Northern Treatment Advisory Group

Minutes of meeting held on the 6th September 2016, 9-12am,

Meeting Room 4, The Durham Centre

Present:

- Ian Campbell (IC), Assistant Director Pharmacy, Newcastle upon Tyne Hospitals NHS Foundation Trust.
- 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.
- Ali Wilson (AW) Chief Officer, Hartlepool & Stockton-on-Tees CCG.

Apologies were received in advance from: Joe Corrigan, Janette Stephenson, Simon Thomas and Tim Donaldson.

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

1) Draft Minutes April Meeting

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

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

2) Matters Arising

a) DOI updated policy

The secretary shared the updated declarations of interest policy with NTAG members. It was noted that the policy had been updated in line with the new NHS England guidance for CCGs. It was agreed that NTAG should work to the same standards as outlined in this document. The updated policy was therefore approved and the group agreed that all declarations would need to be declared one week prior to the meeting.

ACTION: NTAG approved the updated policy and asked that it be updated on NTAG website.

b) PCSK-9 Inhibitors (evolocumab and alirocumab) draft pathway

The group noted that the NICE TAs on the PCSK-9 inhibitors had now been published and were approved for use. A pathway outlining specific criteria when a PCSK9-inhibitor

can be used had been developed by the lipid specialist's network. The pathway had been developed as an appendix to the FATS cholesterol lowering guidance. The group discussed the proposed pathway for use across the North East and Cumbria region. It was noted that use of rosuvastatin within the pathway would need to be discussed at local formulary groups as most formularies are unlikely to contain rosuvastatin as a formulary choice. Whilst there may be a cost impact in the short term the patent for rosuvastatin is due to expire in 2017 and use of rosuvastatin prior to moving onto other options, which may include a PCSK-9 inhibitor, seems sensible.

NTAG approved the pathway for PCSK9 inhibitors.

3) Appraisal: Eluxadoline for IBS

The appraisal report on the eluxadoline for Irritable Bowel Syndrome (IBS) was introduced by the secretary. It was noted that this drug had been identified through horizon scanning and as a first in class drug with a potentially large patient population.

Symptoms of IBS tend to follow a relapsing-remitting course and disease is often life-long. People with a longer history of disease are less likely to ever recover, as are those experiencing chronic stress. IBS therefore has a potentially large impact on quality of life, productivity and psychological wellbeing.

IBS is common in the UK, with an estimated prevalence of 10-20% in the general population. Irritable bowel syndrome with predominant diarrhoea (IBS-D) is a chronic bowel disorder which causes abdominal pain, nausea, and altered bowel habit. Diarrhoea may be accompanied by faecal urgency or incontinence, with attendant loss of productivity and distress.

Eluxadoline (Truberzi®▼, Allergan) is a mixed mu opioid receptor agonist and delta opioid receptor antagonist. It has been suggested that this pharmacology allows opioid analgesia and reduction in intestinal motility, without causing mu-opioid receptor-mediated constipation.

Current first line management for diarrhoea is loperamide, which has been shown to help with diarrhoea but has little effect on abdominal pain. Co-phenotrope and opioids may also be considered, but are not favoured due to their adverse effect profiles. Anti-motility drugs should be used as needed to produce a soft, well-formed stool

In two phase III clinical trials, eluxadoline 75 mg or 100 mg twice daily was compared to placebo for the outcome of treatment response, which was defined as improvement in abdominal pain by ≥30% plus Bristol Stool Form <5 on at least 50% of study days.

Treatment response after 26 weeks was more common with eluxadoline 75 mg (27%) and eluxadoline 100 mg (31%) than placebo (20%, both comparisons p≤0.001). When examined separately, stool consistency was significantly improved over baseline but abdominal pain was not.

There are no available data comparing eluxadoline with other treatments for IBS-D, and efficacy data are limited to 26 weeks. Patients were only eligible for the clinical trials if they were not taking any other anti-diarrhoeal medicines meaning that the trial populations may not be representative of the target population in the UK.

The most common adverse effects were gastrointestinal (e.g. constipation, nausea, abdominal pain). Several cases of pancreatitis and sphincter of Oddi dysfunction were reported in the eluxadoline groups. History of these conditions is a contraindication to use in the USA, where eluxadoline has been marketed for some time.

The cost of eluxadoline is not yet known however US costs indicate that it will be more expensive than loperamide. Loperamide costs £26 to £71 per year, depending on dose used.

