Dr. R. JAYCHANDRA REDDY

Oration

NOVEL INSULINS
Dr. Yash Pal Munjal
MD, FICP, MAMS, FRCP (EDIN), FACP (USA)
FIACM, FIAMS, FIMSA

Medical Director, Banarsidas Chandiwala Institute of Medical Sciences
Chief Consultant, Centre for Diabetes & Lifestyle Diseases, Kalkaji, New Delhi

- Served API as Past President, Past Dean
- Editor in Chief – API Textbook of Medicine – 9th & 10th Editions.
- Around 50 publications to his credit.
- Orations, like Presidential Oration, Dean’s Oration, Rabindra Nath Tagore Oration.
- Principal Investigator in many multicentric as well as multinational trials
- Advisory Committees of prestigious journals like Indian Heart Journal, JAPI, Journal of Clinical Diabetology, Indian Journal of Clinical Medicine etc.
Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research–INDia DIABetes (ICMR–INDIAB) study

R. M. Anjana • R. Pradeepa • M. Deepa • M. Datta • V. Sudha • R. Unnikrishnan • A. Bhansali • S. R. Joshi • P. P. Joshi • C. S. Yajnik • V. K. Dhandhania • L. M. Nath • A. K. Das • P. V. Rao • S. V. Madhu • D. K. Shukla • T. Kaur • M. Priya • E. Nirmal • S. J. Parvathi • S. Subhashini • R. Subashini • M. K. Ali • V. Mohan • on behalf of the ICMR–INDIAB Collaborative Study Group

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These study estimates translate to 62.4 million individuals with diabetes & 77.2 million with prediabetes in India!!!
Goals of Therapy

- Improve patient outcomes
- Minimize the risk of complications and their cost
- Ideally and simultaneously address
  - deteriorating β-cell function
  - A1C, fasting plasma glucose (FPG), and postprandial

An ideal treatment would reduce cardiovascular risk factors as well as control blood glucose levels

- 1% reduction in A1C
  - 37% decrease in risk for microvascular complications
  - 21% decrease in risk of death related to diabetes
INSULIN - 1922

MOST POTENT CONTROLS SUGAR AT ANY LEVEL
Why do we need newer insulins?
More needs to be done earlier to improve glycaemic control

• In type 2 diabetes, improvements in glycaemic control reduce the risk of complications

Hypoglycaemia is a barrier to effective glycaemic management

- High levels of concern over hypoglycaemia
- 60% of patients experienced a hypoglycaemic event in the past 12 months
- 76% of patients said that hypoglycaemia is one of the most fearful parts of having diabetes
- 74% of physicians would treat patients’ diabetes more ambitiously if there was no concern over hypoglycaemic events

Missing doses impacts on glycaemic control

Missing 2 basal insulin injections per week

= 0.2–0.3% increase in HbA₁c

Impact of fixed-administration regimens on daily life

22% of patients said that they planned their daily activities around their insulin injections

Reasons for innovation!

- Patients are in poor blood glucose control
- Insulin doses are being missed or not taken as prescribed
- Patients struggle to remain fully adherent to their insulin regimens
- Patients and physicians are concerned about hypoglycaemia

Key Concepts of Insulin Therapy

- **Basal** insulin
  - Controls hepatic glucose production
- **Food** (prandial) insulin
  - Based on meal carbohydrate content
- **Correction** (supplemental) insulin
  - Treats acute elevation in blood glucose
# A comparison of human and analogue insulins

<table>
<thead>
<tr>
<th>Human insulins</th>
<th>Analogue insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Acting</strong></td>
<td><strong>Rapid acting</strong></td>
</tr>
<tr>
<td>• Absorbed quickly and last for 3-10 hours&lt;br&gt;  e.g., Humulin S®, Insuman® Rapid</td>
<td>• Absorbed very rapidly, last only 3-6 hours - aim to control postprandial glucose&lt;br&gt;  e.g., NovoRapid®, Humalog®, Apidra®</td>
</tr>
<tr>
<td><strong>Intermediate and Long Acting</strong></td>
<td><strong>Long Acting</strong></td>
</tr>
<tr>
<td>• More slowly absorbed, last for up to 24 hours&lt;br&gt;  e.g., Insulatard®, Humulin® I, Insuman® Basal</td>
<td>• More slowly absorbed - designed to provide full 24 hour coverage with low level of insulin throughout day and night&lt;br&gt;  e.g., Leumir®, Lantus®</td>
</tr>
<tr>
<td><strong>Premix</strong></td>
<td><strong>Premix</strong></td>
</tr>
<tr>
<td>• Mixture of short- and long-acting insulin (biphasic human insulin)&lt;br&gt;  e.g., Mixtard® 30, Insuman® Comb</td>
<td>• Mixture of rapid- and intermediate-acting insulin with duration up to 24 hours&lt;br&gt;  e.g., NovoMix® f5555530, Humalog® Mix 25/75</td>
</tr>
</tbody>
</table>

