Northern Treatment Advisory Group

Minutes of meeting held on the 5th September 2017, 9-12am,

Meeting Room 4, The Durham Centre

Present:

Name	Title	Organisation	Sept 2017
Dr Ian Davidson (ID)) *Chair*	Director of Quality and Safety	North Durham CCG & Chair of NTAG.	√
Tim Donaldson (TD)	Chief Pharmacist/Controlled Drugs Accountable Officer	Northumberland Tyne and Wear NHS Foundation Trust	√
Dr Matthew Grove (MG)	Consultant Rheumatologist	Northumbria Healthcare NHS Foundation Trust	√
Dr Andrew Lloyd (AL)	Consultant Anaesthetist and Chair of South Tees D&T,	The James Cook University Hospital (JCUH)	√
Bhavana Reddy (BR) (Professional Secretary)	Head of Prescribing Support	Regional Drug and Therapeutics Centre	√
Dr Simon Thomas (ST)	Consultant Physician,	Newcastle upon Tyne NHS Foundation Trust and RDTC Medical Director.	√
Dr Nick Timlin (NT)	General Medical Practitioner,	Hartlepool & Stockton-on-Tees CCG.	√
Andrea Laudon/Janette Stephenson	Head of Medicines Optimisation	North East Commissioning Support Unit.	√ A Loudon
Ali Wilson (AW)	Chief Officer,	NHS Darlington CCG and NHS Hartlepool & Stockton-on-Tees CCG.	√
Hannah Willoughby (HW)	Medicines Optimisation Pharmacist	Sunderland CCG.	√
Tom Hall (TH)	Consultant in Public Health	South Tyneside Council	A

In Attendance: **Dr Sanjay Pathare, Consultant Rheumatologist, South Tees.**

AL introduced the group to Dr Sanjay Pathare who would be his deputy on the group. The group welcomed him to the meeting.

No declarations were received prior to the meeting on receipt of the agenda and when the Chair invited any declarations of interest to be made, none were made.

1) Draft Minutes June Meeting

The group approved the June minutes with an update to the date which stated February in error. No other changes were made.

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

2) Matters Arising

a) Quoracy

The group noted that Public Health was struggling to attend meetings. The terms of reference had been updated previously to suggest that any items related to public health should have public health involvement however this was no longer practical. It was therefore agreed that the statement in the terms of reference should be updated to state *'If a representative cannot attend the meeting, views will be sought via email prior to the meeting.'*

ACTION: Secretary to update terms of reference as above.

3) Appraisal: Bezlotoxumab for the treatment of C.difficile

The appraisal report was introduced by the secretary. This had been added to the work plan via horizon scanning. There had been no specific requests for it by specialists, however it is likely to be PbR excluded and therefore commissioned by CCGs so was felt to be useful for NTAG to consider. Bezlotoxumab is a human monoclonal antitoxin antibody that binds with high affinity to *Clostridium difficile* toxin B and neutralises its activity. It is indicated for preventing future episodes of diarrhoea in people who are taking antibiotics to treat their *C difficile* infection and who are at high risk of the infection coming back. It is administered as a single one-off intravenous infusion during a course of antibacterial therapy for *C difficile* infection. The group noted the following points from the NICE evidence summary[1]

- Bezlotoxumab has been evaluated in two similar randomised controlled trials (RCTs; MODIFY I [n=1,396] and MODIFY II [n=1,163]). They both compared the efficacy and safety of a single dose of bezlotoxumab (10 mg/kg) with placebo for preventing the recurrence of *C difficile* infection in people taking usual standard-of-care antibiotics (usually metronidazole or vancomycin).

- In a pooled analysis of MODIFY I and MODIFY II, at the 12-week follow-up, 17% of participants given bezlotoxumab had recurrent C difficile infection compared with 27% of those given placebo (statistically significant difference). However the EMA noted that the secondary endpoint of sustained clinical cure (initial clinical cure of the baseline infection and no recurrence for 12 weeks) is more relevant to clinical practice.

[1] https://www.nice.org.uk/advice/es13/chapter/Key-points

- For sustained clinical cure, there was a statistically significant difference between bezlotoxumab and placebo in MODIFY II but not in MODIFY I. When data from both trials is pooled, the difference was statistically significant (64% with bezlotoxumab compared with 54% with placebo).

