AREA PRESCRIBING COMMITTEE MEETING
Birmingham, Sandwell, Solihull and environs
Minutes of the meeting held on
Thursday 13th April 2017
Venue – Birmingham Research Park, Vincent Drive,
Birmingham B15 2SQ – Conference Room A

PRESENT:

Dr Lisa Brownell	BSMHFT (Chair)
Dr Paul Dudley	Birmingham CrossCity CCG
Mark DasGupta	Birmingham CrossCity CCG
Satnaam Singh Nandra	Birmingham CrossCity CCG
Alima Batchelor	Birmingham South Central CCG
Kate Arnold	Solihull CCG
Elizabeth Walker	Sandwell & West Birmingham CCG
Mary Johnson	South East Staffordshire & Seisdon Peninsula CCG
Dr Timothy Priest	HoE NHS FT
Tania Carruthers	HoE NHS FT
Carol Evans	HoE NHS FT/ Solihull CCG
Prof Robin Ferner	SWB Hospitals NHST
Prof Jamie Coleman	UHB NHS FT
Ravinder Kalkat	Midlands & Lancashire CSU
Isabelle Hipkiss	Midlands & Lancashire CSU
Dr Emma Suggett	UHB NHS FT on behalf of I. Singh
Yusuf Asif	Birmingham Children's NHS FT on behalf of J. Aston

IN ATTENDANCE:

Dr S. Bellary	HoE NHS FT for item 0417/05
Natasha Jacques	HoE NHS FT for item 0417/05
Mr M. Foster	HoE NHS FT for item 0417/13

No.	Item	Action

0417/01 Apologies for absence were received from:

- David Harris, Birmingham Community Healthcare NHS FT
- Dr John Wilkinson, Solihull CCG
- Dr William Rea, ROH NHS FT
- Inderjit Singh, UHB NHS FT, deputy attended
- Dr Neil Bugg, Birmingham Children's Hospitals NHS FT
- Jeff Aston, Birmingham Women's and Children's NHS FT, deputy attended
- Dr Sangeeta Ambegaokar, Birmingham Children's Hospitals NHS FT
- Nigel Barnes, BSMHFT
- Jonathan Horgan, MLCSU

It was confirmed that the meeting was quorate.

0417/02 Items of business not on agenda (to be discussed under AOB)

- Isotrex® gel- Discontinued.
- DMARDs- Proposal for a combined shared care document for all agents and indications.
- HIV drugs and steroids- MHRA alert.
- Decline to Prescribe- Paediatrics.
- Desmopressin- New product.

0417/03 Declaration of Interest (DoI)

It was confirmed that DoI forms have been received for all members attending the meeting.

A member declared attending advisory boards for both products on the agenda; these were over two years ago. Another member declared being sponsored by Sanofi for an event, again over two years ago. There were no other interests to declare relating to items on the agenda.

0417/04 Welcome and Introductions

The Chair welcomed everyone to the meeting today. Introductions around the table were carried out for the benefit of the new attendees.

The Chair reminded members, that the meeting is digitally recorded for the purpose of accurate minute taking and once the minutes are approved, the recording is deleted by the APC secretary.

0417/05 Resubmission of New Drug application – insulin glargine 300 units/mL (Toujeo®) - Sanofi.

Interests declared have been noted under item 0417/03.

The Chair welcomed Dr Srikanth Bellary, Consultant Diabetologist, and Natasha Jacques, Principal Pharmacist, from HoE NHS FT to the meeting and invited them to present their application for Toujeo®.

Dr Bellary began by stating that he was resubmitting this drug application on behalf of the Diabetes network, which includes physicians, nurses and pharmacists from secondary and primary care.

The application is for a long-acting basal insulin analogue Toujeo® which is a concentrated form of insulin glargine (300 units per mL) and it delivers the same amount of units but in a third of the volume compared to the 100 units/mL formulation.