**Humulin S, Humulin I and Humalog are registered trademarks of Eli Lilly and Company**

**Insuman Rapid, Insuman Basal, Insuman Comb, Lantus and Apidra are registered trademarks of Sanofi-Aventis**

**Insulatard, Mixtard 30, NovoRapid, NovoMix and Leumir are registered trademarks of Novo Nordisk**
BASAL INSULINS
Limitations of Current Basal Insulins

- NPH has great interpatient variability in absorption rate\(^a\)
- Variable onset of action and unpredictable peak increases risk for hypoglycemia
- Duration of action dose-dependent\(^b\)
## Long –Acting Analouges

<table>
<thead>
<tr>
<th><strong>Detemir</strong></th>
<th>Self associates and has reversible binding to albumin.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glargine</strong></td>
<td>Forms microprecipitates at injection site, and is slowly released into circulation</td>
</tr>
</tbody>
</table>
# Comparison of Human Analogues Insulin

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
<th>Onset of Action</th>
<th>Peak</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human NPH/Lente</td>
<td>1-4 hours</td>
<td>4-12 hours</td>
<td>10-20 hours</td>
</tr>
<tr>
<td>Human Ultralente</td>
<td>6-8 hours</td>
<td>Unpredictable</td>
<td>16-20 hours</td>
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<tr>
<td>Glargine</td>
<td>2-3 hours</td>
<td>Flat</td>
<td>~24 hours</td>
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<tr>
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</tr>
</tbody>
</table>

The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated here should be considered general guidelines only.
Insulin Activity measured by rate of glucose metabolism (Glucose Infusion Rate)

NPH

Glargine steady-state 0.35 U/kg

Glargine 1st injection 0.30 U/kg

Subjects with T1DM Mean ± SEM

sc insulin evening 0.30 U/kg

Time (hours)

Glucone Infusion Rate mg/Kg/min

μmol/Kg/min

Lepore M. et al., Diabetes 49: 2142-8, 2000

Porcellati F. et al., Diabetes Care 30:2447-52, 2007
Insulin Activity measured by rate of glucose metabolism (Glucose Infusion Rate)

- sc insulin evening 0.30 U/kg
- Subjects with T1DM Mean ± SEM
  - Glargine steady-state 0.35 U/kg

**Superiority of Glargine vs NPH in Type 1 Diabetes**
- Less hypoglycaemia (nocturnal)
- Lower or similar A1C
Why do we need improved basal insulins?

- Longer action $\rightarrow$ better basal coverage
- Flatter profile $\rightarrow$ reduced risk of hypoglycemia
- Less variability $\rightarrow$ easier titration
- Potential to combine with short-acting analogue
Insulin DEGLUDEC:
Insulin Degludec

- Insulin degludec molecule retains the human insulin amino acid sequence except for the deletion of ThrB30 and the addition of a 16-carbon fatty diacid attached to LysB29 via a glutamic acid spacer.
- Self-associate to form large multi-hexamer assemblies at the site of injection.
- Half-life longer than 24 hours and is detectable in circulation for at least 96 hours after injection (possible thrice weekly injection).
- The low IGF-1 receptor binding affinity and the low mitogenic/metabolic potency ratio ensuring molecular safety.
Designing insulin degludec: structure

**Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) human insulin**

**desB30 Insulin**

**Hexadecandioyl**

Fatty diacid side chain

**L-g-Glu**

Glutamic acid 'spacer'

**DesB30**

**B29**

**B1**

**A1**

**A21**
Insulin degludec: immediately after injection

Phenol from the vehicle diffuses quickly, and degludec links up via single side-chain contacts

Long multi-hexamer chains assemble
Insulin degludec: slow release following injection

