studies due to reporting of different outcomes (incidence, risk, rate, episodes/person-year, events in patients etc.) and different definitions of severity of hypoglycaemia
- In the reviews, risk differences were more often reported than absolute risks for different SFUs or SFUs in combination with other treatment
- Best estimates of absolute risks for one type of SFU are most likely to be based on UKPDS (for glibenclamide and chlorpropamide)
- Based on the data identified it is not possible to compile a hierarchy of risk between different SFUs; however the data appear to suggest that glyburide (and glibenclamide) are associated with a higher risk of hypoglycaemia compared to other SFUs and that SFUs in combination with other drugs are associated with a higher risk than SFU monotherapy

• There is a large volume of primary studies, however, many of the reviews included mainly RCTs and there appears to be a lack of relevant long-term cohort studies; the subset of RCTs included will depend on the exact question of the review (e.g. comparison of a specific SFU with other treatments or all SFUs alone compared to combination therapy etc.)

4.4 Limitations of this report

This is not a systematic review but a rapid assessment for relevant literature. Search strategies were broad in order to maximise chances of identifying relevant reviews. Although search strategies were limited to systematic reviews for the question on exenatide, it was possible to identify from the reviews the relevant RCTs and study these in detail. This was due to the limited number of relevant RCTs. Search strategies were also limited to systematic reviews for the broader question on SFUs. A search for primary studies would not have been feasible given the volume of literature available on this topic. However, to aid comprehensiveness the reference lists of relevant reviews were scanned for further studies.

The completeness and accuracy of results is likely to be limited by:

- A relatively small amount of evidence on rates of hypoglycaemia in exenatide (+SFU) users based on five RCTs.
- Only one good quality systematic review identified, which looked at hypoglycaemia rates in SFU users and included any study design and any combination of SFU use (Bolen 2007[28]); absolute risks of hypoglycaemia with different types of SFUs were not reported and there was little reporting on the observational studies identified.
- Reporting of different outcome measures (incidence, risk, rate, episodes/person-year, events in patients etc.) and a lack of definitions of these measures making comparisons across studies difficult.
- Heterogeneity between studies in terms of patient and treatment characteristics and study design (particularly loss to follow-up, which has been shown to be associated with hypoglycaemic episodes) again hampering comparisons between studies.
- No consistent use or lack of reporting on the categories of mild-moderate and severe hypoglycaemia.

5 Conclusion

Limited evidence (based on two trials[10,18]) suggests that hypoglycaemic rates are higher in patients using exenatide with an SFU compared to an SFU only (with metformin in one trial, without in the other) and that hypoglycaemic rates are higher in patients taking a higher dose of exenatide (10 μg bid) compared to a lower dose (5 μg bid). Accuracy of absolute episodes/patient-year and incidences reported is dependent on patient, treatment and study characteristics and it is unclear whether these rates would apply to all UK patients who would be eligible for this type of treatment.

A very wide range of risk of hypoglycaemia was identified for (any) patient using (any) SFU and it is probably inappropriate to attempt to determine an overall risk, as there are too many factors that can influence the magnitude of risk (patient characteristics, particularly age and co-morbidities, type of SFU and other treatment and study characteristics, e.g. prospective or retrospective study). The data do appear to suggest that glyburide (and glibenclamide) are associated with a higher risk of hypoglycaemia compared to other SFUs and that SFUs in combination with other drugs are associated with a higher risk than SFU monotherapy. A more focused question in terms of population and a comparison between specific SFUs or other treatment may be more appropriate.

6 Appendices

6.1 Appendix 1 – Details of Request

1 ARIF REQUEST FORM

Date of request	19/12/2007
Lead Medical Adviser issuing request	Name – Dr Simon Rees Secretary to the Diabetes Panel
Contact details	Drivers Medical Group DVLA Sandringham Park Swansea Vale Llansamlet Swansea SA7 0AA [redacted] [redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

1. We need to know the hypo risk of patients who are being treated for any length of time with:-

   a) Sulphonylureas and any other treatment except Exenatide or insulin.
   b) Sulphonylureas and Exenatide and any other treatment except insulin

2. Please give a background to the question. Why has DMG raised this problem?

There is concern about the hypo risk of patients being treated with sulphonylureas and sulphonylureas and Exenatide, which has been brought to our attention.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues,* which might be important for the problems, you describe.

a) Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia 2007 Feb; 50(2): 259-67 Epub 2006 Dec 8.*

b) Buse JB, Klonoff DC, Nielson LL et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clinical Therapeutics. 2007 Jan: 29(1): 139-53.*

c) Renee E. Amori MD, et al. Efficacy and Safety of Incretin Therapy in Type 2 Diabetes. Systematic Review and Meta-analysis. *The Journal of the American Medical Association.*

d) Cvetkovic RS, Plosker GL. Exenatide: a review of its use in patients with type 2 diabetes mellitus (as an adjunct to metformin and/or a sulfonylurea.) *Drugs. 2007; 67 (6): 935-54*

e) Riddle MC, Henry RR et al. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes/Metabolism research and review. 2006 Nov-Dec; 22 (6): 483-91.*

f) UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia 2007 June; 50(6) 1140-1147*
(Ref only, no papers.)

