Reviewer No. 1 checklist for:

Application to Add Glucagon to the WHO Model List of Essential Medicines (Section 18.5)

(1) Have all important studies that you are aware of been included?
   Yes [ ] No ✗ *
* As a matter of fact, there are a few studies which discuss the effect of glucagon itself on the correction of hypoglycaemia. In my own search, studies about hypoglycaemia predominate, both in diabetes and in nondiabetic patients. In general, the systematic reviews or meta-analyses include studies grading low or intermediate quality of evidence, in which hypoglycaemia is not a primary endpoint.

(2) Is there adequate evidence of efficacy for the proposed use?
   Yes ✗ * No [ ]
* Glucagon corrects hypoglycaemia, but, for the previous reasons, the evidence is scarce. The available current information does not demonstrate the necessary evidence for approval.

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Yes ✗ No [ ]

(4) Are there adverse effects of concern?
   Yes [ ] No ✗

(5) Are there special requirements or training needed for safe/effective use?
   Yes [ ] No ✗ *
* Special requirements or training are not needed when intramuscular or subcutaneous routes are used, allowing domiciliary administration.

(6) Is this product needed to meet the majority health needs of the population?
   Yes [ ] No ✗

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Yes ✗ No [ ]

(8) What action do you propose for the Committee to take?
   At this moment, I do not recommend glucagon inclusion, due to the lack of strong specific evidence and the doubt concerning the essentiality of this medicine.
(9) Additional comment, if any.

STRATEGIES USED TO REDUCE THE INCIDENCE OF HYPOGLYCAEMIA**

** Pubmed, Key word: glucagon; Limits activated: Humans, Meta-Analysis, published in the last 5 years: 10
** Pubmed, Key word: glucagon; Limits activated: Humans, Randomized Controlled Trial, published in the last 5 years: 255
** Pubmed, Key word: hypoglycaemia; Limits activated: Humans, Meta-Analysis, published in the last 5 years: 75
** Pubmed, word: severe hypoglycaemia; Limits activated: Humans, Meta-Analysis, published in the last 5 years: 28
** Pubmed, word: neonatal hypoglycaemia; Limits activated: Humans, Meta-Analysis, published in the last 5 years: 7
** Pubmed, word: hypoglycaemia; Limits activated: Humans, Randomized Controlled Trial, published in the last 5 years: 522
** Key word: non-diabetic hypoglycaemia; Limits activated: Humans, Randomized Controlled Trial, published in the last 5 years: 58

1. Hypoglycaemia induced by antidiabetic agents in type 1 and type 2 diabetes mellitus

A large study of intensive glucose lowering in patients with type 2 diabetes evaluated the relationship between severe hypoglycemia and adverse clinical outcomes during 5 years of follow-up. 231 patients (2.1%) had at least one severe hypoglycemic episode; 150 had been assigned to intensive glucose control (2.7% of the 5571 patients in that group), and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group). Severe hypoglycemia was associated with a significant increase in the adjusted risks of major macrovascular events, major microvascular events, death from a cardiovascular cause, and death from any cause ($P<0.01$ for all comparisons). Similar associations were apparent for a range of nonvascular outcomes, including respiratory, digestive, and skin conditions ($P<0.01$ for all comparisons). It is possible that severe hypoglycemia contributes to adverse outcomes. These analyses indicate that hypoglycemia is just as likely to be a marker of vulnerability to such events.

Also, severe hypoglycaemia was associated with a greater risk of dementia among older patients with type 2 diabetes, participants of a large cohort study. The results of this study should be viewed with caution, due to methodological concerns, said Graveling and Frier in a letter. Due to the severity of these outcomes, preventive or curative measures for hypoglycaemia should be available.

a. Control through different antidiabetic agents or different ways of administration

- Subcutaneous insulin infusion or multiple daily injections (“conventional therapy”) for type 1 diabetes