The group noted that Eluxadoline appears to be effective at reducing symptoms of IBS-D. However, IBS is a disease of relapse and remission, and inclusion criteria required that recruited patients had pain, loose stools and a moderate IBS-D global symptom score in the week prior to randomisation. Some of the changes in symptoms scores may therefore be due to the normal natural history of the disease, or "regression to the mean". Patients taking anti-diarrhoeal and anti-spasmodic medicines prior to randomisation were excluded from the pivotal trials. Eluxadoline would likely be used in the UK following failure of the currently available treatment options, which includes, routine use of anti-diarrhoeal's and antispasmodics. The trial populations are therefore likely not representative of the UK target population. Similarly, the efficacy of eluxadoline on patients switching directly from loperamide is not known.

The group therefore did not approve the use of eluxadoline for patients with IBS-D due to the limited evidence base and lack of data in the patient population that eluxadoline is likely to be used in.

4) Appraisal: FreeStyle Libre Glucose Monitoring

This item was referred to NTAG from Cumbria CCG who had received a request for its use. It was noted that several IFRs had been received across the North East and Cumbria region for use of the free style libre glucose monitoring device.

The secretary introduced the evaluation report.

The FreeStyle Libre is a flash glucose monitoring system which allows people to monitor their glucose levels and trends without performing capillary (finger prick) testing. It lies somewhere between a traditional blood glucose meter and a continuous glucose monitoring (CGM) system. CGM sensors measure the glucose levels in interstitial fluid rather than in the bloodstream, with measurements every few minutes, thereby enabling patients to monitor hyper and hypo- glycaemia.

The FreeStyle Libre system consists of sensor worn on the upper arm that measures interstitial glucose every minute and a reader device that is scanned over the sensor to get a result. The FreeStyle Libre system is indicated for measuring interstitial fluid glucose levels in people (age 4 and older) with diabetes mellitus. The indication for children (age 4 - 17) is limited to those who are supervised by a caregiver who is at least 18 years of age. A caregiver at least 18 years old needs to be responsible for supervising, managing, and assisting the child in using the FreeStyle Libre system and interpreting its readings.

Monitoring of interstitial glucose is the same method of measuring sugar levels as that used by conventional continuous glucose meters. Patients are still advised to monitor blood glucose via capillary testing during periods of rapidly changing levels of interstitial glucose

when interstitial glucose levels may not accurately reflect blood glucose levels, if hypoglycaemia or impending hypoglycaemia is reported, or the patient's symptoms do not match the system readings. Patient's will also still need to do finger prick blood tests prior to and during driving to meet DVLA requirements.

The product is classified as a device and received European CE mark certification in August 2014. The other CGM devices don't have CE mark certification. Trial data for the equipment comes from company sponsored trials which indicate accuracy being marginally superior to existing continuous glucose monitoring systems. The majority of the trial data is only available in conference abstracts. The device may offer some advantages in terms of patient acceptability and quality of life but good quality clinical trial data to support long-term clinical effectiveness and cost-effectiveness is lacking

The FreeStyle Libre readers and sensors are not currently prescribable on FP10.

The products are available to buy online (incl. VAT):

FreeStyle Libre Reader + 2 x Sensors: £159.95; FreeStyle Libre Reader: £57.95 (has a 3 year lifespan before requiring a service); FreeStyle Libre Single sensor: £57.95 (each sensor as a life-span of 14 days).

In comparison the cost of continuous glucose monitoring varies according to which system is used. Starter kits which include the transmitter and the receiver cost approximately £1000, or if the system is integrated into an insulin pump the cost is around £500 for the transmitter. Sensors last for between 3 days and 7 days depending on which system is used and cost approximately £40-£60 each.

The group approved the use of FreeStyle Libre as an option for those patients who fulfil the criteria for continuous glucose monitoring. Although there is limited clinical trial data for FreeStyle Libre, this is similar to other CGM devices however FreeStyle Libre is less expensive and has a European CE mark.

ACTION Secretary to draft decision summary as above

5) Appraisal: Ferric Maltol (Feraccru®) for IDA in IBD patients.

This item was referred to NTAG from local APCs. The secretary introduced the appraisal report from London and the cost analysis for NTAG.

Ferric Maltol (Feraccru®) is a novel trivalent iron complex consisting of a single ferric iron ion (Fe3+) chelated with high affinity to three maltol (3-hydroxy-2-methyl-4-pyrone) molecules. It is a new oral iron product indicated for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. It is proposed that its high bioavailability compared to other iron products means that greater amounts of elemental iron can be delivered more easily. Also, as the gastrointestinal mucosa is not exposed to high levels of free iron so it is hypothesised that the potential for tolerability problems is minimised.