- Recurrence of C difficile infection and sustained clinical cure were each improved by about 10% in absolute terms with bezlotoxumab compared with placebo at 12 weeks (giving a number needed to treat of around 10). However, almost three quarters of participants given placebo did not have recurrent infection by week 12 (73% compared with 83% given bezlotoxumab), and around half had sustained cure (54% compared with 64% with bezlotoxumab).

- It was however noted that recurrent C difficile infection is difficult to treat and is associated with more hospitalisations, severe outcomes, and higher costs than initial episodes The European public assessment report states that experts concluded that meaningful clinical relevant results were obtained in the pivotal trials, although the extent of actual benefit will only be established once the medicine has been used more widely.

- Bezlotoxumab was generally well-tolerated in the trials and had a similar adverse effect profile to placebo.

- To note only 4% of participants were taking fidaxomicin in the trials, so it is unclear what benefits bezlotoxumab has in people treated with fidaxomicin.

- The NHS list price for each vial is £2470 (excl VAT). The company estimate that use of bezlotoxumab will be low in the UK, with an estimated peak of 700 eligible people being treated in each 12-month period after 5 years. The estimated number of people eligible in the NTAG region is likely to be around 34 based on data from the company. This equates to an annual drug acquisition cost of around £93,860 for the region.

The group agreed that this may be of some value to those patients who are at risk of recurrent infection and they were minded to approve use in severe cases however they wanted further information from specialists around where they would see this drug fitting in the treatment pathway. It was agreed that further feedback would be sought and this would be discussed again at the meeting in November.

ACTION Secretary to contact specialists for feedback

4) Appraisal: Trevecta®

This item was introduced by the secretary; North of Tyne had received an application and had asked that this be reviewed by NTAG.

Trevecta® is a 3-monthly injection of paliperidone palmitate for the maintenance treatment of adults with schizophrenia who are clinically stable on 1-monthly paliperidone palmitate (Xeplion.) it contains the same active ingredient as 1-monthly paliperidone. Paliperidone 1 monthly injection has already been approved by NTAG and is included in the North of England guidance. It is indicated in patients with chronic schizophrenia who have previously been effectively maintained and stable on monthly paliperidone palmitate injection for at least 6 months.

Trevecta has been evaluated in two phase III trials: one study looked at relapse prevention (*Berwaerts A et al)* and the second looked at efficacy (*Savitz J et al)* compared to 1 monthly paliperidone.

Berwaerts A et al. 2015 is a multicentre double-blind, placebo-controlled, relapse prevention study designed to evaluate the efficacy and safety of the 3-monthly paliperidone palmitate depot verses placebo in delaying time to relapse of schizophrenia symptoms in patients previously treated with 1-monthly paliperidone palmitate for at least 4 months. The primary efficacy outcome was a reduction in relapse, in the 3-monthly paliperidone palmitate group there was reduction in relapse compared to placebo, 23% relapsed in placebo group compared to 7% of 3-monthly placebo group (hazard ratio =3.45; 95% CI,1.73 -6.88; p <0.001). In the final analysis double-blind phase, 29% of patients in placebo group relapsed compared to 9% of treatment group. The tolerability and effectiveness was found to be similar to previous trials with monthly paliperidone.

Savitz A et al. 2016 was a multicentre randomised double-blind study comparing the efficacy and safety of 3-monthly to 1-monthly paliperidone palmitate formulations. All patients received 1-monthly paliperidone palmitate for the first 17 weeks, after which a 3.5 fold fixed dose was given in the 3-monthly arm, with placebo injections between doses. At end point, the percentage of patients who remained relapse free was similar in both treatment groups. The 3-monthly paliperidone palmitate arm was found to be non-inferior to 1-monthly paliperidone palmitate arm during the double blind phase, with similar relapse rate 8% and 9% respectively and with similar PANSS total score improvement from baseline to endpoint. Over 50% of patients in both groups showed symptomatic remission for last 6 months of study.

The 3-monthly paliperidone palmitate depot offers a longer dosing interval, requiring only 4 administrations a year. This potentially offers a wider administration time window that may allow healthcare professionals to intervene if doses have been missed, and may be preferable for patients who dislike injections. However, tolerability and therapeutic effect will need to be established prior initiation. Patients may be administered 3-monthly paliperidone palmitate injection 2 weeks before or after next due date.