There were no obvious differences between these interventions for non-severe hypoglycaemia, but severe hypoglycaemia appeared to be reduced in patients using insulin infusions, according to a Cochrane review. This conclusion was confirmed by another meta-analysis of 22 studies performed in type 1 diabetic patients.
In adolescents and adults with type 1 diabetes, there was unclear impact on minor hypoglycaemia with both administration methods. Outcomes were not different in patients with type 2 diabetes submitted to subcutaneous insulin infusion or multiple daily injections.\(^5\)

- **Short acting insulin analogues versus regular human insulin for type 1 diabetes**
  Short acting insulin analogues were associated with similar episodes of hypoglycemia as regular human insulin.\(^6\)

- **Intermediate acting versus long acting insulin for type 1 diabetes mellitus**
  The odds ratio for a patient on long acting insulin to develop any type of hypoglycaemia was 0.93 (95% CI 0.8 to 1.08) compared to that of a patient on intermediate acting insulin. The OR for severe hypoglycaemic episodes was 0.73 (95% CI 0.61 to 0.87), and 0.70 (95% CI of 0.63 to 0.79) for nocturnal episodes.\(^7\)

The long-acting insulin analogue detemir increased symptom awareness during hypoglycaemia compared to human insulin in 12 healthy individuals, whereas counter-regulatory hormone response and cognitive function were unaltered.\(^8\)

- **Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes**
  Of the 14 studies (22 comparisons) reporting hypoglycaemia in a Cochrane review, 13 demonstrated no significant difference in the frequency of symptomatic or biochemical hypoglycaemia between insulin and combination therapy regimens.\(^9\)

- **Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus.**
  While no statistically significant difference for severe hypoglycaemia rates was shown in any of the trials included in a Cochrane review, the rate of symptomatic, overall and nocturnal hypoglycaemia was statistically significantly lower in patients treated with either insulin glargine or detemir.\(^10\)

Another systematic review found that patients with type 1 and type 2 diabetes mellitus have a lower risk for nocturnal hypoglycemia when receiving long-acting insulin analogues (insulin detemir or insulin glargine), provided that glycemic control is comparable to that provided by traditional human basal insulin.\(^11\)

- **Noninsulin antidiabetic drugs added to metformin in the treatment for type 2 diabetes**
  A meta-analysis of 27 studies that compared efficacy and safety of noninsulin antidiabetic medicines in patients with type 2 diabetes not controlled by metformin alone showed that sulfonylureas and glinides were associated with higher rates of hypoglycemia than with placebo (RR range, 4.57-7.50).\(^12\)

- **Oral antidiabetic agents versus insulin in the management of gestational diabetes**
  A systematic review and meta-analysis (6 studies; n = 1388) showed that the use of oral hypoglycemic agents was not associated with increased risk of neonatal hypoglycemia in comparison with insulin.\(^13\)

**In conclusion:** Different antidiabetic agents and different administration routes for type 1 or type 2 diabetes mellitus treatment do not seem to importantly modify the incidence of hypoglycaemia, except by long-acting insulins that show modest reduction in symptomatic and nocturnal hypoglycaemia and some new oral agents that seem to be not associated with hypoglycaemia.
b. Prevention of hypoglycaemia through glucagon administration in diabetic patients submitted to antidiabetic treatment

A small study randomized 8 type 1 diabetic children on insulin pump therapy to two open-labeled studies. On one occasion, type 1 diabetic subjects received a 60% increase in the insulin bolus-to-carbohydrate ratio with minidose glucagon rescue injections, and on the other occasion type 1 diabetic subjects received 30-45 microg pramlintide with their usual insulin bolus-to-carbohydrate ratio. Pramlintide reduced immediate postprandial hyperglycemia and suppressed glucagon \( P < 0.02 \), and glucagon injections prevented late hypoglycemia with increased insulin. In summary, in type 1 diabetes, glucagon modulation with pramlintide as an adjunct to insulin therapy may prove beneficial in controlling postmeal glycemic swings.\(^{14}\)

