MODERN INSULIN COMBINATIONS (LONG- AND SHORT-ACTING) IN DAILY PRACTICE

KEY MESSAGES

• This review provides best-practice options for using modern insulin combinations in middle-income countries where the cost and complications of poor control place an unsustainable burden on the healthcare system

• The experts are from upper middle-income countries and recommendations are particularly appropriate to South Africa’s healthcare system

• This considered approach to patients who will derive maximum benefit from IDegAsp is easy to introduce in a busy clinical practice.

Havelund S, Hubalek F, Hoeg-Jensen T, et al. Insulin degludec (IDeg) and insulin aspart (IAsp) can be co-formulated such that the formation of IDeg multi-hexamers and IAs. Pharm Res 2015; 32: 2250–2258.
Considerations for the use of modern insulin combinations

An expert group of endocrinologists from upper middle-income countries around the world recently considered the practical use of insulin degludec (IDeg) in combination with the rapid-acting analogue, insulin aspart (IAsp). This combination has been available in South Africa as ‘IDegAsp’ since September 2017*. South African clinicians were involved in the initial global clinical trials’ development programme of this insulin combination, in particular the Ramadan trials in type 2 diabetes. In this review, these clinicians consider the trial results and the pharmacokinetic and pharmacodynamic properties of this novel insulin combination in order to select, on a pragmatic and practical basis, the best patient profile.2

IDegAsp clinical trials – an overview

In type 1 diabetes, IDegAsp has been compared to basal-bolus regimens (insulin detemir/insulin aspart).3 It achieved equal glycaemic control with a lower total insulin dose and reduced nocturnal hypoglycaemia.3

In type 2 diabetes, IDegAsp has been assessed, in a once-daily and a twice-daily dose, for both initiation and intensification of therapy. The results of these trials are summarised in Table 1.3

Pharmacokinetic and pharmacodynamics properties of IDegAsp

The components of this insulin are released independently.6, 7 The ultra-long-acting insulin degludec with its 25-hour long half-life and duration of action of 40 hours has a flat, peakless action-time profile with low intra-variability.6, 7 The insulin aspart is a rapid-acting insulin analogue, with an onset of action of 10-15 minutes, peaking at 90 minutes, and duration of action of 4-5 hours. Importantly, the long-acting insulin does not show any cumulative levels, referred to as stacking (provided that a 6-8-hour treatment gap is maintained between injections). Together, these insulins offer flexibility to certain patients.1

Table 1. Clinical trials with insulin degludec/aspart combination (IDegAsp) 3, 4, 5

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study design</th>
<th>Type of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IDegAsp, once daily at any meal and IAsp at other meals versus insulin detemir and insulin aspart</td>
<td>Randomised, open-label, 26-week, treat-to-target trial1</td>
<td>Type 1 diabetes (n=548)3</td>
<td>Equal ↓ HbA1c to 7.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At least one year duration3</td>
<td>↓ nocturnal hypoglycaemia on IDegAsp (↓37%)3</td>
</tr>
<tr>
<td>2. IDegAsp (70/30 only) versus insulin glargine4</td>
<td>Open-label, 16-week, treat-to-target, randomised trial4</td>
<td>Type 2 diabetes (n=118)4</td>
<td>Mean ↑ in two-hour post-dinner reduction on IDegAsp4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin titrated to target FPG (4-6mmol/l)4</td>
<td>Lower insulin dose on IDegAsp4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDegAsp given at dinner4</td>
<td>Lower rates of hypoglycaemic events in both arms4</td>
</tr>
<tr>
<td>3. IDegAsp versus biphasic IAsp30 – both given twice daily + metformin5</td>
<td>Open-label, three-arm parallel group5</td>
<td>Type 2 diabetes (n=122)5</td>
<td>Mean reduction in HbA1c comparable5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Randomised, 16-week, treat-to-target trial5</td>
<td>IDegAsp, more patients at HbA1c =7% without hypoglycaemia5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower nocturnal hypoglycaemia on IDegAsp5</td>
</tr>
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</table>

* As an aid to the reader, the term ‘IDegAsp’ is used throughout this article to describe this combination.

“IDegAsp achieved equal glycaemic control to basal-bolus with a lower total insulin dose and reduced nocturnal hypoglycaemia.”
Which patients will benefit most?