The key advantages of this presentation are:

- Injection volume reduction which is important in patients requiring large doses of insulin or multiple injections.
- Reduction in perceived pain and discomfort due to reduced volume: volumes above 2-3ml are associated with increased pain and discomfort at injection site.
- Pharmacodynamics studies have shown a more favourable profile with less intra and inter-subject variability which results in a smoother 24 hour-glucose profile.
- A recent study by Berganstal et al published in Diabetes Care in January 2017 concluded that smoother average 24-hr glucose profiles, irrespective of injection time and reduced nocturnal hypoglycaemia, were observed with insulin glargine 300 units/mL compared to insulin glargine 100 units/mL.
- The duration of action of insulin Toujeo® extends beyond 24 hours.

Therefore the cohort of patients which would benefit the most from this concentrated presentation of insulin glargine are:

- Patients requiring large doses i.e. above 80 units per day; there are a few patients who require in excess of 200 units per day. It is estimated that 2-3 % of the population fall into this group.
- Patients with an erratic glucose profile who don't achieve glycaemic control, and fail to titrate up to the maximum dose due to fear of hypoglycaemia.
- Patients requiring twice daily basal insulin treatment.
- Patients requiring support in insulin administration, e.g. the elderly, as the timing of administration can be more flexible due to the duration of action extending beyond 24 hours.

Natasha Jacques went on to outline the insulin safety work carried out by the Diabetes network in order to address the main safety concerns raised by the committee members when this application was first considered in April 2016.

Irrespective of the outcome of this application, insulin safety has been identified as a national priority and in the Acute Trust; especially when considering patients from neighbouring areas where Toujeo® is on the formulary who might be admitted on Trust premises.

The Diabetes network has therefore looked at putting systems in place in all care settings to mitigate the risks associated with all insulins namely high strength insulins, biosimilars and fixed combinations.

She ran through the risk assessment document produced by the Diabetes network which sets out steps and contingency plans that can be put into place to mitigate these risks in a variety of healthcare settings (e.g. GP practices, community and hospital pharmacies, secondary / intermediate care and community administration). This document has a number of appendices which consist of posters or charts to further support and educate healthcare professionals. Each organisation represented in the Diabetes network was tasked with disseminating and implementing this risk assessment tool within

their respective organisations.

Dr Bellary further reported that diabetes colleagues from neighbouring Trusts/CCGs where insulin Toujeo® is on formulary have confirmed that no incidents or major insulin errors involving Toujeo® have been reported to date.

The Chair invited questions and comments from members. Discussion points/concerns raised included:

- A committee member was concerned about GPs initiating Toujeo® in their insulin-resistant patients without prior referral to a secondary care specialist. Dr Bellary confirmed that he saw this product being initially used in a specialist setting or by GPs with specialist interest in diabetes (GPwSI) accreditation, until further experience is gained from using this product.
- A member referred to the application form and sought clarification on the non-inferiority studies quoted therein. Dr Bellary stated that the EDITION trials demonstrated that Toujeo® was non-inferior or had equivalent clinical efficacy in lowering blood glucose as the comparator which was Lantus® (insulin glargine 100 units/mL).
- The member went onto to state that reduction in hypoglycaemia was not a primary outcome of these trials but a secondary endpoint as part of a sub-group post hoc analysis; this was the reason for the committee viewing this evidence as weak when Toujeo® was first considered. Dr Bellary confirmed that there are no published studies with reduction in hypoglycaemia as a primary endpoint; all trials are designed to demonstrate non-inferiority in glucose lowering efficacy as a primary end point. He referred to the Berganstal et al study (quoted earlier) which was a 16-week, exploratory, open-label, parallel-group, two-period crossover study which included hypoglycaemia as an additional end point, but acknowledged that it was not a strong study design compared to RCTs.
- A member further questioned Dr Bellary on the claims made around reduction in volume being beneficial to patients as there was no published patient data to support this; furthermore the maximum dose of Toujeo® that can be injected is 80 units therefore patients requiring more than 80 units will need multiple injections which is just as uncomfortable. Dr Bellary stated that in his clinical experience patients have complained of discomfort when injecting large volumes.
- Dr Bellary was asked to clarify the patient group for whom this product was intended for. It was confirmed that these were:
    - Patients on large doses of insulin, above 80 units a day.
    - Patients with very erratic glucose profiles.
    - Patients who cannot be titrated up due to fear of hypos.
    - The original application did also suggest using it in patients requiring support in insulin administration (e.g. elderly patients having district nurses' visit) in view of its extended duration of action and the flexibility it offered in the timing of administration, but acknowledged that it was a lower priority than the three already identified.
- A member commented that very erratic glucose profiles and fear of hypos was more an issue for patients with Type 1 diabetes (T1DM) than Type 2 diabetes (T2DM) as it was recognised that very tight glucose control is important in T1DM but less critical in T2DM. It was therefore suggested to further clarify the patient group as T1DM patients with very erratic glucose profiles and T1DM patients who cannot be titrated up due to fear of hypos. Dr Bellary concurred that although the majority of these patients would be T1DM, a few would be T2DM and the importance of tight glycaemic control