Another small study (13 adult subjects with type 1 diabetes) compared glucagon versus placebo in a closed-loop insulin delivery system, given at times of impending hypoglycemia. Automated high-gain pulses of glucagon plus insulin delivery, compared with placebo plus insulin, significantly reduced the frequency of hypoglycemic events \( P = 0.01 \) and the need for carbohydrate treatment \( P = 0.01 \).\(^{15}\)

| In conclusion: Larger and longer-term studies are being required to assess the effect of ongoing glucagon treatment on overall glycemic control. |

---

\[ \text{c. Control of hypoglycaemia associated to antidiabetic treatment} \]

\[ \text{Self-management education and regular monitoring of blood glucose} \]

People with diabetes can recognize hypoglycaemia signs and symptoms and learn to prevent episodes of hypoglycaemia by improved understanding of how insulin, food, and activity affect blood glucose levels. In patients in whom the self-education does not fit, having in consequence severe hypoglycaemia, glucagon might be helpful.\(^{16}\)

A randomized controlled trial\(^{17}\) evaluated the long-term effect (31-month follow-up) of an education program (HyPOS) for treating type 1 diabetic patients (n=140) with hypoglycaemia problems, in comparison with controls. At baseline the prevalence of severe hypoglycaemia was 0.8 ± 1.5 and 0.7 ± 1.05 episodes/patient-year in the control and HyPOS groups, respectively. The incidence of severe hypoglycaemia was slightly lower in HyPOS than in the control group \( (0.1 ± 0.2 \text{ vs. } 0.2 ± 0.4 \text{ episodes/patient-year; } P = 0.04) \). In the control group, 26.5% of the patients experienced at least one severe hypoglycemic episode compared with 12.5% in HyPOS group \( \text{OR=} 0.4 \text{ [95\% CI: } 0.2–0.9; P = 0.04) \).

\[ \text{Adequate carbohydrate replacement during and after exercise} \]

During and after exercise in type 1 diabetic patients, hypoglycaemia occurs, and a decrease from 20 to 30% seems reasonable only for a long duration exercise (> 60 min.). A study shows that by replacing adequately the carbohydrates during the practice of physical exercise it is possible to prevent almost all hypoglycaemia episodes, independently of the insulin dosage adjustments.\(^{18}\)

\[ \text{Oral sugar supplements} \]

There is a lack of evidence regarding the most effective treatment option for managing naturally occurring hypoglycemia in children with type 1 diabetes. A
randomized, crossover design study (n=33 participants) found no significant
difference between treatment with glucose and treatment with sucrose, but the
treatment effectiveness for fructose was significantly lower than sucrose.\textsuperscript{19}

\textit{Glucagon rescue for hypoglycemia in diabetic children}
A descriptive study\textsuperscript{20} analyzed 33 episodes of impending or mild hypoglycemia in 28
type 1 diabetic children with an episode of gastroenteritis. Mini-dose glucagon rescue,
using subcutaneous injections, was effective in managing children during the
episodes. However, in 14 children, relative hypoglycemia recurred, requiring
retreatment. In four children, a third dose was required. The glucagon was well
tolerated in 28 of the 33 episodes of impending hypoglycaemia. The children
remained at home and were fully recovered. Five children were taken to their local
hospital because of concerns of dehydration or fever, but none for hypoglycemia.

<table>
<thead>
<tr>
<th>In conclusion: For controlling hypoglycaemic episodes associated with treated diabetes mellitus, easier and less expensive measures could be used, being glucagon injections reserved for exceptional situations.</th>
</tr>
</thead>
</table>

2. Hypoglycaemia associated with non-diabetic conditions

\textit{Neonatal hypoglycaemia}
The definition of hypoglycaemia in the newborn infant has remained controversial
because of lack of significant correlation between plasma glucose concentration,
clinical symptoms, and long-term sequelae. A review article\textsuperscript{21} concluded that there is
inadequate information in the literature to define any one value of glucose below
which irreparable hypoglycemic injury to the central nervous system occurs in a
population of infants or in any given infant. Such lack of definitive measures of
injury specific to glucose deficiency indicates that clinicians should be on the alert for
infants at risk of hypoglycaemia and for clinical signs and conditions that might
herald severe hypoglycaemia. Clinicians should consider the information currently
available, determine a “target” plasma or blood glucose concentration that is
acceptable, and treat infants with glucose concentrations below this value
accordingly.

