Evidence for biosimilars

What is a biosimilar and should I prescribe them in practice?

Dr Kevin Fernando

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Graduated Edinburgh 2000

GP partner and educational supervisor, North Berwick HC

Specialist interests in diabetes and medical education

Education director, GPnotebook Education

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Disclosures

- **Speaker honoraria:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Lilly, MSD, Mylan, Napp, Novo Nordisk, SB Communications, OmniaMed, Roche, Pfizer, NB Medical, Cogora, Internis, Consilient Health, Mundipharma, MGP Ltd.
- **Advisory board honoraria:** AstraZeneca, Bristol-Myers Squibb, Lilly, Boehringer
- Ingelheim, Janssen, MSD, Novo Nordisk, Takeda, Sanofi, Amgen, Mylan
- **Educational grants:** Boehringer Ingelheim, Lilly, Novo Nordisk, Takeda
- **Conference registration & subsistence:** Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Lilly, MSD, Novo Nordisk, Takeda
- • **I have many doubts about modern medicine**

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Learning objectives

- What are biologics and biosimilars?
- How are biosimilars approved?
- What is NICE's guidance on biosimilars implementation?
- Why should we use biosimilars?

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What are biologics and biosimilars?

- Incremental innovation of insulin analogues with improved pharmacodynamic and pharmacokinetic profiles over the last decade[1]

- Biosimilar insulins represent the latest development in insulin therapy

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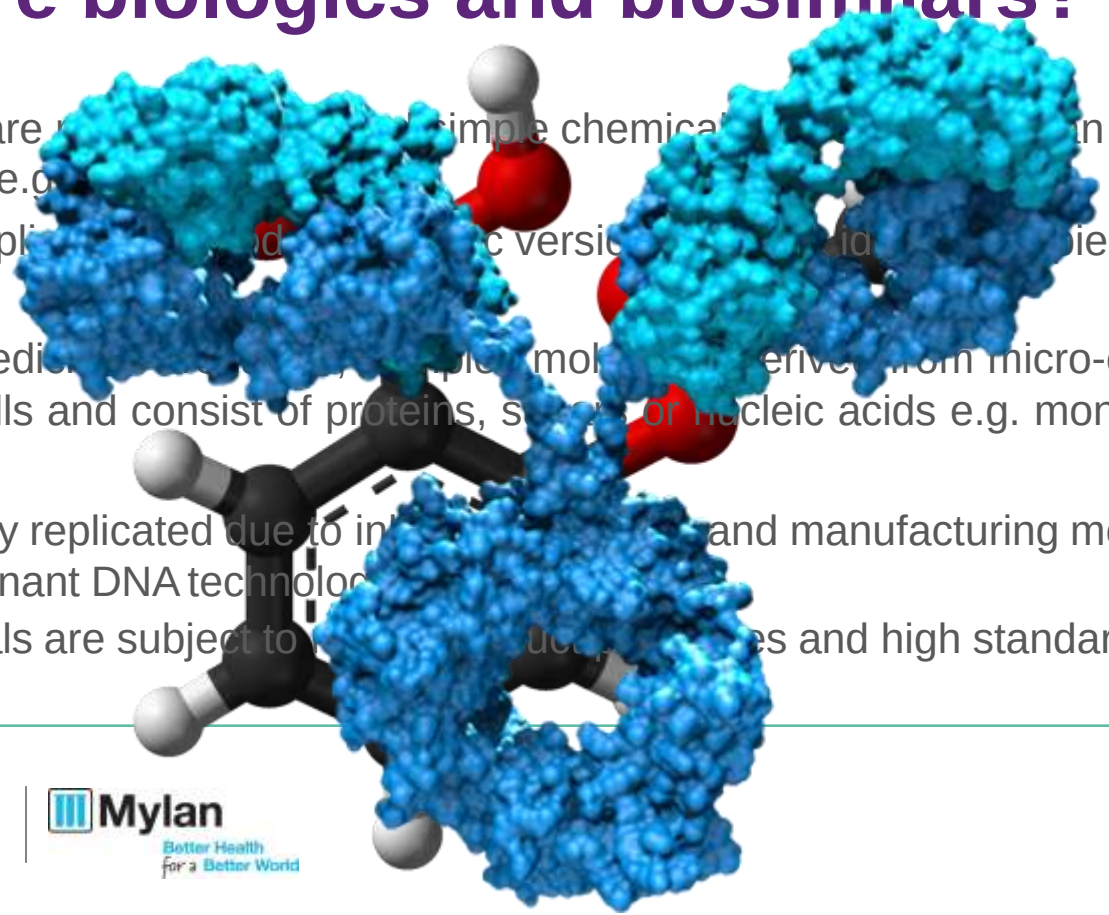
1. Greene J, et al. *N Engl J Med* 2015; 372: 1171-1175.

What are biologics and biosimilars?



- Most drugs are [illegible] simple chemical [illegible] n be chemically synthesised e.g.
  - Easily repli[illegible]d [illegible]c versio[illegible] id[illegible]ies of the reference drug
- Biological medi[illegible] mol[illegible] erive[illegible] from micro-organisms, human or animal cells and consist of proteins, s[illegible] or nucleic acids e.g. monoclonal antibodies or insulin
  - Not easily replicated due to in[illegible] and manufacturing methods (recombinant DNA technolo[illegible]
  - Biologicals are subject to [illegible]duct[illegible]es and high standards of quality control

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What are biologics and biosimilars?

- Biological medicines are not new!
  - Humulin produced by recombinant DNA technology in 1982
  - Humulin S uses same technology to introduce the human insulin gene into *E. coli*
- A biosimilar is a medicine developed to be similar to an existing biological medicine
  - To gain a licence for use, biosimilars have been demonstrated to have the same **safety** and **efficacy** profile as the original reference biological medicine

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Variability between biological medicines

- Consecutive batches of the same biological medicine may show a small degree of variability within the accepted ranges[2]
- The amino acid sequence and biological activity of the protein remain the same in all batches, even when these minor differences in sugar chains are present[2]

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2. European Medicines Agency and European Commission. Biosimilars in the EU: Information guide for healthcare professionals. Available at: www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed May 2019).