was still relevant in this group of patients as they are living longer and clinicians are having to manage their cardiovascular symptoms longer.

- A member enquired if patients with injection-site reactions would be included in this cohort. Dr Bellary stated that these were very rare and mainly due to the excipients rather than insulin itself, but also acknowledged that the volume of injection could be a cause for these reactions.
- A member was concerned about patients on a basal bolus regime as well as Toujeo® and whether it would be a risk having two different strengths of insulin to hand. Dr Bellary and Natasha Jacques did not see this being an issue; the injection devices look quite different and the doses are dialled up in units and not volume.
- A member commended the Diabetes network on the comprehensive work undertaken to develop the risk assessment tool and enquired on the availability and supply of safety-engineered needles recommended for administration by healthcare teams in the community. Natasha Jacques stated that these needles are provided by the Trust to their community nurses as stock, and that GPs should not in theory be asked to prescribe these; however it was the responsibility of the district teams' employer to provide these.
- A question about the scoring system included at the end of the risk assessment was raised; what it was scored out of and what a score of 9 represented. It was confirmed that 9 was a low score, as would be expected after putting all the steps in place and mitigating the risks.
- Further clarification was requested on who was responsible for the dissemination and implementation of this useful resource; as stated earlier each organisation represented in the Diabetes network was tasked with distributing this risk assessment tool internally. However it was pointed out that there was a possible gap with community pharmacies as the contractual responsibility did not lie with the CCGs but with NHS England.
- It was pointed out that the committee recently considered an application for insulin degludec, and that the reasons for using it and patient groups identified within that application were very similar to the ones outlined for Toujeo®. The clinician was asked which product had an overall advantage should the committee have to choose between the two, and approve only one product. Dr Bellary agreed that both insulins had very good kinetic profiles and were similar in reducing hypos, especially nocturnal hypos, when compared to insulin glargine; there are no head to head studies between insulin degludec and Toujeo®. Therefore the main advantage of Toujeo® over insulin degludec is the reduction in injection volume.
- It was recognised that these are two examples of new generation highly concentrated insulins. Dr Bellary was asked whether approval of Toujeo® would preclude further applications for other high strength insulins as they start to come to market. Dr Bellary is aware of rapid-acting insulin analogues that may become available as a concentrated solution, but with regards to long-acting basal analogues he is only aware of Toujeo®. The Diabetes network has already discussed the concentrated rapid-acting analogues and decided not to go ahead with them.
- Although a number of safety concerns have been mitigated with the risk assessment tool, and it was stated that it should be initiated by a specialist in secondary care or a GPwSI, a member emphasised that there would still be a need for some document to support the safe transfer of prescribing to general practitioners. Dr Bellary was asked whether the network has considered this and whether it would agree to develop a shared care document or a RICaD at the very least, should the application be

successful. Dr Bellary and Natasha Jacques verified the network had discussed this and that it would support developing such a document.