Maximising effectiveness and reducing costs of hospitalisation and complications

Ten clinical experts from middle-income countries considered the clinical trial results, as well as the pharmacokinetic and pharmacodynamic characteristics of this combination, to develop a practical clinically easy-to-use category list of patients for whom this insulin should be considered (Table 2).2

Table 2: Patient profiles for insulin degludec/insulin aspart

<table>
<thead>
<tr>
<th>Type of diabetes</th>
<th>Current medication</th>
<th>Efficacy concern</th>
<th>Safety/tolerability concerns</th>
<th>Convenience concerns</th>
<th>Suggested IDegAsp regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td>Insulin-naive, on multiple oral drugs</td>
<td>Poor control on oral drugs</td>
<td>Need for safe insulin, for example, in the elderly and frail</td>
<td>Need to allow flexibility in timing administration</td>
<td>Initiate IDegAsp OD</td>
</tr>
<tr>
<td>Type 2</td>
<td>Basal insulin</td>
<td>Poor prandial control with MTD</td>
<td>Unacceptable hypoglycaemia or weight gain with effective dose</td>
<td>Unwillingness to inject at same time every day or twice</td>
<td>Intensify to IDegAsp OD</td>
</tr>
<tr>
<td>Type 2</td>
<td>Premixed insulin OD; basal plus</td>
<td>Poor fasting control</td>
<td>Nocturnal hypoglycaemia with effective doses</td>
<td>Unwillingness to take two injections</td>
<td>Intensify to IDegAsp OD</td>
</tr>
<tr>
<td>Type 2</td>
<td>Premixed insulin BID</td>
<td>Poor fasting control</td>
<td>Unacceptable hypoglycaemia with effective doses</td>
<td>Unwillingness to take injections with antipodal meals everyday</td>
<td>Intensify to IDegAsp BID</td>
</tr>
<tr>
<td>Type 2</td>
<td>Basal-bolus therapy</td>
<td>Unacceptable variability in control</td>
<td>Unacceptable nocturnal hypoglycaemia</td>
<td>Dissatisfaction with multiple doses</td>
<td>Interchange to IDegAsp OD, with IAsp BID or IDegAsp BID</td>
</tr>
<tr>
<td>Type 1</td>
<td>Newly diagnosed</td>
<td>Need for effective regimens</td>
<td>Need to avoid hypoglycaemia, especially nocturnal hypoglycaemia</td>
<td>Need to keep number of injections to minimum</td>
<td>Initiate IDegAsp OD, with IAsp BID</td>
</tr>
<tr>
<td>Type 1</td>
<td>Basal-bolus therapy</td>
<td>Unacceptable variability in control</td>
<td>Unacceptable nocturnal hypoglycaemia</td>
<td>Dissatisfaction with multiple doses</td>
<td>Interchange to IDegAsp OD, with IAsp BID</td>
</tr>
</tbody>
</table>

MTD: Maximum tolerated dose, OD: Once-daily, BID: Twice-daily, IDegAsp: Insulin degludec aspart

Key comments on pragmatic use of IDegAsp in selected patients (Table 2)

Type 2 diabetes

• Premix insulin has been promoted by the International Diabetes Federation (IDF)2 for first-line insulin use in insulin-naïve patients. IDegAsp can be considered in this category also.

• For patients who wish to retain flexibility when the timing of their main meal changes, this insulin combination can be administered in one injection regardless of when the main meal occurs.

“Premix insulin has been promoted by the IDF for first-line insulin use in insulin-naïve patients.”
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“People on premix insulin could be switched unit-for-unit to IDegAsp either once or twice a day.”

- The low risk of hypoglycaemia is an advantage, particularly for the elderly, the frail and those at high risk of hypoglycaemia (those with renal or hepatic impairment).
- IDegAsp can be used to intensify therapy, without increasing the number of injections in people already on either basal insulin or premix insulin.
- Switching to IDegAsp can be considered in the case of unacceptable hypoglycaemia or weight gain, or where a rigid insulin regimen becomes increased for the patient.2
- When switching, a unit-to-unit switch can be made for the basal component.4 People on premix insulin could be switched unit-for-unit to IDegAsp either once or twice a day.2
- Patients on basal plus therapy (basal and one bolus) may benefit from the convenience of one injection. Equally, those on three injections per day (basal and two boluses) may benefit from a simpler twice-daily injection regimen.

Type 1 diabetes

- IDegAsp can be used as insulin of initiation or as switch therapy in type 1 diabetes.8
- Newly diagnosed, insulin-naïve stable type 1 diabetes patients, not requiring intravenous insulin, can be managed on an IDegAsp-based regimen, i.e. one dose IDegAsp plus two doses of IAsp.9
- IDegAsp-based intensive therapy can also be used in type 1 diabetes patients already on basal-bolus therapy, especially if glycaemic control is not achieved.2

Conclusion

This review is of particular interest to South African healthcare professionals who are seeking a pragmatic approach to the use of this novel insulin combination in selected patients.

References

8. Package insert