3-monthly paliperidone palmitate injections are available in pre-filled syringes and may be administered via gluteal or deltoid muscles.

The cost per person per year would be £2,207- £4,711 excluding VAT which is the same price as the monthly injection. Patients normally attend outpatient appointments for long acting antipsychotic injections to be administered by nursing staff; 3-monthly paliperidone palmitate depot injections will only require 4 clinic visits to see a nurse per patient per year for administration whereas they would need to attend 12 visits for the 1-monthly paliperidone palmitate.

The group agreed that Trevecta® should be recommended as an option as per the updated North of England Guideline.

ACTION Secretary to update recommendation as above.

5) Appraisal: Liraglutide (Saxenda®) for obesity

This item was introduced by the secretary. Liraglutide (Saxenda®, Novo Nordisk) is a glucagon-like peptide-1 (GLP-1) analogue, currently marketed as Victoza® as add-on therapy for the treatment of type 2 diabetes.

The group noted the following points from the NICE evidence summary on Saxenda®:

- Saxenda® is licensed as an adjunct to a reduced-calorie diet and increased physical activity for weight management in obese adults or overweight adults with at least one co-morbidity. Saxenda is administered as a subcutaneous injection with a starting dose of 0.6 mg daily, titrated up to a recommended 3 mg daily. This is substantially higher than the dose used for type 2 diabetes (T2DM) in the UK 1.2-1.8 mg/day).
- The efficacy of liraglutide in weight management has been evaluated in several randomised double-blind placebo-controlled trials.
- After 32 to 160 weeks treatment, there was a statistically significant increased weight loss with liraglutide 3.0 mg daily compared with placebo in all 4 studies (an estimated treatment difference of −5.4 to −4.0% in percentage body weight change from baseline across the 4 studies). However, many participants regained weight after stopping treatment.
- No new safety concerns were raised in the liraglutide trial programme, although known adverse events (AEs) such as nausea and vomiting occurred more frequently at higher doses. However there are several special warnings and precautions for use in the SPC for liraglutide (Saxenda), including warnings on pancreatitis, cholelithasis, and cholecystitis, thyroid disease, heart rate, dehydration and hypoglycaemia in people with type 2 diabetes.
- Orlistat is the only drug currently licensed for obesity in the UK and is recommended for use within licensed indications.
- Saxenda is marketed at an equivalent price to Victoza and costs approximately £2,381 per patient per year. Additional costs may be incurred in training patients to self-inject. In comparison orlistat 120mg three times a day costs £235 per patient per year.

The group noted the comments from the specialist regarding Saxenda® however they had several concerns. Whilst they agreed that Liraglutide 3 mg was more effective than placebo in clinical trials, they felt that evidence is lacking that users will meet the current UK requirement of 5% weight loss in 3 months of therapy for drug treatment to be continued. There is also some evidence of weight regain upon discontinuation. There are no phase III data comparing Saxenda with other drugs for weight loss, and the available comparative data have important limitations. There are no available data assessing the effect of Saxenda on clinical outcomes such as cardiovascular morbidity. Saxenda is considerably more costly than the other pharmacological options for treatment of obesity. The group therefore felt that there is insufficient evidence to recommend the use of Saxenda®.

ACTION Secretary to draft decision summary as above

6) Regional Medicines Optimisation Committee

The secretary and chair gave the group an update on the first meeting of the regional medicines optimisation committee (North). The group noted that the agenda items discussed were biosimilars, antimicrobial resistance and polypharmacy.

7) Work Plan and Topics for next year.

The group discussed the work plan. A request to re-review the fentanyl recommendation was made, however it was noted that this was one of the items included in the national drugs that should not be prescribed in primary care consultation, therefore it was agreed that NTAG would await this recommendation before this was re-reviewed. It was noted that an appeal had been received on pitolisant so that would come to the next meeting also. Avastin for RVO would also be reviewed next time.

8) AOB

Annual Report

The group noted the annual report which was due to go to the next CCG forum meeting. ID would be attending and introducing the report.

No other business was raised and the meeting concluded.

The date of the next meeting was noted to be 21st November 2017.

Minutes produced by B Reddy, Professional Secretary to NTAG, 30th October 2017