How are biosimilars approved?

- Approval of generic drugs only requires demonstration of pharmaceutical and bio-equivalence

- More complex and rigorous requirements for biosimilars required by European Medicines Agency[3]
  - ❑ Preclinical in vitro and in vivo
  - ❑ Pharmacodynamic, pharmacokinetic
  - ❑ Phase III clinical trials

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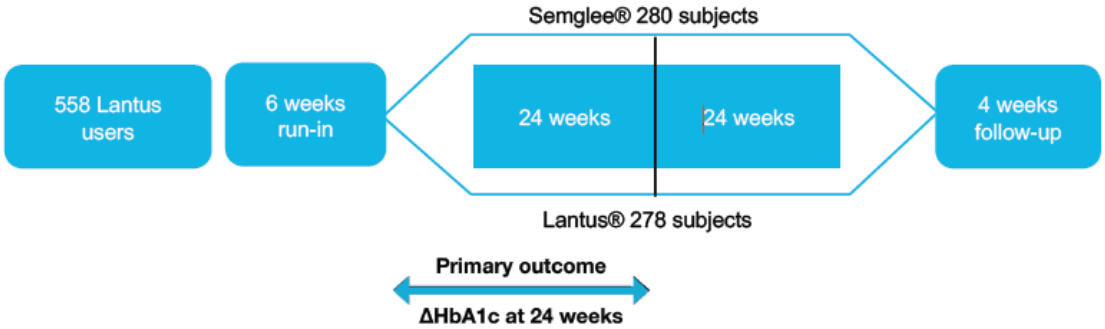
3. European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (accessed May 2019).

How are biosimilars approved?

Example of clinical comparative study4 (INSTRIDE 1)

- Multicentre, randomised parallel phase 3 study
- 558 existing Lantus® users with T1DM
- Randomised 1:1 to continue with Lantus® or switch to Semglee®



4. Blevins TC, et al. Diabetes Obes Metab 2018; 20: 1944-1950.

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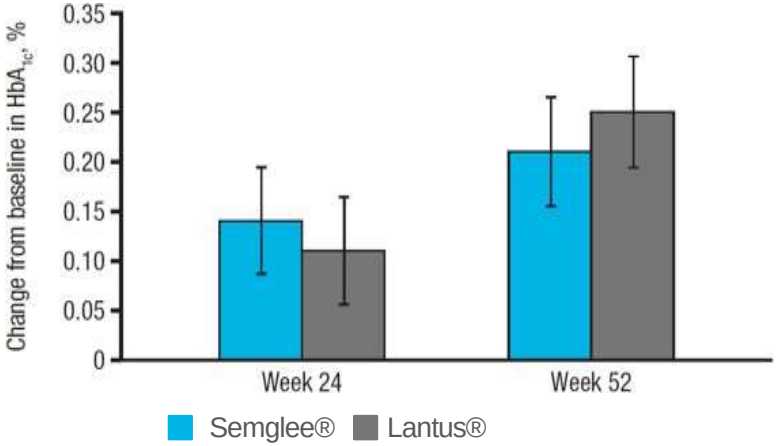
No clinical differences in safety and efficacy

- Primary endpoint:
  - mean change in HbA1C from baseline to W24



- Secondary endpoints:
  - FPG
  - Changes in average SMBG
  - Increase in basal daily insulin
  - Change in mealtime daily insulin dose

- Conclusion:
  - No clinical meaningful differences in safety and efficacy between the two treatments

Same results demonstrated in 560 people with T2DM (INSTRIDE 2)

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4. Blevins TC, et al. *Diabetes Obes Metab* 2018; 20: 1944-1950.

What is NICE's guidance on biosimilars implementation?

- Adverse events with biological drugs (both reference and biosimilar) are more likely than with generic chemical drugs, therefore,
    - Comprehensive post-marketing surveillance is crucial and is in place before commercialisation
- Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of the originator[5]

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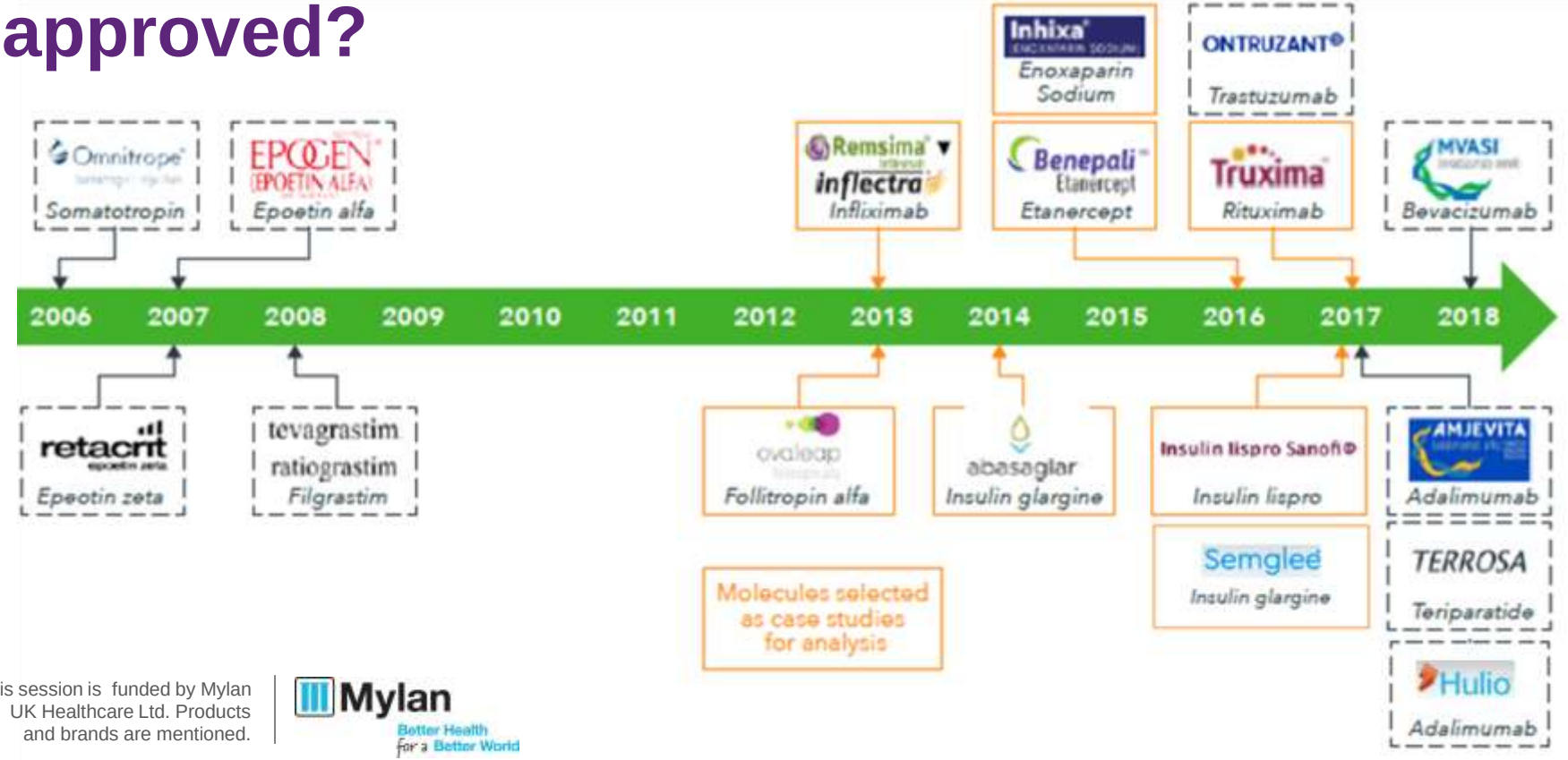
5. NICE. Biosimilar medicines. KTT15. Available at: www.nice.org.uk/advice/ktt15 (accessed May 2019).