- It was confirmed that the Diabetes network has no intention of making an application for insulin degludec 200 units/mL due to the risk of selecting the wrong strength; especially as the brand name is identical for both strengths (Tresiba® 100 units and 200 units per mL), whereas the brand name is different for the two strengths of insulin glargine (Toujeo® 300 units/ mL and Lantus® 100 units/mL).
- The strong recommendation of brand prescribing was highlighted once again, which is supported by the MHRA.
- Further discussion on the risk assessment tool followed, and particular concerns were raised with regards to implementation and communication of all the recommendations which would require time and resources. The lack of electronic prescribing was a particular concern for one of the Trusts' representatives. It was recognised that this was an ongoing process, and would need to take into account the regular turnover of junior doctors and nursing staff.
- One member saw this as a risk-benefit analysis: how many patients would benefit from this treatment option compared to 10 years ago when this concentrated insulin was not available, compared to the risk of harm by introducing this concentrated insulin preparation.
- Dr Bellary was asked how many more patients need larger doses of insulin compared to 10 years ago. He could not provide an exact figure but acknowledged that the numbers are increasing, and quoted 2-3% of T2DM patients would require more than 100 units a day.
- One member stated that process and engineering controls should replace the need for education to manage risk. It was also commented that the risks may be higher in the secondary care setting where patients no longer manage their own insulin regime but nursing staff do.
- A member asked if the Diabetes network had representation from the mental health trust as a recent audit highlighted that 40% of patients with schizophrenia also have diabetes. It was confirmed that the Diabetes network did not have representatives from BSMHFT but would ensure that it was included in further discussions/meetings.

The Chair thanked Dr Bellary and Natasha Jacques for attending the meeting, for answering all the questions from the APC members and advised them that the decision would be relayed within 5 working days, in line with APC policy.

Further discussion points in the absence of the diabetes specialists included:

- The APC secretary relayed comments from Dr Waqar Malik (Consultant Diabetologist at Birmingham Community Healthcare NHS FT) who supported the application for Toujeo® provided it was for specialist initiation and for T2DM patients on more than 100 units basal insulin and especially on twice daily basal insulin.
- A member highlighted that South East Staffordshire & Seisdon Peninsula CCG has had Toujeo® on their formulary for approx. 2 years without any significant incidents. It is for specialist initiation for patients on more than 80 units of insulin glargine and prescribing is maintained in secondary care for 6 months before it is transferred to primary care, supported by a RICaD.
- Several members questioned the fact that, although three times more concentrated, the maximum dose of Toujeo® that can be dialled up is 80 units (0.267mL), so patients on more than 80 units will need 2 or more injections per dose; albeit smaller volumes but multiple injections none the less. It was confirmed that the maximum dose that can be dialled up on a

Lantus® pen is 80 units also (0.8mL).

- There is some overlap between insulin degludec and Toujeo® with regards to indications and patient groups.
- Some patients will potentially benefit in view of the decreased volume of injection and a theoretical reduction in pain. Against that, the APC has to weigh the additional risks, and increase in costs (compared to Abasaglar®).

The Chair directed the members to the Decision Support Tool for completion:

Patient Safety: Three-fold concentrated insulin and potential misuse of device pose considerable risks; however these can be mitigated by implementing recommendations in risk assessment tool presented.

Clinical effectiveness: Non-inferior to insulin glargine 100 units/mL in terms of HbA1c reduction. Evidence for reduction in hypoglycaemia, especially nocturnal hypos, was a secondary endpoint as part of a sub-group post hoc analysis.

Strength of evidence: Sufficient to gain licence from EMA; the manufacturer had to demonstrate that Toujeo® had a similar safety and efficacy profile to that of the reference product Lantus®.

Cost-effectiveness or resource impact: 15% more expensive than Abasaglar®, cost neutral vs Lantus®.

Place of therapy relative to available treatments: Patient cohort identified, could be 2% of all diabetics.

National guidance and priorities: MTRAC issued commissioning guidance in July 2015, SMC accepted for restricted use within NHS Scotland in September 2015.

Local health priorities: Risk is largely in secondary care.

Equity of access: N/A

Stakeholder views: N/A

Implementation requirements: Supporting ESCA or RICaD to transfer prescribing to primary care.

Decision Summary: Approved as AMBER with RICaD, specialist initiation. For patients who require more than 80 units of insulin glargine per day, troubled by nocturnal hypos. Transfer to Primary care should not happen until specialists can demonstrate reduction in nocturnal hypos (e.g. after 3-4 months).