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel Member.

Professor Brian M Frier (Chairman)
BSc Ed MD FRCP
Consultant Physician and Diabetologist
Department of Diabetes
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA
[redacted]

5. What is the nature of the target population of the issue detailed above? Eg. age profile, vocational drivers, young drivers, other co-morbid features.

Drivers of both ordinary driving (odl) and vocational licences, and all ages for drivers being treated as listed at question 1: 1a and 1b.

Ordinary driver licence (car) holders only, of all ages for insulin-treated drivers as listed at question 1: 2a and 2b.

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

The outcome of the hypo risk which may affect future driver licensing decisions/policy.

7. What is the latest date that an ARIF response would be of value

06/03/08

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to: -
Dr David Moore
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Please ring 0121 414 3166 or 6769 if you have any queries, or you want to check the progress with your request.

6.2 Appendix 2 – Outline methods

- To determine

    1) The risk of hypoglycaemic events in diabetic patients being treated with SFUs + exenatide + any other treatment (including no treatment) except insulin

    2) The risk of hypoglycaemic events in diabetic patients being treated with SFUs + any other treatment (including no treatment) except exenatide or insulin

- A search for reviews will be performed in MEDLINE, EMBASE and the Cochrane Library combining terms relating to SFUs and a search filter for identifying reviews, with the addition of the term ‘exenatide’ for question 1
- Detailed searches for articles on individual drugs belonging to the class of SFUs will not be performed
- Identified articles will be screened for relevance
- Recent well-conducted systematic reviews will be preferred over less rigorously conducted reviews
- Reference lists of relevant reviews and the UKPDS (UK Prospective Diabetes Study) database of publications will be scanned
- If primary studies are required, we will focus on large randomised controlled trials (RCTs) or cohorts with long-term follow-up, ideally UK based
- Methodological quality of included studies will be commented on
- Data will be extracted on population characteristics, sample source/study design, treatment strategy and hypoglycaemia risk in relevant treatment arms
- Where possible, hypoglycaemic events will be reported separately as mild/moderate or severe (with ‘severe’ defined as 3rd party involvement being required)
- The likely accuracy of the reported risk(s) of hypoglycaemia will be commented on
- For a direct comparison of hypoglycaemia risk with the two treatment strategies of interest (SFUs with or without exenatide), results from randomised controlled trials will be of most relevance; it will be difficult to compare hypoglycaemia risks across different studies, as there is likely to be substantial heterogeneity in terms of type of SFU, population characteristics and study design
- This report will not assess the relative differences in hypoglycaemia rates for different types of SFUs unless there is a systematic review directly addressing this issue
- This report will not assess the likely consequences for driving outcomes resulting from hypoglycaemic events

6.3 Appendix 3 – Search strategies

6.3.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(October 2007)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments

- NICE guidance (all programmes)
- West Midlands Health Technology Assessment Collaboration
- Evidence Based Commissioning Collaboration (Trent R & D Support Unit). Links to Trent Purchasing Consortia reports and Wessex DEC reports (both no longer published)
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

6.3.2 Search protocol MEDLINE and EMBASE

6.3.2.1 SFUs with exenatide

Database: Ovid MEDLINE(R) <1950 to January Week 4 2008>
Search Strategy:
---
1 sulphonylurea$.mp. (1462)
2 exp Sulfonylurea Compounds/ (13549)
3 sulfonylurea$.mp. (6092)
4 or/1-3 (15658)
5 limit 4 to (humans and "reviews (specificity)") (69)
6 from 5 keep 1-69 (69)
7 exenatide.mp. (406)
8 limit 7 to (humans and "reviews (optimized)") (87)
9 from 8 keep 1-87 (87)

Supplemental search:
Database: Ovid MEDLINE(R) <1950 to January Week 5 2008>
Search Strategy:
---
1 byetta.mp. (16)
2 limit 1 to "reviews (optimized)" (7)
3 from 2 keep 1-7 (7)

Database: EMBASE <1980 to 2008 Week 04>
Search Strategy:
---
1 sulphonylurea$.mp. (1411)
2 sulfonylurea$.mp. (9788)
3 exenatide.mp. (222)
4 Sulfonylurea/ (3945)
5 1 or 2 or 4 (10213)
6 limit 5 to (human and "reviews (1 term high specificity)") (185)
7 from 6 keep 1-185 (185)
8 limit 3 to (human and "reviews (1 term min difference)") (53)
9 from 8 keep 1-53 (53)