How are biosimilars approved?



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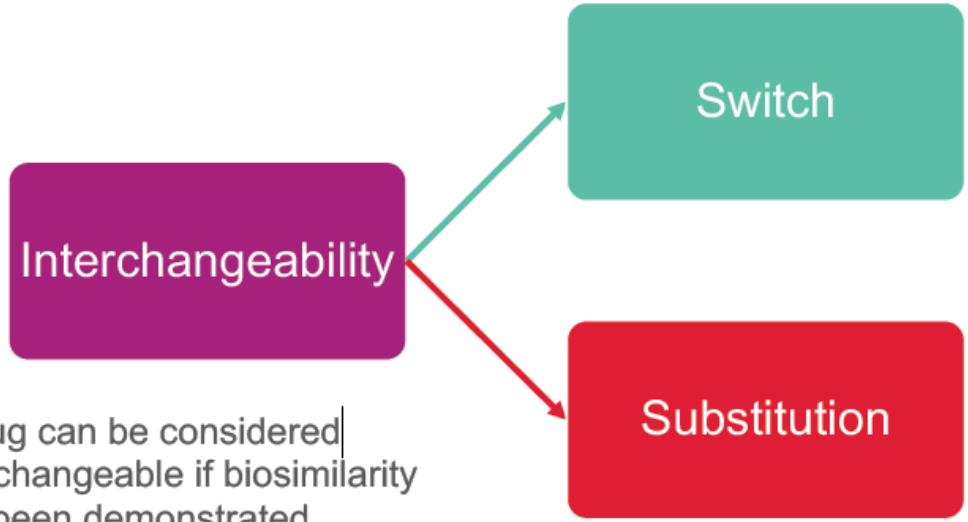
Prescribing: interchangeability and substitution



A drug can be considered interchangeable if biosimilarity has been demonstrated

There should be no safety risk or reduced efficacy if the reference product
is switched with the biosimilar

The MHRA advises against automatic substitution with a biosimilar5

- Biologics and biosimilars must be prescribed by brand[5]
- Supervision, education and specific instructions for each brand and delivery device is required

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5. NICE. Biosimilar medicines. KTT15. Available at: www.nice.org.uk/advice/ktt15 (accessed May 2019).

Why should we use biosimilars?

- The first insulin biosimilar was launched in the UK during September 2015
  - number of biosimilar insulins now available or coming to the UK soon
- Ageing population and 21st century lifestyle is driving prevalence of type 2 diabetes
  - Total spend on diabetes medication continues to rise
  - ~ £80 million spent annually on insulin glargine
- Innovations in medicines and their affordability is required to increase the sustainability of healthcare services in the UK
  - 11–40% cost savings with biosimilar insulins in the EU[6]

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6. James J, et al. *Int Diab Nurs* 2017: 14: 32-35.

Why should we use biosimilars?

- **NHS commissioning statement[7]**
  - Our aim is that at least 90% of new patients will be prescribed the best value biological medicine within 3 months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months, or sooner if possible
- **NICE Key therapeutic topic guidance on biosimilar medicines[5]**
  - Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines
  - The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient

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5. NICE. Biosimilar medicines. KTT15. Available at: www.nice.org.uk/advice/ktt15 (accessed May 2019); **7.** NHS England. Commissioning framework for biological medicines (including biosimilar medicines). Available at: www.england.nhs.uk/publication/commissioning-framework-for-biological-medicines/ (accessed May 2019).

Conclusions

- Biosimilar insulins are not generics
  - The natural variability and more complex manufacturing of biological medicines do not allow an exact replication
  - Biosimilars meet the more complex and rigorous requirements from the European Medicines Agency
- No clinically meaningful differences in efficacy or safety from the reference product have been demonstrated
- Biosimilar insulins are an opportunity to provide cost savings and access to treatment for more patients
- Appropriate patients should be proactively identified
- Medication review provides an opportunity to re-engage with people with diabetes and improve outcome

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Thank you for listening
Any questions?