Actions:

- **Relay decision to Dr Bellary by Monday 24th April 2017.** **APC sec**
- **Diabetes network to develop RICaD for Toujeo®** **Diabetes network**

0417/06 APC relationship with Clinical networks
Deferred to next meeting

0417/07 Veil® cover cream- Further letter from CRS and BCC CCG response
Deferred to next meeting.

0417/08 Availability of licensed preparations for formulary products
Deferred to next meeting.

0417/09 RMOCs- update following regional workshops
Deferred to next meeting.

0417/10 Minutes of the meeting held on Thursday 9th March 2017

The minutes of the meeting held on Thursday 9th March 2017 were discussed for accuracy.

It was confirmed that the minutes are approved, can be uploaded to the APC website and the recording deleted.

The DST for Trevicta® LAI is also approved for uploading to the APC website:

0417/11 Matters arising – Action Table

Deferred to next meeting.

0417/12 NICE Technology Appraisal (TAs)

Deferred to next meeting.

0417/13 Alprostadil cream (Vitaros®) - New drug application. Ferring Pharmaceuticals

Interests declared have been noted under item 0417/03.

The Chair welcomed Mr M. Foster, Consultant Urologist HoE NHS FT, to the meeting and invited him to present the application for Vitaros®.

Mr Foster introduced Vitaros® as a new topical formulation of alprostadil; previous formulations included injections (Caverject®, Viridal®) and the urethral stick MUSE®, which stands for Medicated Urethral System for Erection.

Alprostadil is a vasodilator, and when injected at the base of the penis produces an erection. Most men will achieve a decent erection when alprostadil is injected but this requires self-injection which is undesirable; hence other formulations have been developed.

MUSE® is moderately effective, not guaranteed to work but has a reasonable success rate. It is a pellet which is inserted in the man's urethra and is absorbed into the bloodstream to produced vasodilatation.

Vitaros® is a topical cream which is applied to the tip of the penis around the glands that surround the urethral meatus, then is absorbed into the penis to

produce a reasonable erection.

In terms of efficacy there are no head to head trials against MUSE® but anecdotally it is better and easier to use administer than MUSE®; Mr Foster is also aware of current supply issues with MUSE®. He therefore identified a gap in the market.

Vitaros® would be a step up from oral phosphodiesterase type 5 (PDE5) inhibitors; approximately 40% of men who do not respond to or cannot take oral PDE5-inhibitors will respond to this drug and this presentation would offer a step in their management before having to self-inject.

The Chair invited questions and comments from members. Discussion points/concerns raised included:

- A member commented that PDE5 inhibitors are contraindicated in patients taking long term daily oral nitrates, but requested Mr Foster's view whether occasional use of GTN sprays would constitute a contraindication. Mr Foster is aware of GPs willing to prescribe PDE5 inhibitors in patients taking occasional GTN, and advises these patients not to use their GTN spray should they have an angina attack soon after taking an oral PDE5 inhibitor. He also confirmed that alprostadil cream was not contraindicated in these patients.
- A member highlighted vulvovaginal disorders (i.e. itching or burning) as side effects reported by partners. Mr Foster concurred that treatment of erectile dysfunction (ED) involved the patient and his partner. The summary of product characteristics states that partners of Vitaros® users can experience adverse events, most commonly vaginal irritation. A condom barrier is therefore recommended.
- Cost comparison against other formulations was discussed: Vitaros® costs £10 per single application, MUSE® costs around £11.30 per single application; the costs of the injection vary from £7.73 to £21.58 depending on the strength.
- The patient group was identified as patients who do not respond to PDE5 inhibitors or in whom these are contraindicated. When asked for patient numbers, Mr Foster suggested 200 patients across Birmingham would fall in this category; this was based on MUSE® usage figures. He estimated that 15-20% of patients who present with ED in Primary care would fall into this patient group. When asked for the number of patients who currently receive alprostadil injection, he was unable to provide an exact figure.
- A member asked Mr Foster what the health economy as a whole would gain from the introduction of this preparation which is significantly more expensive than sildenafil which costs pence compared to £10 per dose of Vitaros®. He acknowledged the member's concern and stated that expenditure would be protected by Schedule 11 (SLS criteria) and therefore can only be prescribed to a defined category of patients.
- The member went on to ask which drug this would replace within Mr Foster's area of expertise; he stated that it would be used in patients who would otherwise have gone onto MUSE®. He saw it as a direct replacement for MUSE®; it is more effective than MUSE®, slightly cheaper and readily available. He did not anticipated usage figures to be higher than MUSE®.
- It was highlighted that MUSE® is not currently on the APC formulary; an application for the urethral sticks was noted in the action table as an outstanding item during the harmonisation of this BNF chapter. Alprostadil injection is currently amber on the formulary.