Supplemental search:
Database: EMBASE <1980 to 2008 Week 06>
Search Strategy:
---
1 byetta.mp. (174)
2 limit 1 to (human and "reviews (1 term min difference)") (18)
3 from 2 keep 1-18 (18)

6.3.2.2 SFUs without exenatide

Database: Ovid MEDLINE(R) <1950 to January Week 4 2008>
Search Strategy:
---
1 sulphonylurea$.mp. (1462)
2 exp Sulfonylurea Compounds/ (13549)
3 sulfonylurea$.mp. (6092)
4 or/1-3 (15658)
5 limit 4 to (humans and "reviews (specificity)") (69)
6 from 5 keep 1-69 (69)

Database: EMBASE <1980 to 2008 Week 04>
Search Strategy:
---
1 sulphonylurea$.mp. (1411)
2 sulfonylurea$.mp. (9788)
3 exenatide.mp. (222)
4 Sulfonylurea/ (3945)
5 1 or 2 or 4 (10213)
6 limit 5 to (human and "reviews (1 term high specificity)") (185)
7 from 6 keep 1-185 (185)

6.4 Appendix 4 -Excluded studies exenatide

Buse 2007[43]	Report of open label extension in 3 trials (DeFronzo, Buse and Kendall)-similar analysis to Riddle, presents pooled results; cannot use as includes DeFronzo which is excluded
Blonde 2006[8]	Report of open label extension in 3 trials (DeFronzo, Buse and Kendall)-similar analysis to Riddle, presents pooled results; cannot use as includes DeFronzo which is excluded
Davis 2007[11]	Only 4/51 patients meet criterion of being on SFUs
DeFronzo 2005[12]	All patients on metformin +/- exenatide, no SFUs
Fineman 2003[13]	78% of patients taking SFU and hypoglycaemic events occurring in these patients only; however, results not reported by exenatide or placebo arms, only for total
Fineman 2004[14]	Exenatide in exenatide naïve or exenatide primed patients; background treatment with diet and/or metformin and/or thiazolidinediones; no SFUs
Poon 2005[44]	No SFUs

6.5 Appendix 5 Main characteristics and results tables

Table 1 Main study characteristics and risk of hypoglycaemia in patients treated with exenatide

Study, year, author	Population	Data source/ duration of study	Treatment arms	Risk of hypoglycaemia SFU + any other treatment	Risk of hypoglycaemia SFU + exenatide + any other treatment	Comment
Barnett 2007[7], multi-national	• n=138 • 47% male • 54.9 ± 0.8 years • Type II diabetes • Stable dose of metformin (55%) or optimally effective dose of a SFU (45%) for 3 months	Open-label, randomised, two-period crossover study, 26 sites, multi-national 32 week duration (16 weeks for each crossover period)	A) Exenatide 5µg b.i.d. for 4 weeks, then 10µg b.i.d. All patients received exenatide, either during first or second crossover period; 62 patients using a SFU 45% treated with a SFU (type(s) not stated)	No relevant treatment arm	A) incidence of 30.0% in patients taking a SFU Also expressed as 4.1 episodes/ patient-year (overall hypoglycaemia in patients taking a SFU) 0.86 episodes/ patient-year (nocturnal hypoglycaemia) No episodes of severe hypoglycaemia	• According to study protocol, patients could decrease their SFU dose in response to hypoglycaemia during exenatide treatment • All patients treated with exenatide during first or second crossover period, but only those patients also treated with a SFU relevant; are looking at a sub-group of patients (NB randomisation not stratified by background treatment but equal amounts of patients treated with a SFU in both treatment arms) • No washout period between treatment periods; test for carryover based on sequence effect was performed and no evidence of a carryover effect from treatment period 1 to 2 • Hypoglycaemia defined as any sign or symptom associated with hypoglycaemia and/or a serum glucose concentration of <3.3 mmol/L; severe hypoglycaemia defined as a symptomatic episode in which the patient required another person's assistance and was associated with either a glucose level <2.8 mmol/L or recovery after the administration of oral carbohydrate, glucagons, or intravenous glucose • Safety profiles were analysed in all randomised patients or the ITT population " as appropriate" to capture hypoglycaemic episodes (ITT population = patients who took at least one dose of study drug) • Approximately 81% of patients treated with a SFU completed treatment; unclear how missing data handled in terms of hypoglycaemia rates • Hypoglycaemia not listed as an adverse event leading to