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@drkevinfernando
Kevin Fernando

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Biosimilars part 2: use of insulin biosimilars in diabetes

Su Down

Diabetes nurse consultant and clinical lead
Intermediate Diabetes Community Services,
Somerset

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Disclosures

I have received honoraria from the following companies for advisory boards and speaker meetings:

- Sanofi
- Novo Nordisk
- Eli Lilly
- Astra Zeneca
- MSD
- Boehringer Ingelheim
- Janssen
- Bayer
- Abbott
- NAPP
- Mylan

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What do prescribers need to consider when prescribing an insulin or a biosimilar?

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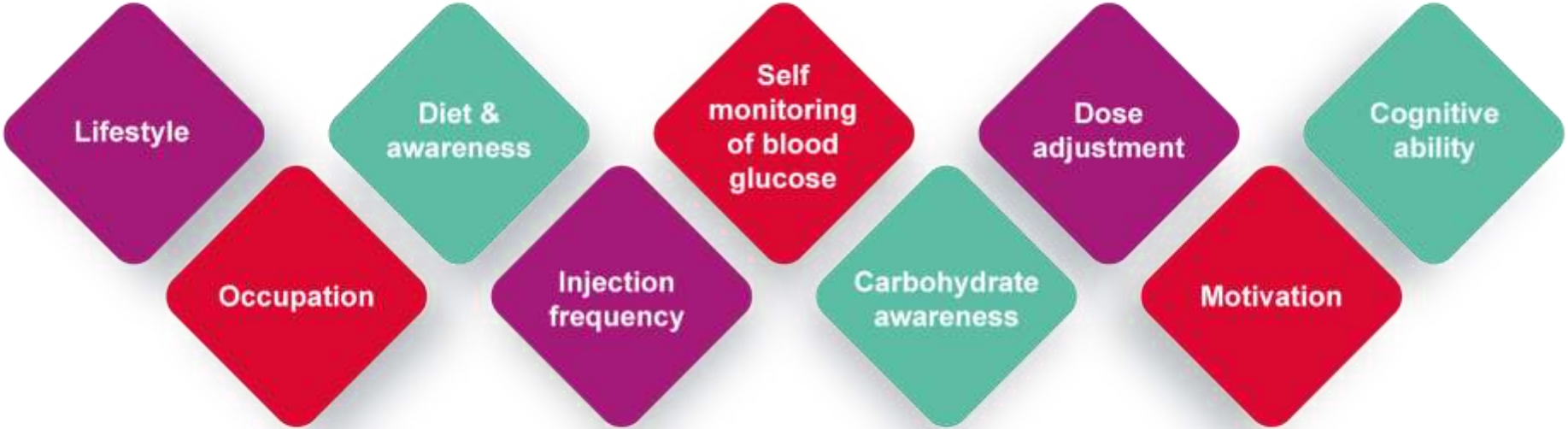
Factors that should influence choice of insulin and regimen



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Confusion over names of different insulins

- There are over 30 different insulin preparations and many of these have differing actions but similar sounding names
- This causes confusion for prescribers and those administering insulin, and can lead to error and harm

Lilly

Humalog® Mix25
Humalog® Mix50
Humulin® I
Humulin® M3
Humulin® S
Humalog® U100
Humalog ® U200
Abasaglar ® insulin glargine 100 units/ml

novo nordisk®

Actrapid®
Insulatard®
Levemir®
NovoMix® 30
NovoRapid®
Tresiba® U100 insulin
Tresiba® U200 insulin
Xultophy®
Fiasp®

SANOFI

Lantus® Insulin Glargine 100 units/ml
Apidra® Insulin Glulisine
Insuman® Basal Human Insulin 100 units/ml
Insuman® Comb 15 Human insulin 100 units/ml
Insuman® Comb 25 Human Insulin 100 units/ml
Insuman® Comb 50 Human Insulin 100 units/ml
Insuman® Rapid Human Insulin 100 units/ml
Toujeo ® Insulin Glargine 300 units/ml
Insulin Lispro Sanofi ® 100units/ml

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Semglee® insulin Glargine 100 units/ml

WOCKHARDT

Hypurin® Bovine Isophane
Hypurin® Bovine Lente
Hypurin® Bovine Neutral
Hypurin® Bovine PZI
Hypurin® Porcine 30/70
Hypurin® Porcine Isophane
Hypurin® Porcine Neutral

1. electronic Medicines Compendium (eMC). Available at: www.medicines.org.uk

"All biological medicines, including biosimilar medicines, should be prescribed by brand name so that products cannot be automatically substituted at the point of dispensing"

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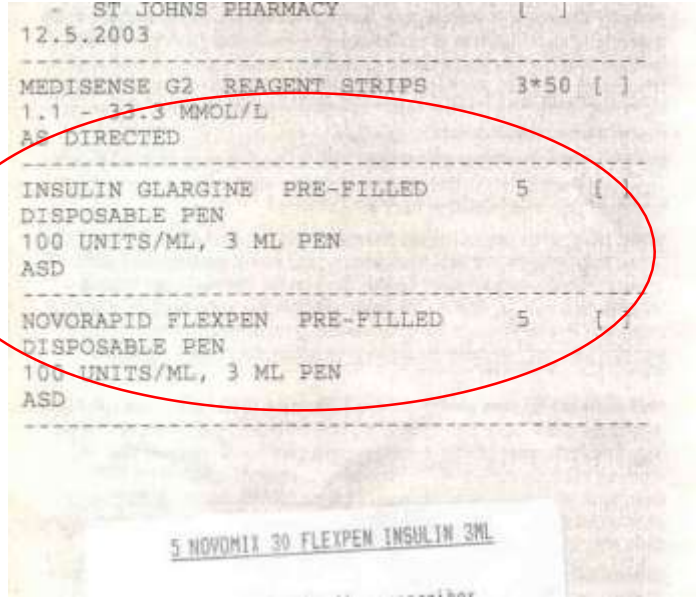
Abasaglar is a registered trademark of Eli Lilly and Company Limited.