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

Monomers are absorbed from the depot into the circulation
The terminal half-life of IDeg is 25 hours – twice as long as for IGlar

<table>
<thead>
<tr>
<th>Half-life (hours)</th>
<th>IDeg 0.4 U/kg</th>
<th>IDeg 0.6 U/kg</th>
<th>IDeg 0.8 U/kg</th>
<th>IGlar 0.4 U/kg</th>
<th>IGlar 0.6 U/kg</th>
<th>IGlar 0.8 U/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25.9</td>
<td>27.0</td>
<td>23.9</td>
<td>11.8</td>
<td>14.0</td>
<td>11.9</td>
</tr>
<tr>
<td>Mean half-life (hours)</td>
<td>25.4</td>
<td></td>
<td></td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are harmonic means

Heise et al. IDF 2011:P-1444; Diabetologia 2011;54(Suppl. 1):S425; Diabetes 2011;60(Suppl. 1A):LB11
Insulin degludec = 0.6 U/kg

Duration of action studied in 42h clamps

Duration of action >42 hours

Kurtzhals et al. Diabetologia 2011;54(suppl. 1):S426; Diabetes 2011;60(suppl. 1A):LB12
Study design

**Patients with type 2 diabetes (n=687)**

- **IDeg OD Flex ± OADs (n=229)**
- **IGlar OD (according to label†) ± OADs (n=230)**
- **IDeg OD (main evening meal) ± OADs (n=228)**

**Inclusion criteria**
- Type 2 diabetes ≥6 months
- Previously treated with OADs and/or basal insulin
- HbA1c:
  - OADs only 7–11%
  - Basal insulin ± OADs 7–10%
- BMI ≤40 kg/m²
- Age ≥18 years

†IGlar dosed any time of the day but the same time each day

**References**
- BMI, body mass index; IDeg, insulin degludec; IGlar, insulin glargine; met, metformin; OAD, oral antidiabetic drug; OD, once daily; pio, pioglitazone; SU, sulphonylurea
- Atkin et al. Diabetologia 2011;54(Suppl. 1):S53; Meneghini et al. Diabetes 2011;60(Suppl. 1A):LB10
Insulin degludec vs. Insulin glargine in T2DM: flexible dosing arm

Forcing flexible dosing in extremes

T2DM, type 2 diabetes mellitus
HbA$_{1c}$ over time

Mean±SEM; FAS; LOCF

Comparisons: estimates adjusted for multiple covariates
Atkin et al. Diabetologia 2011;54(Suppl. 1):S53; Meneghini et al. Diabetes 2011;60(Suppl. 1A):LB10
Conclusion

- Insulin degludec administered flexibly in a treat-to-target regimen effectively improves HbA$_{1c}$ by 1.28% in patients with type 2 diabetes similarly to insulin glargine and insulin degludec administered once daily.

- FPG is reduced more (0.42 mmol/L) with insulin degludec dosed flexibly than with insulin glargine dosed once daily.

- The rate of overall hypoglycaemia with flexible dosing is similar to the comparators.
  - 23% lower rate of nocturnal hypoglycaemia compared with insulin glargine (ns).

- Insulin degludec administered in a flexible regimen is well tolerated.

BEGIN™: a truly global programme

40 countries
9138 patients randomised
Degludec summary

**Achieve glycaemic control**

**Efficacy**
- Excellent improvement in HbA$_{1c}$
- Superior FPG reduction

**Avoid hypos**

**Safety**
- Less hypoglycaemia
- Reduction of up to 36% in nocturnal hypoglycaemia

**Flexibility**

**Convenience**
- Dosing flexibility: administration any time on any day
Degludec Summary

- Insulin degludec is a new generation ultra-long acting basal insulin.
  - Unique protraction mechanism (multi-hexamer formation in subcutaneous depot).
  - Half life is 25.4 hours twice that of glargine.
    - Ultra-long action >42 hours.
  - Flat and stable PK/PD profile, 4 times lower intra-subject variability.
  - Good molecular safety profile.
  - Low hypoglycemia with degludec molecule.
- Flexible dose timings an added feature of degludec.
DegludecPlus

- Insulin degludec (IDeg) is a novel insulin analog that forms soluble multi-hexamer assemblies after s.c. injection, resulting in ultra-long duration of action.
- IDegAsp is a soluble insulin product comprising IDeg (70%) and insulin aspart (IAsp, 30%).
- IDegAsp provided comparable overall glycemic control to IGlar at similar rates of hypoglycemia, but with the additional benefit of post-dinner PG control.
Basal Insulin LY2605541