Study, year, author	Population	Data source/ duration of study	Treatment arms	Risk of hypoglycaemia SFU + any other treatment	Risk of hypoglycaemia SFU + exenatide + any other treatment	Comment
						withdrawal
Buse 2004, USA[10]	• n=377 • 60% male • 55 ± 11 (22-76) years • Type II diabetes • Maximally effective dose of a SFU as monotherapy ≥ 3 months	Triple-blind, randomised, placebo controlled, study, 101 sites in the US 30 week duration	A Exenatide 5µg b.i.d. (n=125) B Exenatide 10µg b.i.d. (n=129) C Placebo (n=123) (NB originally 2 placebo arms, collapsed into 1 for analysis) All treated with SFU (45% glipizide, 33% glyburide, 20% glimepiride, 1% tolazamide, 0.3% chlorpropamide)	C n=4 (3%) mild/mod No severe episodes	A n=18 (14%) mild/mod No severe episodes B n=46 (36%) mild/mod No severe episodes	• Protocol recommended progressive 50% reductions in SFU doses, eventual discontinuation if 1 documented event of hypoglycaemia (or 2 suspected events) • Stated that hypoglycaemic episodes based on ITT population, but is in fact evaluable population (n=255, 68%, see Table 1) • 1 withdrawal due to hypoglycaemia from 5µg b.i.d. exenatide arm • Hypoglycaemic episodes defined as mild/moderate (reporting of symptoms consistent with hypoglycaemia, which may have been documented by a plasma glucose concentration value (<60mg/dl)) or severe (subjects required the assistance of another person to obtain treatment for hypoglycaemia including IV glucose or intramuscular glucagon) • Incidence of treatment-emergent, dose-dependent hypoglycaemia peaked during initial weeks of dosing then decreased over time • Results appear to refer to number of patients with hypoglycaemic episodes rather than number of episodes (this information not stated); unclear if patients could be double-counted
Heine 2005, multi-national[15]	• n=551 • 55% male, exenatide group • 59.8 (8.8) years (exenatide group) • Type II diabetes • Stable and maximally effective doses of metformin and a SFU for ≥ 3 months Patients excluded if more than 3 episodes of	Open-label, randomised, controlled trial, 82 centres 26 week duration	A Exenatide 5µg b.i.d. for 4 weeks, then 10µg b.i.d. for remainder of study n=282 All treated with a SFU (type(s) not stated)	No relevant treatment arm	7.3 episodes/patient-year (nocturnal: 0.9 episodes/patient-year; daytime: 6.6 episodes/patient-year) This refers to overall rate and includes severe episodes 4/282 patients experienced a	• 50% reductions in SFU dose if hypoglycaemic episode • Symptomatic hypoglycaemia defined as blood glucose measurement less than 3.4 mmol/L or hypoglycaemia accompanied by symptoms such as sweating, shaking, pounding heart or confusion; severe hypoglycaemia defined as episode in which patient required assistance from another person and had a blood glucose measurement less than 2.8mmol/L or had promptly recovered after an oral carbohydrate or glucagons injection or IV glucose • Hypoglycaemic events appear to be reported for ITT population • Approximately 81% of patients completed treatment; unclear how missing data handled in terms of hypoglycaemia rates

Study, year, author	Population	Data source/ duration of study	Treatment arms	Risk of hypoglycaemia SFU + any other treatment	Risk of hypoglycaemia SFU + exenatide + any other treatment	Comment
	severe hypoglycaemia within 6 months before screening				severe episode	• No withdrawals due to hypoglycaemia
Kendall 2005, USA[18]	• n=733 • 55.9%-59.3% male • 55(9)-56 (10) years • Type II diabetes • Stable and maximally effective doses of metformin and a SFU for ≥ 3 months	Double-blind, randomised, placebo-controlled trial 30 week duration	A Exenatide 5µg b.i.d. (n=245) B Exenatide 5µg b.i.d. for 4 weeks then 10µg b.i.d. (n=241) C Placebo (n=247) (NB originally 2 placebo arms, collapsed into 1 for analysis) NB patients randomised to maximally effective SFU dose or minimum recommended dose to assess influence of concurrent SFU dosage on hypoglycaemia risk (43% glipizide, 42% glibenclamide, 14% glimepiride, 3% glibenclamide combination with metformin, <1% tolazamide, <1% chlorpropamide)	C n=31 (12.6%)	A n=47 (19.2%) 1 case of severe hypoglycaemia B n=67 (27.8%) NB lower incidence of hypoglycaemia in patients taking minimum recommended dose of SFU (data not stated)	• Protocol recommended progressive 50% reductions in SFU doses, eventual discontinuation if 1 documented event of hypoglycaemia (or 2 suspected events) • Hypoglycaemic episodes defined as mild/moderate (reporting of symptoms consistent with hypoglycaemia, which may have been documented by a plasma glucose concentration value (<3.33mmol/L)) or severe (subjects required the assistance of another person to obtain treatment for hypoglycaemia including IV glucose or intramuscular glucagon) • Safety analyses in ITT population; 81% completed study, unclear how missing data handled in analysis • No withdrawals due to hypoglycaemia • Results appear to refer to number of patients with hypoglycaemic episodes rather than number of episodes (this information not stated); unclear if patients could be double-counted
Nauck 2007, multi-national[25]	• n=505 • 49%-53% male • 58(9)-59(9) years • Optimally effective metformin and SFU therapy for at least 3 months Patients excluded	Open-label, randomised, controlled trial 52 week duration	A Exenatide 5µg b.i.d. for 4 weeks then 10µg b.i.d. n=255 All patients taking a SFU (no details on type) and metformin	No relevant treatment arm	A 4.7 (0.7) episodes/patient-year (least-squares mean ± SEM) Incidence (=number of patients experiencing at least 1 episode)	• 50% reductions in SFU dose if hypoglycaemic episode • Hypoglycaemic episode defined as any time a patient experienced a sign or symptom of hypoglycaemia or noted a blood glucose level <3.4 mmol/L during self-monitoring, whether or not this level was associated with signs, symptoms or treatment; the severity (mild, moderate or severe) and timing (nocturnal or daytime) of each event was assessed by the investigator • Hypoglycaemia rates measured in ITT population (501/505 patients who received at least 1 dose of study medication and who