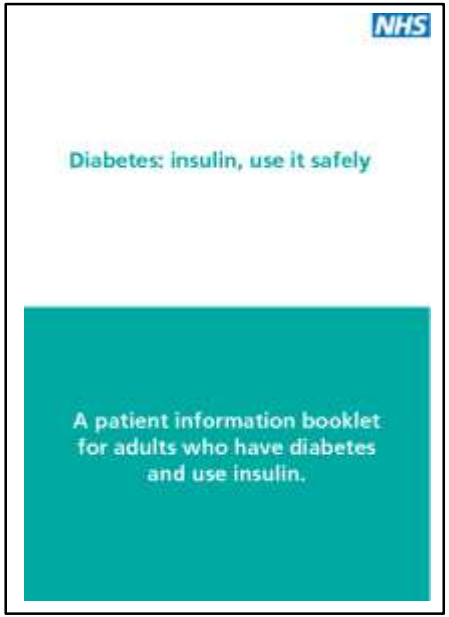
2. National Institute for Health and Care Excellence. ESNM64 Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar). London, NICE, 2015.

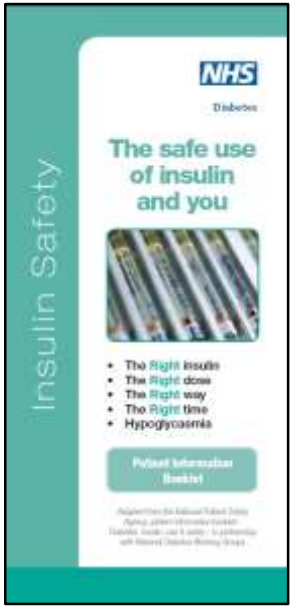
Tip to minimise the risk

- Audit search of all generic insulin prescribing:
  - Glargine
  - Detemir
  - Aspart
  - Lispro
  - Glulisine



Insulin passport





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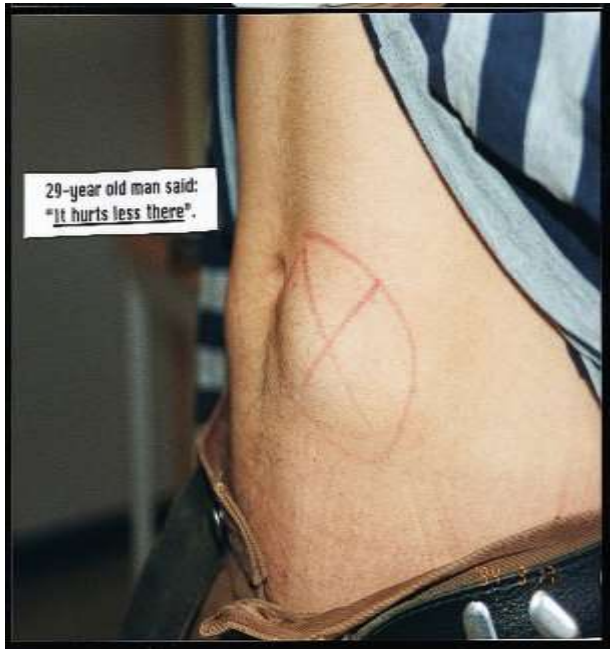
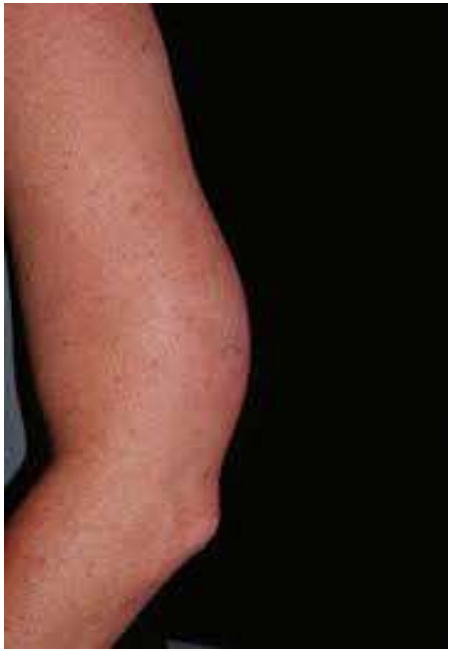
Liperhypertrophy can impact on insulin absorption





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How to explain changes to patients?

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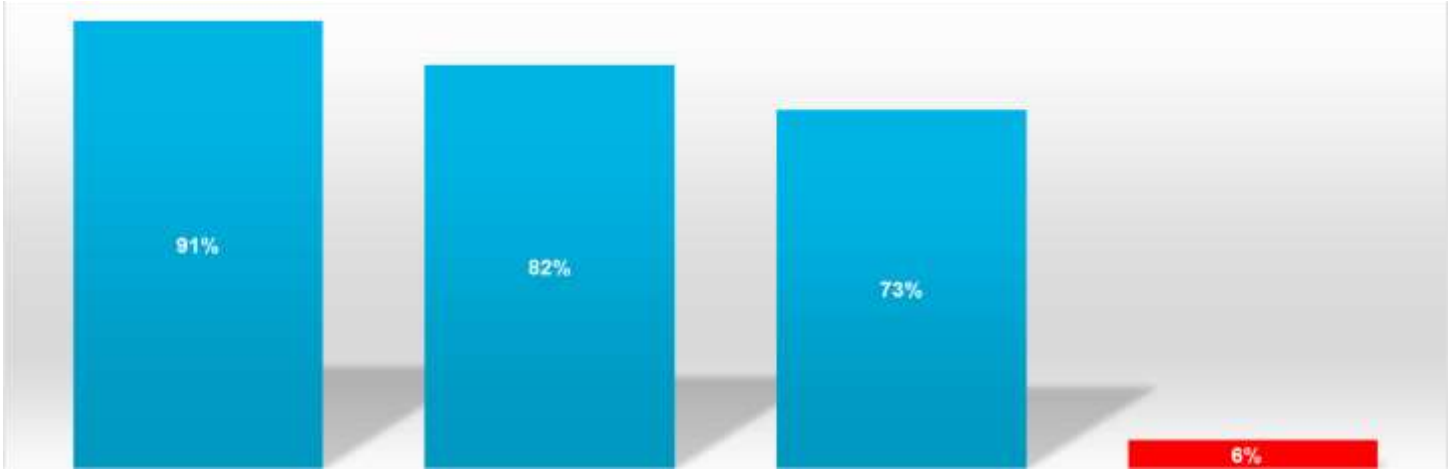
Use of biosimilars in other therapy areas is higher than in diabetes