It was noted that there is an unmet need for effective and well tolerated treatments for IDA in IBD that are easy and safe to administer. This can affect compliance and reduce the likelihood of desired treatment outcomes (raised serum iron levels) being achieved. It is

thought that oral ferric maltol will be better tolerated than other iron salts such as ferrous sulphate and unlike IV iron; it can be safely self-administered by the patient at home.

The manufacturer intends Feraccru® to be second-line to currently available oral iron products and an alternative option in patients with mild to moderate IDA with either CD or UC who have reported intolerance to oral ferrous salts due to adverse effects. In these patients, it should be considered as an alternative to IV iron if there is no urgent need to raise Hb levels (e.g. prior to surgery).

The pivotal phase III trial programme of Feraccru® consisted of two identical prospective randomised, double blind, placebo-controlled, multicentre trials; AEGIS-1 and AEGIS-2 which involved 128 patients with mild to moderate IDA associated with (stable) IBD. After 12 weeks, Feraccru® led to a statistically significant improvement in Hb of 2.25g/dL from baseline to week 12 compared to placebo ($p<0.0001$) with the median time to normalisation of Hb levels being 57 days. Ferritin and transferrin saturation also improved over 12 weeks compared to placebo. Hb levels continued to increase to an average maximum of 14g/dL at 48 weeks in the open label extension study with continued use of Feraccru®.

The AEGIS studies were relatively small, of short duration and only compared Feraccru® with placebo. They included only patients with mild to moderate IDA at baseline so it is not clear how these results would apply to patients with more severe IDA.

A direct comparison study of Feraccru® vs. Ferinject® (n=240) is currently in progress and aims to report data in 2017.

Data from the AEGIS studies suggest that Feraccru® may be well tolerated in many patients with previous intolerance of oral ferrous salts. The most commonly reported adverse effects were arthralgia and mild to moderate gastrointestinal effects - abdominal pain, reflux, flatulence, rectal haemorrhage, abdominal distension and constipation. The EMA notes in the EPAR for Feraccru® that it did not exacerbate IBD during the AEGIS studies or during the open label extension study.

The proposed pathway is as follows: Mild to moderate IDA patients will get oral iron but if this isn't tolerated or it hasn't raised iron levels then they could try ferric maltol, if this fails they would get IV iron. Severe IDA patients who need levels correcting would get IV iron straightaway.

The estimated budget impact per100,000 population is - £12,740 i.e. a cost saving using ferric maltol. This would therefore be a cost saving of - £412,763 for the North East and Cumbria region due to a reduction in outpatient appointments. The group then discussed the application from the specialist. It was agreed that at least two oral iron salts should be tried prior to moving onto the next option due to the differences in cost. The group also raised the issue of whether ferric maltol should be prescribed in primary care. It was felt that it would be useful to limit use initially to gastroenterologist use only, so that data on outcomes can be collated and tolerability assessed. Whilst it was not the remit of NTAG, it was agreed that it would be useful for local APCs to request that specialists audit use of Ferric Maltol in 6-12 months' time.

The group was minded to approve the use of ferric maltol for IBD patients with IDA initiated and prescribed by gastroenterologists only and for second line use following intolerance to or failure of at least two oral ferrous salts.

ACTION Secretary to draft decision summary as above

6) Regional Medicines Optimisation Committees (RMOC) Consultation

The group discussed the regional medicines optimisation committees' proposal and responded to the questions posed. It was agreed that the current process for review of new high cost drugs in the North East and Cumbria works well and recommendations made by NTAG are implemented by CCGs; it is therefore difficult to see how RMOCs would be able to get the same level of local input into their decisions and therefore may just add an extra layer of decision making rather than reduce duplication which is the intention. The group agreed that a response should be sent.

ACTION BR to collate points made during discussions and email response by the 19th September deadline.

7) Work Plan and Topics for next year.

The group discussed the work plan. It was noted that there were a few items for discussion for the November meeting:

Lycra Suits, Alpha pumps, Re-review of Qutenza® recommendation and lurasidone proposed protocol for use.

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.

8) AOB

No other business was raised and the meeting concluded.

The date of the next meeting was noted to be 22nd November 2016.

Minutes produced by B Reddy, Professional Secretary to NTAG, 12th September 2016.