Study, year, author	Population	Data source/ duration of study	Treatment arms	Risk of hypoglycaemia SFU + any other treatment	Risk of hypoglycaemia SFU + exenatide + any other treatment	Comment
	if more than 3 episodes of severe hypoglycaemia within 6 months prior to screening				of nocturnal hypoglycaemia 17% (44/253) No severe hypoglycaemic episodes	had at least 1 post-baseline measurement) • Approximately 79% of patients in exenatide arm completed study; unclear how missing data handled in terms of hypoglycaemia rates • No details on withdrawals due to hypoglycaemia • Overall hypoglycaemia rates were decreased following SFU dose reductions

Table 3 Reviews of rates of hypoglycaemia in patients taking a SFU

Review	Comment on methodology	Types of studies included	Main results	Comments
Bolen 2007[28]	Comprehensive search strategy (English language studies only) Well documented study selection, data extraction, quality assessment and data synthesis process; processes performed in duplicate	RCTs and observational studies Oral diabetic agents including SFUs First-generation SFUs excluded	167 primary studies and two Cochrane reviews identified for any type of adverse event; 2/3 RCTs, 1/3 observational; not stated how many studies reporting hypoglycaemia in patients using SFUs • Hypoglycaemic episodes more frequent in patients receiving second-generation SFUs (particularly glyburide) compared to metformin or thiazolidinediones (with absolute risk differences ranging from 4% to 9%) • Levels of hypoglycaemic risk ranged from 0% to 36% for second-generation SFUs • 10-year follow-up from UKPDS reported annual rates of minor and major hypoglycaemia as 17.5% and 2.5% respectively (glibenclamide group) • Results from observational studies were consistent with those of UKPDS (data not reported) • Glyburide and glibenclamide conferred slightly higher risk of hypoglycaemia compared to other second-generation SFUs • Incidence of minor and major hypoglycaemia was higher with combinations that included SFUs compared to metformin or SFU monotherapy Meta-analysis of RCTs reporting hypoglycaemia Weighted absolute risk differences (95% CI) (Comparator 1 more harmful, higher values indicate more hypoglycaemic events) -SFU versus repaglinide, 0.02 (-0.02, 0.05) based on 5 studies -Glyburide versus other SFU 0.03 (0, 0.05) based on 6 studies -SFU versus metformin 0.04 (0, 0.09) based on 8 studies -SFU + thiazolidonedione versus SFU 0.08 (0, 0.16) based on 3 studies -SFU versus thiazolidonedione 0.09 (0.3, 0.15) based on 5 studies -SFU + metformin versus SFU 0.11 (0.07, 0.14) based on 8 studies -SFU + metformin versus metformin 0.14 (0.07, 0.21) based on 9 studies NB First 4 results all include 0 (no difference) in confidence intervals	Well conducted SR looking broadly at effectiveness and safety of different types of oral diabetic agents; some limitations in that only English language studies included and unclear how many studies estimates of hypoglycaemia are based on Large range of hypoglycaemic risk reported, likely to be due to heterogeneity of populations and/or additional and previous treatments etc. Distinction between mild-moderate or severe hypoglycaemia not made No definition of risks or rates given Data likely to be most useful for gauging differences in risk between different types of SFU or other oral diabetic agents
Gangji 2007[31]	Comprehensive search strategy (English language studies only) Well documented	Parallel design RCT All studies comparing glyburide with	12 RCTs reporting hypoglycaemic events in patients taking glyburide compared to an oral hypoglycaemic agent • Patients experiencing at least one hypoglycaemic episode (any severity) were between 3% and 29% (glyburide, 12 studies), 2%-7% (glicazide, 2 studies), 11%-12% (Glimiperide, 2 studies), 0%-12% (chlorpropamide, 3	Well conducted SR focusing on comparison between glyburide and other oral hypoglycaemic agents Length of RCTs and loss to follow-up not stated