Infliximab
NHS Trust Range:
26%–100%

Etanacept
NHS Trust Range:
4%–100%

Rituximab
NHS Trust Range:
3%–100%

Insulin Glargine
Market Share
MAT 7/18

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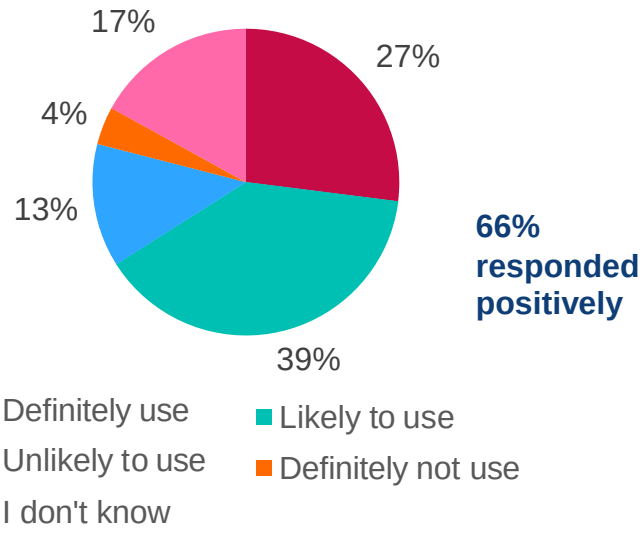
3. Data export from NHS Business Services Authority Medicine Optimization Dashboard (obtained October 2018)

How do you approach this in practice?

- Occurs regularly with oral medications
- Recently, with glucose monitoring strips
- Most patients are used to having different brands of oral medications on a regular basis
- It is important that insulin patients know to only have their branded insulin and not to accept a change unless discussed with their HCP

Patient perception

- Survey including 3,214 people with T1 or T2DM
- ‘Would you switch to a hypothetical less expensive biosimilar insulin that was approved by your provider?’
- 66% of respondents reported that they would ‘definitely’ or ‘likely’ use a biosimilar
- Similar experience in clinical practice



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4. Wilkins AR et al. *J Diabetes Sci Technol* 2014 Jan; 8(1): 23–25.

Ideal candidates to start or switch

- New to insulin
- Stable or optimised
- Unstable or non-optimised

Practical implementation and monitoring

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Advice on dose change

	Stable and HbA1c >58mmol/mol	Stable and HbA1c <58mmol/mol	Unstable with hypos	Unstable without hypos
Lanarkshire CCG[8]	General advice: dose for dose			
North West Surrey CCG[9]	Change to biosimilar, dose for dose	Reduce dose by **10%** and titrate in 1 week	Reduce dose by **10%** and titrate in 1 week	Change to biosimilar dose for dose
Worcestershire CCG[10]	Change to biosimilar, dose for dose	Reduce dose by **20%** and titrate in 1 week	Reduce dose by **20%** and titrate in 1 week	Change to biosimilar dose for dose

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8. NHS Lanarkshire. Guidelines for people changing from Lantus Solostar® Pens to Abasaglar KwikPens®. Available at: www.nhslanarkshire.scot.nhs.uk/download/diabetes-patient-information-leaflets/?wpdmdl=5302&ind=1553773646049 (accessed June 2019). **9.** Ashford and St. Peter's Hospitals NHS Foundation Trust. Consensus Guidance for Switching from Lantus® to Abasaglar® insulin glargine. Available at: pad.res360.net/Content/Documents/Guide_for_Switch_from_Lantus%20to%20Abasaglar%20July%202016.pdf (accessed June 2019). **10.** NHS Redditch and Bromsgrove CCG, NHS South Worcestershire CCG, NHS Wyre Forest CCG. Potential Lantus to Abasaglar switch for adult T2DM patients. Available at: www.southworcsccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=141095 (accessed June 2019).

Guidelines

11. https://www.guidelinesinpractice.co.uk/supplements/guideline-for-the-managed-introduction-of-biosimilar-basal-insulin/454944.article

