Northern Treatment Advisory Group

Minutes of meeting held on the 24th November 2015, 9-12am,

Meeting Room 4, The Durham Centre

Present:

- Ian Davidson (ID) Director of Quality and Safety, North Durham CCG & Chair of NTAG.
- Matthew Grove (MG) Consultant Rheumatologist and Head of Service, Northumbria Healthcare NHS Foundation Trust.
- Andrew Lloyd (AL) Consultant Anaesthetist and Chair of South Tees D&T, The James Cook University Hospital (JCUH)
- Andrea Loudon (AL) Clinical Pharmacy Lead, Cumbria CCG.
- Jill McGrath (JM) Head of Finance, Newcastle Gateshead CCG.
- Bhavana Reddy (BR) Head of Prescribing Support, RDTC (professional secretary)
- Toks Sangowawa (TS) Clinical Director of Public Health, Tees Valley Public Health Shared Service.
- Roger Wheeler (RW) General Medical Practitioner, Middlesbrough

Apologies were received in advance from: Joe Corrigan, Simon Thomas, Neil Watson, Ali Wilson, Tim Donaldson and Chris Gray.

The Chair invited declarations of interest relating to the agenda. None were made. The group were reminded that the annual declarations would need to be renewed in the New Year.

1) Draft Minutes September Meeting

The group approved the September minutes with no changes. Actions within the minutes were verified.

ACTION: Secretary to publish September minutes on the NTAG website.

2) Matters Arising

a. Membership Update

The secretary updated the group on the result of the approach to Durham Health Watch. The group noted that a patient representative had put themselves forward and would be in touch with the secretary to follow this up.

The group also noted that the vacancy that had arisen due to the resignation of Sunderland Trust would also need to be filled. The secretary fed back that other district generals would be approached to fill the vacancy.

The group agreed that agenda items 3 and 4 would be discussed together although the appraisal reports were presented separately.

3) And 4) Appraisals: alirocumab and evolocumab.

The appraisal reports regarding use of the two monoclonal antibodies that inactivate proprotein convertase subtilisin–kexin type 9 (PCSK-9 inhibitors): alirocumab and evolocumab were introduced by the secretary. Both drugs are licensed for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia.

Dyslipidaemia is an abnormal amount of lipids (e.g. cholesterol and/or fat) in the blood. In developed countries, most dyslipidaemias are hyperlipidaemias; that is, an elevation of lipids in the blood. This is often due to diet and lifestyle. Hypercholesterolaemia is a form of dyslipidaemia characterised by high levels of cholesterol in the blood. Familial Hypercholesterolaemia (FH) affects 1 in 200 people and is an inherited condition caused by a genetic defect which causes high cholesterol levels from birth. Most affected people have heterozygous FH which is when you inherit a defective gene from one parent only. Homozygous FH is a rare condition that affects 1 in 1000000 and is when you have inherited a defective gene from both parents. Hypercholesterolaemia cannot be controlled by diet and lifestyle changes. The two new drugs being discussed are monoclonal antibodies that inactivate a specific protein (PCSK9 – proprotein convertase subtilisin–kexin type 9) in the liver. Inactivating this protein reduces the amount of harmful LDL cholesterol circulating in the blood stream.

Alirocumab:

Alirocumab is licensed for the treatment of primary hypercholesterolaemia (familial and non-familial) and mixed dyslipidaemia in adults as an adjunct to diet:

- In combination with a statin or statin with other LMTs in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- Alone or in combination with other LMTs in patients who are statin-intolerant, or for whom a statin is contraindicated.

It acts by reducing circulating levels of low-density lipoprotein cholesterol (LDL-C).

Clinical trial data summary:

Across ten phase 3 trials evaluating patients with HeFH and non-FH at high and moderate CV risk, alirocumab demonstrated a substantial reduction in the primary endpoint of LDL-C reduction after 24 weeks. On top of standard care (maximally tolerated statin +/- other lipid modifying treatments), a reduction of 39% to 62% compared to placebo was observed. Compared with ezetimibe, a reduction of 30% was found on top of standard care, 24% to 36% on less than maximal statins, and 30% to 32% without statin background therapy. The primary endpoint analyses were supported by consistent changes in the secondary lipid profile endpoints across all studies. The effect of alirocumab on cardiovascular morbidity and mortality has not been established. None of the trials completed to date had mortality associated with CV events as a pre-specified primary outcome although a trial is under way.

The safety profile of alirocumab was comparable to that of the control groups (placebo or ezetimibe). The most common treatment-emergent adverse events were nasopharyngitis, injection site reaction, upper respiratory tract infection, influenza, headache, myalgia, and arthralgia. The number of patients discontinuing treatment or experiencing serious adverse events was low. None of the safety concerns commonly associated with other LMTs, such as liver disorders, renal disorders, diabetes and musculoskeletal disorders, was evident with alirocumab treatment. However, the long-term safety of alirocumab remains to be established.

Evolocumab:

Evolocumab is licensed for the treatment of adults aged 18 and over with primary hypercholesterolemia (heterozygous familial or non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of the statin or,
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

It acts by reducing circulating levels of low-density lipoprotein cholesterol (LDL-C). Treatment for homozygous FH is commissioned by NHS England, and was therefore not discussed.