Review	Comment on methodology	Types of studies included	Main results	Comments
	study selection, data extraction, quality assessment and data synthesis process; processes performed in duplicate	another SFU or meglitinides or insulin	studies), 1% (glipizide, 1 study); time frames not stated • Meta-analysis showed that glyburide causes significantly more hypoglycaemia than other SFUs • In two studies that reported major hypoglycaemia there were greater numbers of hypoglycaemic events in patients treated with glyburide compared to other SFUs	No distinction between mild-moderate and severe hypoglycaemia in main analysis Large range of hypoglycaemic risk reported, likely to be due to heterogeneity of populations and/or additional and previous treatments etc.
Mukai 2007[36]	Fairly comprehensive search strategy (not EMBASE; English and Japanese language studies only) Well documented study selection, data extraction, quality assessment and data synthesis process; processes not performed in duplicate	RCTs Studies comparing a SFU treatment arm with an SFU + another treatment (biguanides, α-glucosidase inhibitors, thiozolidinediones)	6 RCTs reporting hypoglycaemic events in patients taking a SFU only compared to an SFU with another treatment • 0%-4.2% of patients with hypoglycaemic episode with SFU alone • Consistently fewer hypoglycaemic episodes for patients treated with SFU alone compared to SFU with another treatment	Reasonably well conducted SR focussing on comparison between a SFU only compared to an SFU with another treatment Length of RCTs and loss to follow-up not stated No distinction between mild-moderate and severe hypoglycaemia
Salas 2002[37]	Comprehensive search strategy (no language limitations) Documented study selection and data synthesis process No details on data extraction or quality assessment Processes not performed in duplicate	Any study design SFUs only	No summary of number/types of study reporting hypoglycaemic events; partly narrative, partly tabular reporting of study results • Severe hypoglycaemia rates vary between 4-26% per patient-year, with broader variation for milder episodes (other study referenced, not a finding of this review) • Incidence for glimepiride between 0.9% and 14.2% (6 studies); for glibenclamide 31.5%, 23 events in 13 patients over 12 months and 110 complaints of hypoglycaemia in 9 patients over 15 months (3 studies); for glipizide 11/204 patients or 11/143 patients in two 16 week studies • 3 additional studies discussed in text • Van Staa (see also primary studies table): 1.8% annual risk of hypoglycaemia with highest risk with glibenclamide • Four reports of UKPDS (see also primary studies table): proportion of	Reasonably well conducted review, though result reporting is unstructured Various outcome measures used (incidence, patients, events in patients etc.) making it difficult to compare different studies or SFUs Large range of hypoglycaemic risk reported, likely to be due to heterogeneity of populations and/or additional and previous treatments etc. Distinction between mild-moderate or severe hypoglycaemia not always

Review	Comment on methodology	Types of studies included	Main results	Comments
	Unstructured reporting of results		patients reporting one or more hypoglycaemic events was 17%; cumulative incidence of severe hypoglycaemia over 6 years was 3.3%; additional report: 16% of patients on chlorpropamide had hypoglycaemic episode over 10 years and 21% on glibenclamide (or 1% and 1.4% episodes annually respectively); 31% and 7% of patients using glibenclamide and chlorpropamide respectively experienced hypoglycaemic symptoms during the first year • Berger: severe hypoglycaemia of 1.9-2.5 per 100 patients per year	made No definition of risks or rates given

Table 4 Primary UK studies reporting rates of hypoglycaemia in patients taking an SFU