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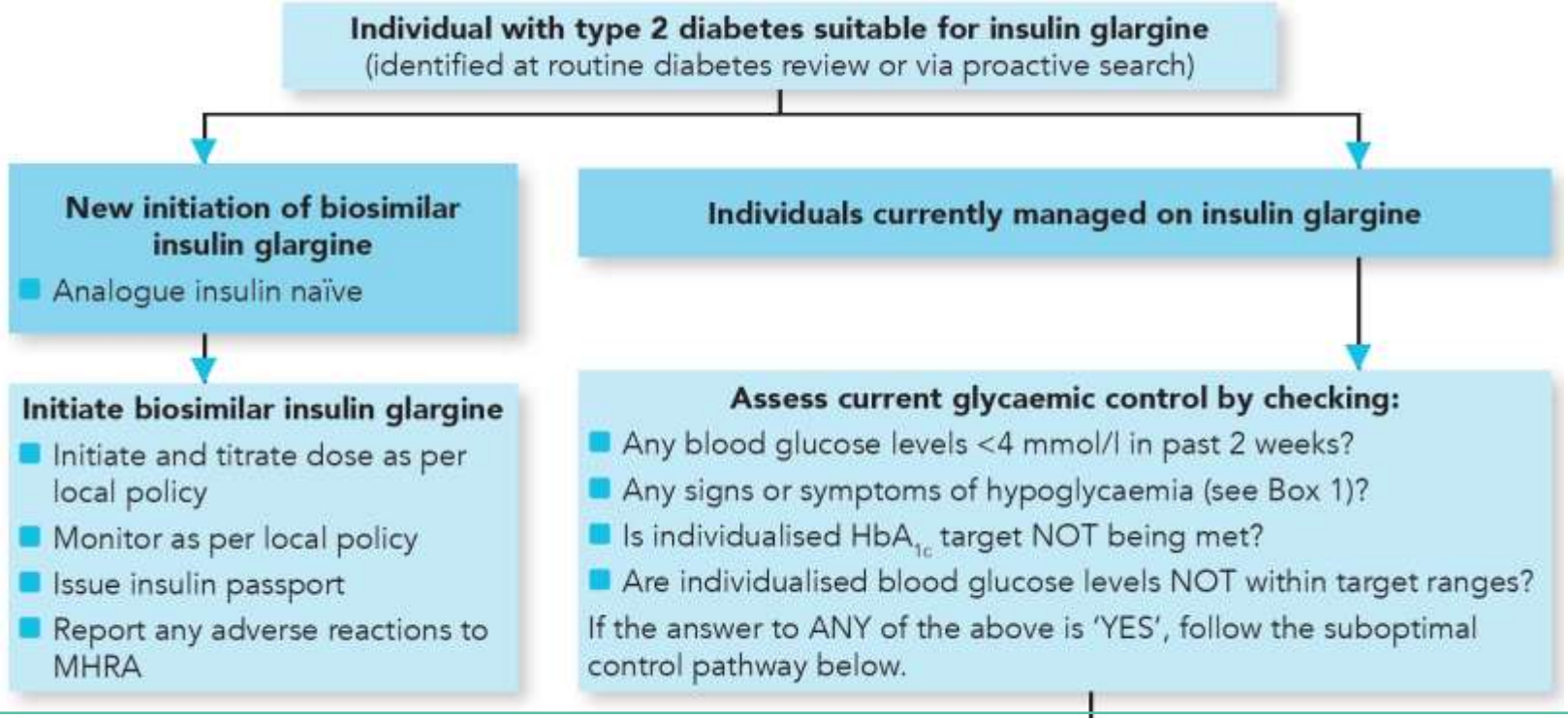
Guidelines



11. https://www.guidelinesinpractice.co.uk/supplements/guideline-for-the-managed-introduction-of-biosimilar-basal-insulin/454944.article

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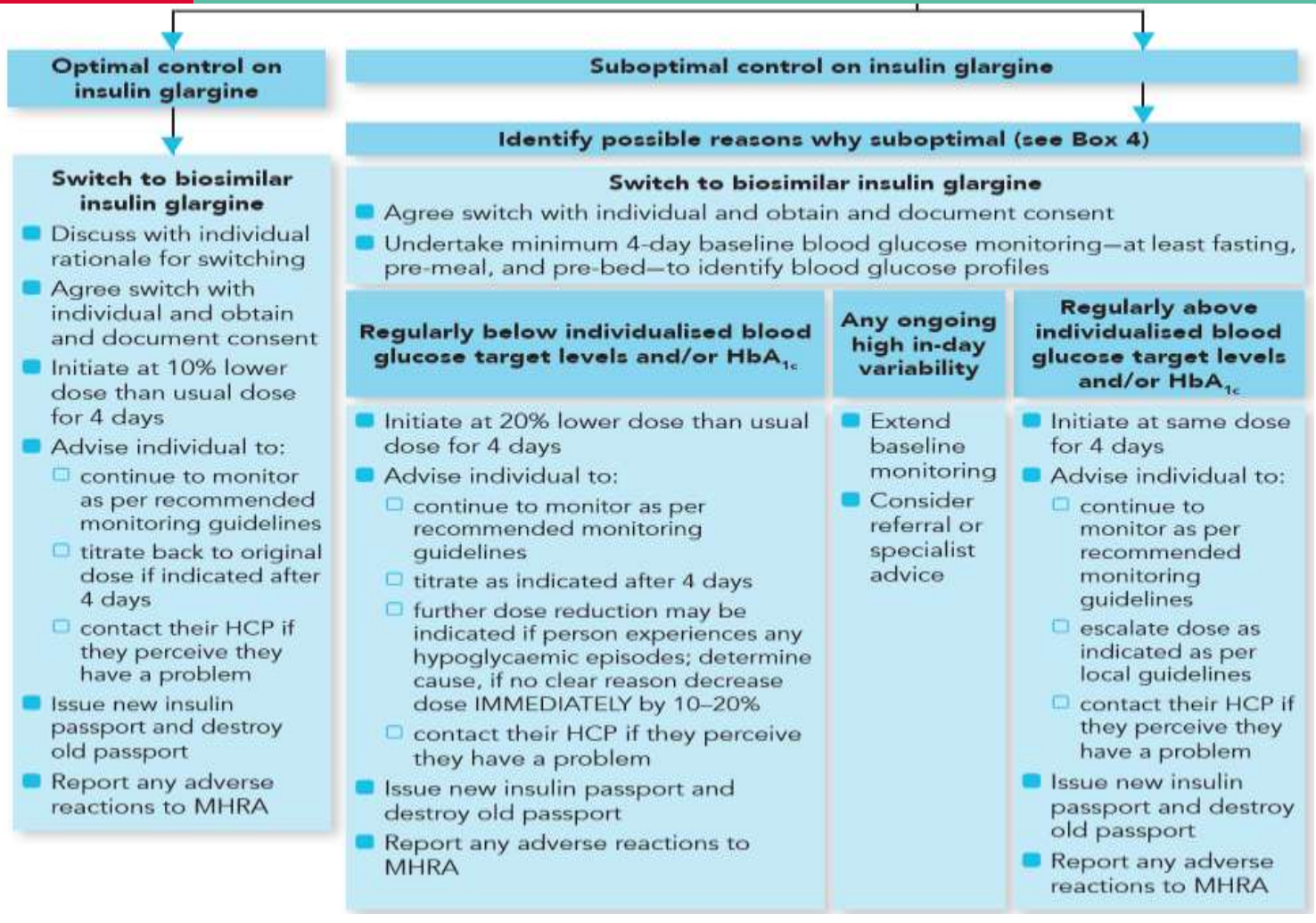
Who? Ideal candidates to start or switch

- **New to insulin**
  - No discussion required
- **Stable or optimised**
  - Financial discussion
  - Instilling confidence
- **Unstable or non-optimised**
  - Exploring injection technique
  - Changing regimen
  - Highly likely to need dose adjustment

Box 4: Reasons for suboptimal control on insulin

- Poor or suboptimal adherence
- Poor injection technique (e.g. storage, site selection, site rotation, injection process)
- Injection timing
- Psychological causes
- Presence of lipohypertrophy
- Diet and lifestyle
- Intercurrent or concurrent illness
- Interacting drugs, e.g. recent steroid therapy or antipsychotic drugs.

