Northern Treatment Advisory Group

Minutes of meeting held on the 4th April 2016, 9-12am,

Meeting Room 4, The Durham Centre

Present:

- Phil Argent (PA) Asst. Head of Finance, Newcastle Gateshead CCG.
- 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.
- Bhavana Reddy (BR) Head of Prescribing Support, RDTC (professional secretary)
- Toks Sangowawa (TS) Clinical Director of Public Health, Tees Valley Public Health Shared Service.
- Janette Stephenson (JS) Head of Medicines Optimisation, North East Commissioning Support Unit
- Roger Wheeler (RW) General Medical Practitioner, Middlesbrough
- Ali Wilson (AW) Chief Officer, Hartlepool & Stockton-on-Tees CCG.

Apologies were received in advance from: Joe Corrigan, Andrea Loudon, Simon Thomas, Neil Watson, Tim Donaldson, Chris Williamson, Helen Huck, Nick Quinn and Chris Gray.

The Chair invited declarations of interest relating to the agenda. None were made.

1) Draft Minutes November Meeting

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

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

2) Matters Arising

a) DOI forms

Members were reminded to forward on completed DOI forms to the secretary; a 'nil' declaration could be made by email.

b) PCSK-9 Inhibitors (evolocumab and alirocumab) draft NICE TA update

The group was updated on the status of the NICE TA's on evolocumab and alirocumab. It was noted that whilst NTAG hadn't approved use the NICE appraisal consultation document on evolocumab now approves use. The group noted the potential high costs of treatments. It was agreed that a patient pathway for use would be useful and it was felt that if this could be done once across the North East and Cumbria it would prevent duplication of effort across area prescribing committees. It was agreed that a letter would be sent to the clinical networks asking if they could work on pathway for the region. The group agreed to wait for publication of the TA prior to contacting the network lead specialist.

ACTION BR to monitor NICE website and to draft email to specialists on behalf of NTAG

Post meeting note: Both NICE TA's were now due to be published in June and not in April as previously thought.

3) Appraisal: Etanercept Biosimilar – Benepali®

The appraisal report on the etanercept biosimilar- Benepali® was introduced by the secretary.

In February 2016, a biosimilar formulation of etanercept was launched in the UK under the brand name of Benepali®. Benepali® is only licensed to be given as a 50 mg once-weekly dose, and is therefore not licensed for the paediatric indications of Enbrel® (the reference product) for paediatric plaque psoriasis and juvenile idiopathic arthritis.

To gain approval in the EU, biosimilar medicines must demonstrate that they are as safe and as effective as the reference medicine, and have the same quality characteristics.

In an extensive comparability exercise it was shown that all major physicochemical characteristics and biological activities of Benepali® (etanercept biosimilar) are comparable to those of Enbrel®, the originator product. The clinical trial program demonstrating bio-similarity consisted of a phase III efficacy and safety study in patients with active rheumatoid arthritis and a phase I pharmacokinetic (PK) study in healthy volunteers.

In the Phase III, randomised, double-blind, study in 596 subjects with moderate to severe RA despite methotrexate therapy, the efficacy of Benepali® was shown to be comparable to that of Enbrel in the primary outcome of ACR20 response at week 24. The secondary efficacy outcomes at week 24 support the primary findings, and response rates were sustained to a similar degree in both treatment groups up to week 52.

As the 95% confidence intervals for the difference in ACR20 were contained within the predefined equivalence margin of ±15% the results are sufficient to demonstrate equivalent efficacy.

Overall, the type and incidence of treatment-emergent adverse events (TEAEs) observed in the pivotal study were similar between the two treatment groups and were in line with the well-characterised safety profile of Enbrel as outlined in the SPC. The majority of TEAEs were of mild to moderate severity, and no significant new safety signals, were reported.

Although the clinical studies were only performed in patients with RA, efficacy and safety for other indications is assumed from the demonstration of equivalence to the reference product in accordance with regulatory procedures. Based on the totality of evidence, the EMA concluded that similarity has been convincingly demonstrated enabling extrapolation of Benepali approval to all other indications for which the reference product Enbrel® is approved, except the aforementioned paediatric indications.

On 1st April 2016, a new CMU contract which will include the TNF inhibitors is due to start. The current list price for Benepali® is 10% below that of the reference product however locally negotiated discounts may be available.

A second etanercept biosimilar currently known only as 'GP2015' was filed in the EU by Sandoz in December 2015 for all indications included in the Enbrel® label. The results of

the pivotal EGALITY study are expected to be published at EULAR in June 2016. Licensing is anticipated in Q1 2017, subject to regulatory approval.

The group approved use of Benepali® first line for existing and new patients. For existing patients consideration should be given to switching where it is clinically appropriate and as part of a clinician led management programme which has appropriate monitoring in place.