Study	Sample source/ study type	Number of participants, characteristics	Length of follow-up	Loss to follow-up	Types of SFU/ additional treatment (not insulin or exenatide)	Risk of hypoglycaemia Mild-moderate	Risk of hypoglycaemia Severe	Comments
UK Hypoglycaemia Study Group, 2007[42]	Cohort 6 UK secondary care diabetes centres	n=383 (total) n=108 SFU 78.7% male Mean age 60.8 (9.3)	Prospective 9-12 months	72% returned self-reports at 9-12 months Results for SFU group based on 103/108 (95%)- timescale unclear	Not stated	Mean episodes/ person-year (95% CI) 1.92 (1.2, 2.6)	Mean episodes/ person-year (95% CI) 0.1 (0.0, 0.4)	• Severe hypoglycaemia defined as requiring assistance, mild-moderate hypoglycaemia defined as self-treated; all self-reported
Van Staa 1997[39]	Cohort 719 clinical practices in the UK	Study population of 33,243 52% male 39% aged 20-64 61% aged>65	Retrospective For each user, the time-frame was variable, based on length of SFU prescription	Retrospective	Glibenclamide (56%), glicazide (22%), tolbutamide (14%), chlorpropamide (8%), glipizide (6%)	Annual risk of hypoglycaemia (=number of cases divided by number of therapy years) 1.8% Glibenclamide 1.6% Glicazide 1.7% Tolbutamide 0.7% Chlorpropamide 1.3%		• No distinction made between mil-moderate or severe hypoglycaemia; not possible to determine from records whether hypoglycaemia was confirmed or self-reported; data more representative of diagnoses made by GPs after patient visit or report (more likely to be more severe cases)
UKPDS 33, 1998[40]	RCT 23 UK clinical centres	n=4209 randomised n=1573 to SFU Data in this report from n=1234 on SFU (15 centres) 60% male Mean age 54(8) or 54(9)	Prospective 15 years Data reported for 10 years (very small patient numbers at 15 years)	61% remaining on allocated therapy at 5 years, 28% at 10 years and 3% at 15 years	50% each on chlorpropamide and glibenclamide	Over 10 years, mean proportion of patients per year with episode: ITT population, any hypoglycaemic episode: 16% chlorpropamide 21% glibenclamide Assigned	Over 10 years, mean proportion of patients per year with episode: ITT population, major hypoglycaemic episode: 1.0% chlorpropamide 1.4% glibenclamide Assigned	•Hypoglycaemic episodes defined as minor if patient able to treat symptoms unaided, or major if third-party help or medical intervention was necessary

Study	Sample source/ study type	Number of participants, characteristics	Length of follow-up	Loss to follow-up	Types of SFU/ additional treatment (not insulin or exenatide)	Risk of hypoglycaemia Mild-moderate	Risk of hypoglycaemia Severe	Comments
						treatment, any hypoglycaemic episode: 11% chlorpropamide 17.7% glibenclamide	treatment, major hypoglycaemic episode: 0.4% chlorpropamide 0.6% glibenclamide	
Wright, 2006 (UKPDS)[41]	RCT 23 UK clinical centres	n=5063 n=1687 randomised to an SFU 59% male Mean age 52.4 (8.8)	Prospective 6 years	70% remained on their allocated therapy>6 years and included in analyses Results for SFU users based on 1418/1687 (84%) patients-timescale unclear	Not stated	Grades I-IV: all hypoglycaemia Annual % of patients reporting at least one hypoglycaemic episode (95% CI) 7.9 (5.1, 11.9) Reported by allocated therapy	Grades II-IV: all hypoglycaemia, except grade I Annual % of patients reporting at least one hypoglycaemic episode (95% CI) 1.2 (0.4, 3.4) Not reported for severe only Reported by allocated therapy	•Hypoglycaemia defined as grade I: transitory symptoms not affecting normal activity; grade II: temporarily incapacitated but patients able to control symptoms without help; grade III: incapacitated and required assistance to control symptoms and grade IV: required medical attention or glucagons injection

NB the Wright and UKPDS 33 study refer to same study population but have a different follow-up and method of presenting results

7 References

1. Diabetes and Driving in Europe. URL:http://ec.europa.eu/transport/roadsafety/behavior/doc/diabetes_and_driving_in_europe_final_1.pdf. Accessed February 2008.

2. Harrower ADB. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Safety* 2000; **22**(4):313-320.

3. Holstein A,.Egberts E-H. Risk of Hypoglycaemia with Oral Antidiabetic Agents in Patients with Type 2 Diabetes. *Experimental and Clinical Endocrinology and Diabetes* 2003;**111**(7):405-414.

4. Treatment with Exenatide (Byetta) or Gliptins. URL: http://www.dvla.gov.uk/medical/Treatment%20with%20Exenatide.aspx. Accessed February 2008.

5. UK Prospective Diabetes Study Publications. URL: http://www.dtu.ox.ac.uk/index.php?maindoc=/ukpds/. Accessed February 2008.

6. Barnett A. Exenatide. *Expert Opinion on Pharmacotherapy* 2007;**8**:2593-608.

7. Barnett AH, Burger J, Johns D, Brodows R, Kendall DM, Roberts A *et al*. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: A multinational, randomized, open-label, two-period, crossover noninferiority trial. *Clinical Therapeutics* 2007;**29**(11):2333.-2348.

8. Blonde L. Clinical trial results of GLP-1-related agents: The early evidence. *Advanced Studies in Medicine 2005;***5**(10):S1074-S1078.

9. Bray GM. Exenatide. *American Journal of Health-System Pharmacy* 2006;**63**:411-8.

10. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004;**27**(11): 2628-2635.