- Insulin lispro modified with a 20-kDa polyethylene glycol (PEG) moiety
- Larger size delays absorption and slows clearance
- Preferential hepatic uptake and greater lipolysis observed in a dog model
  - Hypothesized potential for less lipogenesis, increased lipid oxidation and weight loss

Rosenstock J et al. Poster #1026-P 2012 Scientific Sessions of the ADA
Large hydrodynamic size of BIL may allow slow absorption of monomers predominantly via the lymphatic system

Hypothesis: BIL is believed to be transferred from the lymphatic vessels to the systemic circulation

BIL is believed to enter the bloodstream at the subclavian veins from the thoracic and right lymphatic ducts
Glycemic Control after 8 wks of LY2605541 Compared to Once Daily Glargine in Type 1 Diabetes

LEFT:
- Baseline for both
- insulin GL
- LY2605541

RIGHT:
- Baseline for both
- insulin GL
- LY2605541

* $P < 0.01$

Rosenstock J. et al, Diabetes Care 2013;36(3): 522-528
Basal Insulin LY2605541 compared to Insulin Glargine in Type 1 Diabetes

A next generation insulin glargine formulation
New insulin glargine formulation: glucose control and hypoglycemia in people with Type 2 diabetes using basal and mealtime insulin (EDITION I)

Matthew C Riddle¹, Geremia B Bolli², Monika Ziemen³, Isabel Muehlen-Bartmer³, Florence Bizet³, Philip D Home⁴
# U300 vs U100 Glargine in Type 2 Diabetes (EDITION I)

<table>
<thead>
<tr>
<th></th>
<th>Glargine U300</th>
<th>Glargine U100</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔA1C at 6 months</td>
<td>-0.83%</td>
<td>-0.83%</td>
<td>-0.11-0.11</td>
<td></td>
</tr>
<tr>
<td>Any hypoglycemia</td>
<td>83.4%</td>
<td>88.6%</td>
<td>0.94</td>
<td>0.89-0.99</td>
</tr>
<tr>
<td>Any nocturnal</td>
<td>45.3%</td>
<td>59.7%</td>
<td>0.76</td>
<td>0.66-0.87</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>5.0%</td>
<td>5.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Imagine a “Smart” Insulin

- Once-a-day injection
- No hypoglycemia
- Near-perfect glucose control
- Significantly fewer finger-sticks
- Minimal dietary restrictions
Glucose-responsive SmartInsulin technology

1. IPC and GBM combine to form insoluble network
2. Free glucose molecules displace the IPC from the GBM
3. The matrix erodes from the surface inward
4. The released IPC lowers glucose levels in the body
5. The matrix stops eroding until the next glucose challenge
Brief history of rapid-acting insulin

1921  Banting & Best discover insulin
1922  Banting, Best & Collip use bovine insulin extract in humans
1955  Frederick Sanger determines the amino acid sequence of insulin
1975  Fully synthetic insulin (CGP 12 831) developed in the laboratories of Ciba-Geigy in Basel
1978  Genentech using a plasmid of *E. coli* bacteria produce recombinant human insulin
1980  Recombinant DNA ‘human’ insulin tested on 17 non-diabetic volunteers in England
1982  Humulin R approved for use in the USA
1996  Rapid-acting analogs enter the market (lispro)
Comparison of Human Insulins and Analogues

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<th>Onset of Action</th>
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<th>Duration of Action</th>
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<tr>
<td>Lispro/Aspart</td>
<td>5-15 minutes</td>
<td>1-2 hours</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Human Regular</td>
<td>30-60 minutes</td>
<td>2-4 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Human NPH/Lente</td>
<td>1-4 hours</td>
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The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated here should be considered general guidelines only.
# Rapid Acting Analouges

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Modification</th>
<th>Cost /100u*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular (Actrapid, Humulin R)</td>
<td>30–60 minutes</td>
<td>2–3 hours</td>
<td>8–10 hours</td>
<td>N/A</td>
<td>2.65–2.97</td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td>5–15 minutes</td>
<td>30–90 minutes</td>
<td>4–6 hours</td>
<td>Substitute lysine for proline at position 28 of the insulin β chain</td>
<td>3.16</td>
</tr>
<tr>
<td>Aspart (NovoRapid)</td>
<td>5–15 minutes</td>
<td>30–90 minutes</td>
<td>4–6 hours</td>
<td>Substitute aspartic acid for proline at position 28 of the insulin β chain</td>
<td>3.16–3.51</td>
</tr>
</tbody>
</table>