- A member asked about the place of vacuum pumps in the treatment of ED; Mr Foster explained that vacuum pumps are a completely different way of treating ED; they do have a place in therapy but are quite cumbersome and often end up in patient's cupboards unused. They are prescribable as a one-off item and, if effective, are cost-effective in the long term. They require some degree of dexterity, manipulation and perseverance.
- A member was concerned about creep in Primary care prescribing and Vitaros® cream being used ahead of PDE5 inhibitors. Mr Foster understood the concern but could not foresee this happening in view of the ease of use of oral medication.

The Chair thanked Mr Foster for attending the meeting, for answering all the questions from the APC members and advised him that the decision would be relayed within 5 working days, in line with APC policy.

Further discussion points in the absence of the Urology specialist included:

- Some members commented that at a time when CCGs are cutting essential services in the context of the national agenda and having to go out to consultation for stopping prescribing certain items such as gluten-free foods, considering this treatment was not a priority.
- A member highlighted that the current formulary pathway starts with generic sildenafil then moves onto on-demand tadalafil (note: daily tadalafil is not on the formulary as not deemed cost-effective). It has been announced by NHS England that they are looking at the top 10 most expensive drugs, and tadalafil features in this list. It could therefore been seen as a signal from NHSE that this is not a priority area. This product is more expensive than tadalafil on-demand tablets which cost £7 a dose.
- A member felt that there is a cohort of patients who would prefer to apply a cream than insert a pellet into their penis and therefore felt that the market would be much greater than for MUSE®, and would lead to an increase in prescribing.
- A secondary care member pointed out that ED clinics are already at capacity due to maintaining prescribing responsibility for patients diagnosed as suffering severe distress resulting from erectile dysfunction.
- A lengthy discussion ensued on the appropriate RAG status.

<u>The Chair directed the members to the Decision Support Tool for completion</u>:

<u>Patient Safety</u>: Relatively safe. Reports of local adverse effects in partner. Safer than PDE5 inhibitors in individuals on long term daily nitrates.

<u>Clinical effectiveness</u>: 40% of PDE5 failures get benefit from this treatment.

<u>Strength of evidence</u>: No head to head comparison, anecdotal evidence that it is better than MUSE®.

<u>Cost-effectiveness or resource impact</u>: Significantly more expensive than PDE5 inhibitors. Less expensive than the injections.

<u>Place of therapy relative to available treatments</u>: Second line for PDE5 failures or patients on long term nitrates.

<u>National guidance and priorities</u>: NHSE- not a high priority.

<u>Local health priorities</u>: CCGs did not see as a priority.

Equity of access: N/A

Stakeholder views: N/A

Implementation requirements: None required.

Decision Summary: Approved as AMBER, for patients who would otherwise use alprostadil injection. Specialist initiation.

Actions:

- **Relay decision to Mr Foster by Monday 24th April 2017.** **APC sec**
- **Add Vitaros® cream to APC formulary as AMBER, specialist initiation.** **APC sec**

Any other business:
Deferred to next meeting

The Chair thanked the members for their input today. The meeting closed at 16:50 pm.

Date of next meeting: Thursday 11th May 2017 14:00 – 16:45
Conference Room A,
Birmingham Research Park,
Vincent Drive.
Birmingham B15 2SQ.