11. Davis SN, Johns D, Maggs D, Xu H, Northrup JH, Brodows RG. Exploring the substitution of exenatide for insulin in patients with type 2 diabetes treated with insulin in combination with oral antidiabetes agents. *Diabetes Care* 2007;**30**(11):2767-2772.

12. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2. *Diabetes Care* 2005;**28**(5):1092-1100.

13. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A *et al*. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 2003;**26**(8):2370-2377.

14. Fineman MS, Shen LZ, Taylor K, Kim DD, Baron AD. Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. *Diabetes/Metabolism Research and Reviews* 2004;**20**:411-7.

15. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial. *Annals of Internal Medicine* 2005;**143**(8):559-569.

16. Iltz JL, Baker DE, Setter SM, Keith CR. Exenatide: an incretin mimetic for the treatment of type 2 diabetes mellitus.*Clinical Therapeutics* 2006;**28**:652-65.

17. Joy SV, Rodgers PT, Scates AC. Incretin mimetics as emerging treatments for type 2 diabetes. *Annals of Pharmacotherapy* 2005;**39**:110-8.

18. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS *et al*. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005;**28**(5):1083-1091.

19. Lam S,.See S. Exenatide: a novel incretin mimetic agent for treating type 2 diabetes mellitus. *Cardiology in Review* 2006;**14**:205-11.

20. Mikhail NE. Is exenatide a useful addition to diabetes therapy? *Endocrine Practice* 2006;**12**:307-314.

21. Stephens JW,.Bain SC. Safety and adverse effects associated with GLP-1 analogues. *Expert Opinion on Drug Safety* 2007;**6**:417-22.

22. Yoo BK, Triller DM, Yoo DJ. Exenatide: a new option for the treatment of type 2 diabetes. *Annals of Pharmacotherapy* 2006;**40**:1777-84.

23. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis.*JAMA* 2007;**298**:194-206.

24. Cvetkovic RS,.Plosker GL. Exenatide: a review of its use in patients with type 2 diabetes mellitus (as an adjunct to metformin and/or a sulfonylurea). *Drugs* 2007;**67**:935-54.

25. Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A *et al*. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type II diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007;**50**:259-67.

26. Riddle MC, Henry RR, Poon TH, Zhang B, Mac SM, Holcombe JH *et al*. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes/Metabolism Research and Reviews* 2006;**22**(6):483-491.

27. Bell DS. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. *Clinical Therapeutics* 2004;**26**:1714-27.

28. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S *et al*. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Annals of Internal Medicine* 2007;**147**:386-99.

29. Campbell A. Glycaemic control in type 2 diabetes. *BMJ Clin Evid* 2006;**7**:1-15.

30. DeWitt CR, Heard K, Waksman JC. Insulin & C-peptide levels in sulfonylurea-induced hypoglycemia: a systematic review. *Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology* 2007;**3**:107-18.

31. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care* 2007;**30**:389-94.

32. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 2002;**287**:360-72.

33. Levetan C. Oral antidiabetic agents in type 2 diabetes. *Current Medical Research & Opinion* 2007;**23**:945-52.

34. Massi-Benedetti M. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. *Clinical Therapeutics* 2003;**25**:799-816.

35. Melander A, Donnelly R, Rydberg T. Is there a concentration-effect relationship for sulphonylureas? *Clinical Pharmacokinetics* 1998;**34**(3):181-188.

36. Mukai J, Tada H, Watanabe Y, Miura M, Katsuyama S, Shoji T *et al*. Lipids behavior and adverse effects for oral antidiabetic agents in patients with Type 2 diabetes treated with sulfonylureas alone

based on systematic review. *Yakugaku Zasshi - Journal of the Pharmaceutical Society of Japan* 2007;**127**:1747-56.

37. Salas M,.Caro JJ. Are hypoglycaemia and other adverse effects similar among sulphonylureas? *Adverse Drug Reactions & Toxicological Reviews* 2002;**21**:205-17.

38. Del Prato S, Aragona M, Coppelli A. Sulfonylureas and hypoglycaemia. *Diab Nutr Metab* 2002;**15**:444-51.

39. van Staa T, Abenhaim L, Monette J. Rates of hypoglycemia in users of sulfonylureas. *J Clin Epidemiol* 1997;**50**:735-41.

40. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33). *The Lancet* 1998;**352**:837-53.

41. Wright AD, Cull CA, Macleod KM, Holman RR. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. *Journal of Diabetes and its Complications* 2006;**20**:395-401.

42. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;**50**:1140-7.

43. Buse JB, Klonoff DC, Nielsen LL, Guan X, Bowlus CL, Holcombe JH *et al*. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: An interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clinical Therapeutics* 2007;**29**(1):139-153.

44. Poon T, Nelson P, Shen L, Mihm M, Taylor K, Fineman M *et al*. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: A dose-ranging study. *Diabetes Technology and Therapeutics* 2005;**7**(3):467-477.