*Based on PBS dispensed price for maximum quantity (includes dispensing fee and pharmacy mark up)
Pharmacokinetics of rapid-acting insulin analogs

Graph showing serum insulin levels over time after insulin injection:
- Blue line: Rapid-acting insulin analogs
- Black line: Regular human insulin

*Glulisine uses polysorbate 20 instead of zinc
What are the benefits of rapid-acting analogs compared to Regular human insulin?
Potential advantages of rapid-acting insulin analogs

- Earlier onset & peak of biologic activity
- Shorter duration of action
- Less biologic variability

= Lower post-prandial glucose
= Less late prandial hypoglycemia
= Less glycemic fluctuations
# Halozyme’s insulin aspart/lispro/glulisine + PH20

## Key facts

<table>
<thead>
<tr>
<th><strong>Key facts</strong></th>
<th><strong>Details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active drug</strong></td>
<td>• <strong>Insulin aspart, insulin lispro and insulin glulisine</strong></td>
</tr>
</tbody>
</table>
| **Formulation**   | • Insulin is formulated with **hyaluronidase (PH20)**  
• Hyaluronidase splits hyaluronic acid in the subcutaneous tissue, thereby enhancing dispersion and absorption of insulin  
• The tissue is restored within 18-24 hours |
| **Status**        | • **Phase 3**                                                                                                                                                                                              |
| **Advantages**    | • Faster onset of action and improved postprandial glucose vs NovoRapid® and Humalog  
• Reduced variability in pump vs NovoRapid® in T1DM  
• Non-inferior HbA1c reduction vs Humalog in T1DM and T2DM |
| **Disadvantages** | • IV administration may not be feasible                                                                                                                                                                   |
| **Uncertainties** | • Safety of long-term use with multiple injections per day is unknown  
• Stability is unknown.                                                                                                                        |
Lispro in combination rHuPH20
VIAject™ (human insulin + ethylene diamine tetra acetic acid + citric acid), a very rapid-acting form of injectable human insulin for meal-time use by patients with Type 1 or Type 2 diabetes.

- VIAject™ formulation promotes a more monomer formation
- Currently undergoing Phase III clinical studies.
- The two studies, one involving 400 patients with Type 1 diabetes and the other involving 400 patients with Type 2 diabetes, are comparing the effects of VIAject™ to recombinant human insulin.
Linjeta vs. regular human insulin

[Graph showing concentration over time for Linjeta and regular human insulin]
Adocia’s **Hinsbet/BioChaperone Humalog** –

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Human insulin and insulin lispro</th>
</tr>
</thead>
</table>
| **Formulation** | • Insulin forms a reversible complex with the polymer dextran, which is grafted with carboxylate groups and hydrophobic amino acids  
• The technology, BioChaperone, aims to reduce interaction with the subcutaneous tissue, thereby causing insulin to diffuse faster |
| **Status**      | • **Hinsbet (human insulin): phase 2**  
• **BioChaperone Humalog: phase 1 in collaboration with Eli Lilly** |
| **Advantages**  | • Human insulin formulation has similar onset of action, local tolerance, and variability as NovoRapid® |
| **Uncertainties** | • Many uncertainties exist as few data have been released. These include safety, stability and long-term efficacy |
### Alternative Routes

<table>
<thead>
<tr>
<th>Insulin route</th>
<th>Features</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet injectors</td>
<td>High-pressure stream → SQ</td>
<td>Painful</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK profile ?Δed</td>
</tr>
<tr>
<td>Iontophoresis</td>
<td>Electric current</td>
<td>Efficacy affected by hair</td>
</tr>
<tr>
<td>Low-freq u/s</td>
<td>1 h tid → 36 U qd</td>
<td>Too slow</td>
</tr>
<tr>
<td>Intranasal</td>
<td>60-120 U ↓postmeal glucose in T2 DM</td>
<td>↓bioavailability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abs enhancers ↑nasal irritation</td>
</tr>
<tr>
<td>Oral</td>
<td>Many products in development</td>
<td>↓bioavailability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzymatic degradation</td>
</tr>
<tr>
<td>Buccal spray</td>
<td>Small trials in T1 &amp; T2 DM</td>
<td>Abs enhancers required</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>Most extensively studied</td>
<td>Low bioavailability</td>
</tr>
</tbody>
</table>
Alternative Routes