11. https://www.guidelinesinpractice.co.uk/supplements/guideline-for-the-managed-introduction-of-biosimilar-basal-insulin/454944.article


Optimal control on insulin glargine
Switch to biosimilar insulin glargine
Discuss with individual rationale for switching
Agree switch with individual and obtain and document consent
Initiate at 10% lower dose than usual dose for 4 days
Advise individual to:
continue to monitor as per recommended monitoring guidelines
titrate back to original dose if indicated after 4 days
contact their HCP if they perceive they have a problem
Issue new insulin passport and destroy old passport
Report any adverse reactions to MHRA
Suboptimal control on insulin glargine
Identify possible reasons why suboptimal (see Box 4)
Switch to biosimilar insulin glargine
Agree switch with individual and obtain and document consent
Undertake minimum 4-day baseline blood glucose monitoring—at least fasting, pre-meal, and pre-bed—to identify blood glucose profiles
Regularly below individualised blood glucose target levels and/or HbA1c
Initiate at 20% lower dose than usual dose for 4 days
Advise individual to:
continue to monitor as per recommended monitoring guidelines
titrate as indicated after 4 days
further dose reduction may be indicated if person experiences any hypoglycaemic episodes; determine cause, if no clear reason decrease dose IMMEDIATELY by 10–20%
contact their HCP if they perceive they have a problem
Issue new insulin passport and destroy old passport
Report any adverse reactions to MHRA
Any ongoing high in-day variability
Extend baseline monitoring
Consider referral or specialist advice
Regularly above individualised blood glucose target levels and/or HbA1c
Initiate at same dose for 4 days
Advise individual to:
continue to monitor as per recommended monitoring guidelines
escalate dose as indicated as per local guidelines
contact their HCP if they perceive they have a problem
Issue new insulin passport and destroy old passport
Report any adverse reactions to MHRA

Ongoing monitoring after change of regimen

HbA1c

- As with any change to regimen, 3-monthly HbA1c monitoring is prudent to ensure targets have been reached

Home blood glucose monitoring

- Does this reflect HbA1c?
- Continue with current levels of monitoring or increase in the short term
- Ask to report any hypos or injection site issues

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Patient scenarios

Scenario 1: insulin-naïve patient

52-year-old man on oral antidiabetic drug triple therapy and failing to meet HbA1c target (e.g., HbA1c > 58mmol/mol):

Discussion

- No explanation on biosimilar required

Dosing

- Start with 10 units once daily at night

Monitoring

- CBG first thing in the morning, titrate up until glucose levels fall within agreed target range (likely to aim for 4–7mmol/L)

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CBG, capillary blood glucose.

QUESTION

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Question

A basal insulin was chosen. This was started at 10 units and it was agreed to give 10 units before bed. How would this be titrated until target glucose had been achieved?

A. 2 units weekly
B. 2 units daily
C. 1 unit daily
D. 20% dose increase if the average of three morning readings were above target

Scenario 2: stable or controlled patient

55-year-old lady, been on reference glargine for 10 years (16 units nightly), no hypos for the past 8 years, HbA1c well and tightly controlled at 56mmol/mol:

Discussion

- Financial discussion, saving incentive
- Instill confidence

Dosing

- Reduce dose by 10% and titrate up

Monitoring

- CBG same frequency as before, titrate up as per fasting CBG readings

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CBG, capillary blood glucose.

QUESTION

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Question

Why would you reduce the initial dose by 10%?

A. To prevent hypoglycaemia
B. The biosimilar insulin has a different action
C. The biosimilar is a different concentration
D. The HbA1c is too low

Scenario 3: unstable or uncontrolled patient

65-year-old lady, been on Lantus for 10 years (40 units nightly), CBG range from 4–20mmol/L, HbA1c not well controlled at 78mmol/mol:

Discussion

- Financial discussion, saving incentive
- Instil confidence

Dosing

- Due to range of glucose levels 20% reduction in dose advised

Monitoring

- CBG for 4 days before switching to biosimilar for a baseline, check CBG same frequency after switch

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CBG, capillary blood glucose.

QUESTION

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Question

What could the cause of variation in daily glucose levels?

A. Lipohypertrophy

B. Carbohydrate variation on a day-by-day basis

C. Lifestyle variation

D. Dose changes in response to pre-bed glucose level

Scenario 4: patient on Premix

88-year-old house-bound man, requires District Nurse service for insulin injections, been on Premix twice daily, CBG range from 4–17mmol/L, HbA1c 51 mmol/mol, eGFR 36:

Discussion

- Reducing number of injections to once daily

Dosing

- Take total daily dose and give reduce by 30%

Monitoring

- CBG same frequency as before although if only taken by community nurses then this would drop to daily, titrate up/down as per fasting CBG readings

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CBG, capillary blood glucose; eGFR, estimated glomerular filtration rate.

QUESTION

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Question

What is the target HbA1c for this gentleman?

A. 53mmol/mol
B. 58mmol/mol
C. 68mmol/mol
D. 78mmol/mol
E. No target – aim for symptom-free control

Summary

- Insulin prescribing can be complex
- It is changing rapidly in terms of type, concentration and combination
- Prescribing by brand name is imperative
- Annual check ups provide an opportunity to review injection technique, insulin safety and regimen
- Biosimilars and cost saving is necessary for sustainability and access to innovative therapy such as CGMs
- Identify the right patients and give the right counselling and advice

Any questions?

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