Clinical trial data summary:

Five published trials assess the efficacy of evolocumab for the reduction of LDL-C in various populations. Evolocumab produced greater reductions in LDL-C than either placebo or ezetimibe in all trials. Reductions were around 55-60% at the end of 12 weeks treatment, compared to typical reductions of 15-20% in the groups assigned to ezetimibe. LDL-C reductions in the 52 week DESCARTES trial were slightly lower than in the 12 weeks studies at 45-50%. The efficacy in the two weekly and monthly dosing groups was comparable at 12 weeks. Significant reductions in other lipid parameters were also observed. Whilst there are no head to head trials, evolocumab appears to result in slightly greater LDL-C reductions than alirocumab, but variances in the underlying populations studied may explain these relatively small differences. The effect of evolocumab on cardiovascular morbidity and mortality has not been established. Rates appear to be lower than in control groups, but the number of events collected in published trials was low. A 5 year cardiovascular outcomes trial is currently underway. The safety profile of evolocumab was comparable to the comparators. The most common AEs were nasopharyngitis, upper respiratory tract infection, headache and back pain. Rates of serious AEs and AEs leading to discontinuation were low. However the long-term safety of evolocumab remains to be established.

The group agreed that the clinical trial data showed a substantial reduction in the primary end point of LDL-C reduction after 24 weeks for both drugs. However there is currently insufficient data on the effect of alirocumab or evolocumab on CV morbidity and mortality and therefore questions remain around the level of risk reduction and therefore the cost effectiveness of treatment. The group noted that as highlighted in the draft NICE guidance on evolocumab that the ongoing FOURIER trial will test whether LDL-C is a valid surrogate for CV outcomes, which the ERG considered to be a key area of uncertainty in the current evidence. The group is also aware that outcome based clinical trials for both drugs are currently ongoing however they will not report till 2017 or 2018.

The group then reviewed the information presented by the specialist regarding use of the PCSK9 inhibitors and in which patient group they may be most cost effective. The specialist proposed us in a specific subgroup of patients who would otherwise be eligible for apheresis. Whilst the group could see the potential benefits there is insufficient information on efficacy of PCSK-9 inhibitors in this patient population. The group was concerned about the level of clinical benefit (i.e. risk reduction) versus the high cost of both these drugs in this patient group. It was noted that the current cohort of patients were not receiving apheresis and reasons for this should be explored first.

It was agreed that both alirocumab and evolocumab may be suitable for those patients with heterozygous familial hypercholesterolemia (HeFH) who are at very high risk however it was felt that these patients should be managed on a case by case basis. It was also agreed that alirocumab and evolocumab should not be recommended for use currently. The group is aware that a NICE technology appraisal review is currently underway and agreed that NICE is best place to assess cost effectiveness due to the current gaps in the data and will await this guidance.

ACTION:
Secretary to draft decision summary's as above.

5) Appraisal: Insulin Glargine Biosimilar (Abasaglar®)

The appraisal report on the insulin glargine biosimilar 100 units/ml – Abasaglar® was introduced by the secretary. This was referred to NTAG by a local APC.

Abasaglar® is the first biosimiliar insulin approved in the European Union. This long acting insulin analogue has an identical amino acid sequence to that of the active ingredient in the reference product – Lantus® (insulin glargine 100 units/ml). Abasaglar® also has the same licensed indications, dosing regimen, pharmaceutical form and strength as the reference product. Abasaglar® differs from Lantus® with respect to excipients used, but the final quantitative formulation is the same.

In order to gain approval in the EU a biosimilar medicine must demonstrate that they are as safe and as effective as the reference medicine, and have the same quality characteristics. The EU regulatory process demands an extensive comparability exercise is performed through a stepwise process that begins with structural, physicochemical and biological analysis, non-clinical, then pharmacokinetic (PK) and pharmacodynamic studies (PD), followed by clinical safety and efficacy trials. In the extensive comparability exercise it was shown that the PK and PD profiles, the relative bioavailability and the duration of action of Abasaglar® are comparable to those of Lantus®.

In addition to this, the clinical efficacy of Abasaglar® given once daily was compared to that of once-daily Lantus® in two similarly designed randomised, active-control, parallel group studies. ELEMENT 1 was a 52 week study (24-week treatment period and 28-week extension) in patients with T1DM, and ELEMENT 2 was a 24-week study in patients with T2DM. Adult patients aged ≥18 years of age with a screening HbA1c of ≤11.0% for insulin pre-treated patients and ≥7.0% to ≤11.0% in insulin naïve patients were eligible for the studies. Exclusion criteria were largely unrestrictive and reflect the general population with diabetes mellitus. Both studies were designed to show non-inferiority of Abasaglar® versus Lantus® based on the primary endpoint of change in HbA1c from baseline to 24 weeks, with a non-inferiority margin of 0.4% HbA1c, and if met 0.3%. Results from both clinical trials demonstrated that Abasaglar® was non-inferior to Lantus® in reducing HBA1c in both T1DM and T2DM at both non –inferiority margins. There were also no clinically significant treatment differences in any secondary efficacy measures, including FBG, insulin dose, and body weight at 24 weeks.