4) Appraisal: Transanal irrigation systems

This item was referred to NTAG from a local GP who had been requested to prescribe a new anal irrigation system by a local consultant. The IFR team had advised that this needed to be reviewed by NTAG before any prescribing in primary care could take place.

The secretary gave the group a bit of background on the indications for transanal irrigation systems. It was noted that transanal irrigation systems are indicated for use in neurogenic bowel dysfunction, chronic constipation and chronic faecal incontinence.

Treatment of chronic constipation involves identifying and eliminating the causes. However, this can be difficult and impractical, particularly where causes are multi-factorial or irreversible. A stepwise treatment approach is usually recommended, beginning with behavioural or lifestyle changes. Pharmacological and minimally invasive management strategies should then be employed. Where these fail, more invasive methods, including surgery, may be considered.

Transanal irrigation (TAI, also known as rectal irrigation) is generally considered to be a minimally invasive process. The term describes the introduction of water (or another solution) into the rectum and left colon, via the anus. The fluid stimulates peristalsis, resulting in retained stools and the irrigation fluid being passed out within 10 - 30 minutes. TAI is therefore purported to be of value is relief of chronic constipation or faecal incontinence, as well as prevention of faecal impaction through regular use.

A variety of TAI systems are available commercially. They are classed as medical devices, and all are CE marked. Some use a manual pump whilst others are electronically controlled. Some have balloon catheters which allow the catheter to be self-retaining and facilitate ease of use. Others use a rectal cone, which needs to be held in place throughout the TAI process. Most products are designed for use over a toilet or commode, but one is specifically designed for bedridden patients.

As TAI systems are not medicinal products they don't have to undergo any efficacy trials however it was acknowledged that robust randomised trials are difficult to design and undertake and given the invasive nature of TAI, adequate blinding is virtually impossible and placebo interventions would be problematic.

There is a reasonable volume of evidence assessing the efficacy of TAI, but the majority of it is of low quality and relates mainly to the peristeen product. To date, one randomised controlled trial has been undertaken. The rest of the available evidence consists of case series, outcome studies, or qualitative research.

The efficacy of TAI in managing faecal incontinence and constipation in adults with central neurological disease has however been assessed in a Cochrane review. The efficacy of TAI

in managing faecal incontinence and constipation in adults with central neurological disease was assessed in a Cochrane Review. The review included one small 10 week randomised trial (n=87), which had a small risk of bias. Participants used the Peristeen® system either daily or every other day in addition to conservative bowel care, or conservative bowel care alone. Statistically significant improvements in constipation scores, NBD scores, and faecal incontinence scores was found in the TAI group versus conservative care. TAI also resulted in a significantly reduced time for bowel care and increased satisfaction. No other relevant studies were found and no trials compared TAI with other interventions.

TAI is generally considered a safe procedure, providing users are adequately trained in its use. The most serious risk is that of bowel perforation, which can be potentially fatal. There are no reliable estimates of incidence at this time, but some evidence seems to suggest an overall risk of 20 perforations per million procedures. In 2011, the product information for Peristeen was updated to reflect the rare risk of perforation. The MHRA released a Medical Device Alert reminding healthcare professionals to ensure that patients and carers: *Have received comprehensive training and are competent in the use of the system before using it unsupervised and are aware of the risk of bowel perforation, how to recognise the symptoms, and action to be taken.*

The group noted that TAI is recommended as an option in the NICE clinical guideline for the management of faecal incontinence in adults, where initial management has failed. It is listed as a potential component of a specialist continence service, alongside pelvic floor muscle training, bowel retraining, specialist dietary assessment and management, biofeedback, and electrical stimulation. In addition the Royal College of Surgeons produced a faecal incontinence commissioning guide in 2014. Similar to NICE, they list TAI as a component of a nurse or therapist-led specialised bowel management service for level 2 patients.

The group approved use of TAI systems as an option for treatment when all other treatment options have failed or proved ineffective and if initiated and monitored by a specialist. It was agreed that taking into account any patient factors it would seem reasonable to use the system with the lowest acquisition cost first (this is currently the IryPump® S).

ACTION Secretary to draft decision summary as above

5) Appraisal: e-Voke® electronic cigarette.

This item was referred to NTAG from local APCs. The secretary introduced the paper and gave the group some background on the changes in legislation with regards electronic cigarettes and the newly licensed e-Voke® product.