Hypoglycaemia is associated with poor prognosis in many severe childhood illnesses
especially in sub-Saharan Africa where the prevalence of malaria, diarrhoea and
malnutrition remains high. A study\textsuperscript{22} analysed a large set of data on blood glucose
levels and associated outcomes of paediatric admissions in a rural hospital over an
11-year period. Current definitions and treatment protocols for hypoglycaemia are
based on \textit{observational data} and \textit{expert opinion}. Future large pragmatic randomized
trials would help to define optimal treatment thresholds. Emerging evidence
suggests that \textit{sublingual sugar} is a feasible and effective therapy for correction of
hypoglycaemia, and should be considered where intravenous glucose is delayed or
impossible.

A total of 121 newborn infants with hypoglycaemia were randomized to receive
either 20\% (60 infants) or 15\% (61 infants) glucose infusions into peripheral veins,
which were initiated at 8 mg/kg/min rates and tapered according to the blood
plasma glucose levels. Thirty-six infants in group 20\% and 37 in group 15\% developed some
phlebitis. So there was no difference in local reaction through 20% and 15% glucose infused solutions in neonates.\textsuperscript{23}

| In conclusion: Treatment protocols for hypoglycaemia are based on observational data and expert opinion. Future large pragmatic randomized trials would help to define optimal treatment thresholds. Neonatal hypoglycaemia could be treated by glucose infusions or sublingual sugar where intravenous glucose is delayed or impossible. |

**Idiopathic reactive hypoglycaemia**

Idiopathic reactive hypoglycaemia (IRH) is a condition characterized by aggravated postprandial glucose excursions in otherwise healthy individuals. Reactive hypoglycaemia in the postprandial state is rather exceptional. It is generally associated with adrenergic symptoms and, less often, with cognitive disturbances. In a small study\textsuperscript{24} the incidence of IRH was found in 12.4% and a normal glucose tolerance in 56.4% of the 12 adult participants. This reactive glucose pattern following intake of a high glycaemic load could be modulated by 2-week dietary fibre supplementation. Other dietary advice includes frequent small split meals and limitation of carbohydrates with high glycaemic index. Acarbose, a specific inhibitor of gut alpha-glucosidase enzymes, may be helpful in case of diet failure.\textsuperscript{25}

| In conclusion: Idiopathic reactive hypoglycaemia, an exceptional condition, can be controlled by dietary care, such as, frequent small split meals, limitation of carbohydrates and fiber supplementation. |

**Hypoglycaemia in children with severe falciparum malaria**

Fasting emerges as an important potential risk factor. Length of fasting should be included in studies on hypoglycaemia in malaria. Full recognition of this risk factor for hypoglycaemia in malaria could change both advice to the population, especially mothers, and treatment guidelines in the health sector.\textsuperscript{26}
Post-treatment hypoglycaemia was also less frequent in patients assigned to artesunate than in those assigned to quinine (1.8% vs. 2.8%; OR= 0.63; 95%CI: 0.43-0.91; \(P=0.0134\)).\textsuperscript{27}
Hypoglycaemia is a poor prognostic indicator in severe malaria. Intravenous infusions are rarely feasible in rural areas. A pilot controlled trial\textsuperscript{28} randomly assigned 23 hypoglycaemic children with severe malaria to receive either intravenous 10% glucose (IVG; \(n = 9\)) or sublingual sugar (SLS; \(n = 14\)). In SLS, a teaspoon of sugar, moistened with a few drops of water, was gently placed under the tongue every 20 minutes. All children were treated for malaria with intramuscular artemether. There was no significant difference between the groups in the primary outcome (treatment response), defined as reaching a blood glucose concentration \(\geq 60\) mg/dl within 40 minutes after admission. There was one fatality in each group. Sublingual sugar appears to be a child-friendly, well-tolerated and effective promising method of raising blood glucose in severely ill children. More frequent repeated doses are needed to prevent relapse. Sublingual sugar could be proposed as an immediate "first aid" measure while awaiting intravenous glucose. In many cases it may avert the need for intravenous glucose.
In conclusion: In children with severe falciparum malaria, the associated hypoglycaemia could be controlled with rapid measures against fasting, either through intravenous glucose infusion or sublingual sugar in repeated doses.