Oral Insulin

Biocon, Nova Nordisk, Biodal Inc., Oramed
Delivers insulin in physiological manner
- It is safe
- well tolerated
- effective in a dose related manner
- Lowers Prandial Sugar upto 50 mg per dl

Insulin Patch pumps / Insulin Patch
- Disposable
- Semi Disposable
INHALED INSULIN
# MannKind’s Afrezza (Inhaled Insulin)

<table>
<thead>
<tr>
<th>Key facts</th>
<th></th>
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<tbody>
<tr>
<td><strong>Active drug</strong></td>
<td>• Human insulin</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>• <strong>Technosphere</strong> dry powder formulation of human insulin</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>• Commercial inhaler, Gen2C, different from the MedTone inhaler used in the phase 3 programme</td>
</tr>
<tr>
<td></td>
<td>• Cartridges in blister packs</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>• Non-invasive insulin therapy</td>
</tr>
<tr>
<td></td>
<td>• Fast onset of action</td>
</tr>
<tr>
<td></td>
<td>• Potential benefits on body weight and hypoglycaemia</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Adverse events related to the respiratory tract</td>
</tr>
<tr>
<td></td>
<td>• Cessation of action may be too fast</td>
</tr>
<tr>
<td></td>
<td>• Potentially carcinogenic</td>
</tr>
<tr>
<td><strong>Uncertainties</strong></td>
<td>• FDA’s benefit/risk evaluation,</td>
</tr>
<tr>
<td></td>
<td>• Comparability between the commercial inhaler (Gen2C) and the inhaler used in the pivotal trials (MedTone)</td>
</tr>
<tr>
<td></td>
<td>• Long-term safety</td>
</tr>
<tr>
<td><strong>Upcoming key events</strong></td>
<td>• Completion of phase 3 trial vs Aspart in T1DM (2012)</td>
</tr>
</tbody>
</table>
Afrezza® Inhaled Human Insulin

- FDA approved June 2014
- Patients with type 1 and type 2 diabetes
- Ultra rapid-acting insulin
Afrezza® Inhaled Human Insulin
Pharmacokinetics

Baseline-Corrected Glucose Infusion Rate (A) and Baseline-Corrected Serum Insulin Concentrations (B) after Administration of AFREZZA or Subcutaneous Insulin Lispro in Type 1 Diabetes Patients*

* Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro.

Afrezza(R) [package insert]. Danbury, CT: MannKind Corporation; 2014.
Adverse Reactions

- Hypoglycemia
- Cough
- Throat pain/irritation
- Acute bronchospasm in patients with chronic lung disease
- Decline in pulmonary function
- Lung cancer
- Diabetic ketoacidosis (DKA)
- Hypersensitivity reactions
Oral insulin formulations

Barriers to absorption of drug in the intestine (Soltero et al)
General approaches to ORAL delivery of insulin

<table>
<thead>
<tr>
<th>Approach</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Encapsulation</td>
<td>Chitosan, poly(lactic-co-glycolic acid), alginate, cyanoacrylate particles, $\beta$-cyclodextrin, liposomes</td>
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<tr>
<td>Microparticles and nanoparticles</td>
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<tr>
<td>Permeation enhancers</td>
<td>Zonula occludens toxin (ZOT), fatty acid salts and esters</td>
</tr>
<tr>
<td>Protection against enzymes</td>
<td>Pegylation, enteric coated particles, pH responsive gels, protease inhibitors</td>
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</tbody>
</table>
Summary

- Oral insulins have shown promise in early clinical development but still no well conducted global clinical trials – bioavailability in fed state / dose titration??

- Inhaled insulin may become available in the near future but long term pulmonary safety (neoplasm) is not clear.

- Various basal insulin formulations are in development with primary focus on reducing risk of hypoglycemia and making insulin treatment more flexible.

- Health care professional have a critical role in making the use of these innovations in clinical practice.

- Next generation insulin analogues Degludec and DegludecPlus appear to be welcome addition to diabetologist’s armamentarium.
thank you