An e-cigarette normally consists of three components: a battery, an atomiser and a cartridge or ‘tank’ containing the nicotine liquid called e-liquid or e-juice. The liquid nicotine is suspended in propylene glycol or glycerine and water. The level of nicotine in the cartridges may vary and some also contain flavourings. When a user sucks on the device, a sensor detects air flow and the battery heats the liquid through a small heating element in the cartridge causing it to evaporate. This vapour then delivers the nicotine and flavours to the user. E-cigarettes are currently regulated as consumer products, but legislation to be implemented this year will require that available products meet safety and quality standards.

Products not meeting the new standards can instead apply for a medicines marketing authorisation.

The e-Voke® device is the first electronic cigarette in the UK to seek regulatory approval as a medicine. The marketing authorisation is held by Nicovations Ltd, which is part of Nicoventures, a division of British American Tobacco.

The e-Voke device consists of a stainless steel vaporiser and battery unit which are screwed together by the patient before first use. The battery is rechargeable, and must be unscrewed from the vaporiser in order to be charged. The device is supplied with a USB charging adaptor. The battery is designed to last roughly 130 inhalations before needing to be recharged, and charging takes 2-3 hours.

One clinical study was submitted to support the marketing authorisation application for e-Voke. This was a pharmacokinetic study with a crossover design, comparing the bioavailability of nicotine when delivered by: e-Voke 10 mg or 15 mg cartridges with Nicorette® 15 mg Inhalator or smoking a cigarette (Benson & Hedges Gold). Plasma nicotine levels were higher with e-Voke 10 mg and 15 mg than the Nicorette 15 mg inhalator at all-time points. Nicotine levels associated with cigarette smoking were considerably higher than all other methods. The conclusion was that e-Voke electronic inhalers are at least comparable with the reference product (Nicorette) and as safe (in terms of nicotine consumption) as cigarettes. No new safety concerns were highlighted.

There are currently no published clinical trial data showing a reduction in harms related to smoking due to the use of e-Voke or an increase in the numbers of quit rates compared to other stop smoking therapies.

Concerns were raised that e-cigarettes may be used for harm reduction purposes rather than as stop smoking aids. All other treatments used on the NHS are prescribed as stop smoking aids therefore this is the indication for which e-Voke® was reviewed. It was noted that use for harm reduction may lead to longer use than current nicotine replacement therapies which would lead to a substantial cost to the NHS. However the NICE guidance on Tobacco Harm Reduction, recommends that quitting all forms of nicotine use is the best option for smokers due to the long-term effects of nicotine, which include addiction, increased risk of heart diseases, decline in insulin levels, cancer and premature aging.

E-Voke is thought to cost ~£20 for the kit plus ~£10 for a cartridge although a definite price is not yet available. One cartridge contains roughly 130 inhalations depending on the depth and length or user inhalations. The maximum dose is 5 cartridges per day.

It was agreed that more rigorous data showing the benefits of e-Voke® as a stop smoking aid must be available prior to e-cigarettes being approved for use.

ACTION Secretary to draft decision summary as above

6) Lurasidone

The group discussed a letter that had been sent to NTAG from Dr Angus Bell who was the clinical lead for mental health at the northern clinical network. The group had been asked to re-consider their recommendation on lurasidone and a potential place in therapy had been

identified by the author. Whilst there isn't currently any particular clinical trial data backing up use in the way proposed (for patients who can't tolerate aripiprazole) it was noted that a pooled analysis showed that lurasidone was weight neutral and had no mean effect on glucose, lipids or cholesterol over 12 months. The group also noted that the manufacturers have been particularly active in speaking to specialists about their drug and noted the letter they had also sent to the group. The data included in the letter was data that the group had seen previously. It was agreed that if specialists wanted to use lurasidone in the patient group proposed then they should put forward some guidance, backed by all three MH trusts that NTAG could review. As there wasn't a mental health representative at the meeting this proposal would need to be agreed by MH representatives prior to it being sent.

ACTION Secretary to contact mental health representatives to agree way forward.

Post meeting note: After discussion with MH representatives it was agreed that the secretary would respond to Dr Angus and request that he put forward a pathway/guideline for lurasidone use that NTAG could review.

7) Regional Medicines Optimisation Committees

The group discussed the new development of the regional medicines optimisation committees. There was a concern that these new committees would take on some (but not all) of the work of NTAG but would not have the local engagement or buy in that NTAG does. There were discussions around what the remit of these new committees would be and how they would get engagement across such a wide geography. A lot of the questions raised were yet to be answered; it was therefore agreed that NTAG would continue meeting for the foreseeable future until further clarification had been received.

8) 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 but there may be sufficient for the June meeting to go ahead however this would be confirmed nearer the time as it would depend on licensing approval.

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.

9) AOB

No other business was raised and the meeting concluded.

The date of the next meeting was noted to be 7th June however as discussed above this would be confirmed nearer the time.

Minutes produced by B Reddy, Professional Secretary to NTAG, April 26th 2016.