Glucagon as a cardiac stimulant after beta-blocker or calcium channel blocker overdose

A systematic review was done in order to evaluate the evidence supporting glucagon use in beta-blocker and calcium channel blocker overdoses. The search found no study in humans. In the five studies of animal models of beta-blocker overdose included, glucagon appeared to consistently increase the heart rate at least transiently but appeared to have no effect on mean arterial pressure even though it possibly increased cardiac output. Its effect on the survival rate in animal models of beta-blocker overdose was unclear. In the six studies of animal models of calcium channel blocker overdose included, glucagon appeared to increase heart rate and cardiac output and reverse second and third degree AV blocks, all at least transiently. Glucagon appeared to have no effect on survival rate. The included studies for both overdoses were not blinded, had limited numbers of animals, and some had inadequate glucagon regime. Despite the lack of evidence, Shepherd considers high-dose glucagon as the first-line antidote in poisoning by beta-blockers where symptomatic bradycardia and hypotension are present. For cases of calcium channel blocker poisoning in which cardiotoxicity is evident, a combination of calcium and epinephrine should be used initially, reserving high-dose insulin with supplemental dextrose and potassium therapy for refractory cases.

In conclusion: The evidence supporting the use of glucagon in the management of patients with beta-blocker and calcium channel blocker overdoses is limited to animal studies with questionable quality.

FINAL COMMENTS

In my point of view, glucagon demonstrates efficacy for the rapid reversion of hypoglycaemic episodes in diabetic patients, despite the absence of evidence that is only provided by high methodological quality studies. If the Expert Committee decides to maintain the selection criteria based on the best evidence, anecdotal reports or small descriptive studies do not provide robust justification for the inclusion. For non-diabetic conditions (neonatal hypoglycaemia, idiopathic reactive hypoglycaemia, and falciparum malaria hypoglycaemia), the evidence of efficacy is scarce, as well. As a cardiac stimulant after beta-blocker or calcium channel blocker overdose, there are no studies in humans that support this indication. Oral sugar supplements and glucose infusions have similar efficacy in diabetic and non-diabetic conditions, but glucagon presents more effectiveness, due to no need of enteral or intravenous routes in patients who cannot ingest or in whom intravenous access is not possible. However, sugar supplement administered by sublingual or buccal (between gum and cheek) routes is a feasible alternative to the first patients. The glucagon safety is not a concern when used for hypoglycaemia correction. Regarding comparative cost, there are decreasing costs with oral glucose, dextrose 5% injections and glucagon. Glucagon treatment could be cost-effective in comparison with the cost of long-term care if severe hypoglycaemia persists enough
to cause hospitalization and the need of complications management. Therefore, I did not find a cost-effectiveness analysis.

Concerning essentiality, glucagon is especially indicated for severe hypoglycaemia in treated-diabetic patients. But that condition (at least one severe hypoglycemic episode in follow-up period of 5 years) occurred in 2.1% of 11,140 patients with type 2 diabetes and in 2.7% of the 5571 patients that received intensive glucose control (Zoungas et al., 2010). However, in these patients, non-severe hypoglycaemia predominates, and there are other measures (education programmes, regular monitoring of blood glucose, adequate carbohydrate replacement, oral sugar supplements, glucose infusions) able to prevent or manage hypoglycaemic problems.

References:
3. Alex J. Graveling AJ, Frier BM. Dementia and Hypoglycemic Episodes in Patients With Type 2 Diabetes Mellitus. *JAMA* 2009; 302 (8): 843.


17. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Long-Term Effect of an Education Program (HyPOs) on the Incidence of Severe Hypoglycemia in Patients With Type 1 Diabetes. Diabetes Care 2010; 33 (3); e36.