The safety profile of Abasaglar® has been well characterised in the context of the extensive comparability exercise. In clinical studies the overall safety profile of Abasaglar® was

comparable to Lantus® and in line with the documented profile of the reference product. There were no major safety findings or signals identified. The list price of Abasaglar is currently approximately 15% lower than that of Lantus®.

The group therefore agreed that Abasaglar® should be considered for all new patients requiring insulin glargine in line with NICE guidelines. Individual Trusts may also wish to consider a managed therapeutic switch between products for existing patients who are not currently on a stable dose. Abasaglar® has been shown to be bioequivalent to Lantus® and the efficacy of the two products are comparable. Nevertheless, as with other biosimilar medicines, some patients may still need an adjustment in dose so must be monitored closely during any switching process. All insulin glargine products must be prescribed by brand name to prevent any confusion around product prescribed.

ACTION Secretary to draft decision summary as above

6) Appraisal: Insulin Glargine 300 units/ml – Toujeo®.

The appraisal report concerning the use of high strength insulin glargine-Toujeo® was introduced by the secretary. This was also referred to NTAG from a local APC.

Toujeo® is a higher-strength formulation (300 units/mL), than the existing insulin glargine product on the market (Lantus®, 100 units/mL). Toujeo is intended to have a flatter and more prolonged pharmacodynamic profile than Lantus® and it is licensed for the treatment of Diabetes Mellitus in adults. In clinical trials, Toujeo® was shown to be non-inferior to Lantus in reducing HBA1c in both T1DM and T2DM. The incidence of nocturnal severe and/or confirmed hypoglycaemia was a significantly lower with Toujeo in T2DM trials, but showed no difference in patients with T1DM. The overall safety profile of Toujeo® was comparable to the well-established safety profile of Lantus®. No new or unexpected safety signals were detected with respect to injection site reactions, insulin antibody response, hypersensitivity reactions and cardiovascular safety.

In T1DM, NICE NG17 (2015) recommends multiple daily insulin injection basal-bolus regimens, rather than twice-daily mixed insulin regimens as the insulin injection regimen of choice for all adults with T1DM. Twice-daily insulin detemir should be offered as basal insulin therapy. If a twice-daily insulin regimen is not acceptable, consider once-daily insulin glargine or detemir. Once-daily insulin glargine should also be considered if insulin detemir is not tolerated.

In T2DM, NICE CG87 (2009) recommends that NPH insulin is the preferred choice when insulin therapy is needed to treat T2DM. Long-acting insulin analogues may have a role in treating specific patients.

Toujeo® represents an additional treatment option for patients that require a long-acting insulin analogue who are not currently able to achieve optimal glycaemic control. Due to a flatter and more prolonged pharmacodynamic profile Toujeo® is thought to allow patients' greater flexibility in the timing of their once-daily injection compared with Lantus®. . It also offers the advantage of a smaller volume of subcutaneous injection and so may be less painful. However, switching from Lantus® to Toujeo® is not straightforward, as the drugs are **not bioequivalent** and are not directly interchangeable.

A switch can be done on a unit-to-unit basis, but higher doses of Toujeo® (approximately 10-18%) may be required to achieve similar levels of glucose control.

The per unit acquisition cost of Toujeo® is lower than Lantus® but similar to the biosimilar.

Several new insulin products have come to market recently, and healthcare professionals and patients need to understand the insulin strength of these products and how to use them correctly to minimise the risk of medication errors such as the wrong insulin dose being administered. An organisational risk minimisation strategy around use of high strength and biosimilar insulin's would be advisable to reduce the risk of errors, particularly around the interface i.e. on hospital admission or discharge.

The group approved the use of Toujeo® as an option for use in adults who are eligible for treatment with insulin glargine as per NICE guidance (NG17, 2015).

If used Toujeo® must be prescribed by brand name to prevent any confusion. It should be noted that the Solostar® pen will only discharge a maximum of 80 units in one injection.

ACTION Secretary to draft decision summary as above

7) Work Plan and Topics for next year.

The group discussed the work plan. It was noted that there were not many items on the agenda for discussion. It was felt that the etanercept biosimilars were the highest priority of the items remaining on the work plan; however these would not be launched by the February meeting. It was therefore agreed that the February meeting should be either cancelled or postponed. Most other items were due to be discussed by NICE or were items for re-review. It was noted that Exogen® ultrasound device was still on the work plan however it was unclear whether this was still required, it was agreed that specialists would be contacted to confirm a need prior to reviewing.

It was agreed that new items would need to be added from horizon scanning as and when launch dates were available and that APC's could be contacted for other suggestions.

ACTION: Secretary to re-arrange next meeting and to contact manufacturers for the etanercept biosimilar to enquire about launch dates.

8) AOB

No other business was raised and the meeting concluded.

The date of the next meeting was noted to be 24th February however as discussed above it was likely that this meeting would be cancelled.

Minutes produced by B Reddy, Professional Secretary to NTAG, 4th December 2015