Northern Treatment Advisory Group

Minutes of meeting held on the 2nd June 2015, 9-12am,

Meeting Room 4, The Durham Centre

Present:

- Joe Corrigan (JC) Chief Finance & Operating Officer, Newcastle & Gateshead Alliance CCGs
- Ian Davidson (ID) Director of Quality and Safety, North Durham CCG & Chair of N-TAG.
- Chris Gray (CG) Medical Director, County Durham and Darlington NHS Foundation Trust.
- Andrea Loudon (AL) Clinical Pharmacy Lead, Cumbria CCG.
- Nick Quinn (NQ) Consultant Physician, South Tees Hospitals NHS 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.
- Simon Thomas (ST) Consultant Physician, Newcastle upon Tyne NHS Foundation Trust
- Roger Wheeler (RW) General Medical Practitioner, Middlesbrough
- Chris Williams (CW) Chief Pharmacist, Tees, Esk and Wear Valleys NHS Foundation Trust
- Ali Wilson (AW) Chief Officer, Hartlepool & Stockton-on-Tees CCG.

In attendance: Angela Dixon (AD) Medicines Optimisation Pharmacist, NECS.

Apologies were received in advance from: Zahra Irannejad, Craig Steele, and Tim Donaldson

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

1) Draft Minutes April Meeting

Following a minor update, 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. Terms of Reference

The group discussed the changes that had been agreed to the terms of reference regarding the quoracy as identified at the last meeting. It was noted that the public health representative was not classed as a full voting member and had historically been identified as support. The group agreed that public health input was invaluable into the decision making process of the group, they therefore opted to make the public health representative a full voting member; this would also ease any quoracy problems. The group approved the updated terms of reference following the changes to the section on public health membership as proposed above.

ACTION: Secretary to publish the updated TOR on NTAG website.

b. Letter to membership

The secretary fed back that a letter had been sent to all NTAG members as had been proposed at the last meeting. Most members had confirmed continuing input into the group however it was noted that some changes had taken place. Northumbria Trust had resigned their membership from the group as they did not feel that they required specific separate membership. The group agreed that this vacancy should be opened up to other DGHs. It was noted that no response had been received from Sunderland Foundation Trust however current members had indicated that they were no longer able to attend on a regular basis. Sunderland CCG had informed the secretary of a change in primary membership. Zahra Irannejad, Chief Pharmacist Sunderland CCG, was now the primary member; this would be updated on the membership list.

The issue of patient representation was raised again. The secretary fed back that conversations had taken place with the Chair of the North Tyneside patient forum in order to identify suitable representation. JC fed back that he had also had preliminary discussions with the new chief executive of Health Watch Newcastle and this may be another avenue that could be explored.

ACTIONS:
Secretary to send letter to acute Trusts to fill vacancy from Northumbria Trust.
Secretary to update membership list with changes outlined above.

3) Appraisal: Omnipod® continuous subcutaneous insulin infusion pump system

A request had been received from the regional network for children and young people with diabetes asking the group to re-review the old NETAG recommendation on OmniPod®.

The group discussed the updated appraisal report looking at the OmniPod® insulin pump management system and noted the following points:

- Continuous subcutaneous insulin infusion (CSII) systems have been recommended by NICE in specific circumstances for particular patient groups. Most available systems consist of an integrated control unit and pump attached to a subcutaneous cannula or needle via tubing.
- The OmniPod® system is externally tubeless, using a disposable adhesive ‘pod’ controlled via a wireless control unit.
- The OmniPod system may therefore permit greater physical freedom and reduced psychological effects on image self-awareness compared with conventional systems; however, comparative evidence of such an effect is lacking.
- Clinical advantages have only been demonstrated in low quality studies and are limited to demonstrating more consistent insulin delivery and small improvements in glycaemic control compared with other CSII systems.
- CSII systems are costly at about £2,000 to £3,000 per patient per annum. The mean annual cost of the OmniPod system is higher than other CSII systems. However, the UK supplier is offering a discount which brings the mean annual cost down to a similar level as other systems.

- The main advantages of the OmniPod® system appear to be to the patient; the system is an innovative design, featuring a tubeless system using a disposable adhesive pod controlled via a wireless control unit. There is limited data showing improvements in quality of life however these have not yet been fully published.

The group also noted that the changes in commissioning arrangements since the previous recommendation in 2011 meant that those patients who are under 19 and attend a paediatric specialist pump clinic at the two specialist centres will now be offered a choice of all CSII systems. It was agreed that this practice should be adopted across the NTAG region for all patients.

The group therefore approved the use of the OmniPod® continuous subcutaneous insulin infusion pump system as an option for new patients. It was agreed that in the interests of reducing wastage, existing users should only be offered the choice of the OmniPod system only when they are approaching the end of their 4 year pump lifecycle.

It was unclear how many patients this decision would affect across the NTAG region as no data was available for numbers of type 1 diabetics who would be suitable for insulin pump therapy. The group agreed that it would be useful to look at this information prior to issuing the recommendation. It was agreed that the IFR team at NECS should be approached for further data and once received the recommendation could be signed off via chairs action.

ACTION:
Secretary to draft decision summary and contact NECS to request data around patient numbers.
Chair to sign off recommendation once information is received.

Post meeting note: Information has now been received on the numbers of patients requesting CCG funding of insulin pump therapy across the region. This figure is lower than the current NICE estimate contained within their costing template for NICE TA 151. However it should be noted that this estimate also covers patients that are currently funded by NHS England. The average annual cost of insulin pump therapy used within this template appears comparable to annual costs of OmniPod quoted within the appraisal document.

4) Appraisal: Infliximab Biosimilars (Remsima® & Inflectra®)

The appraisal report concerning the infliximab biosimilars was introduced by the secretary. It was noted that this request had come from the North of Tyne area prescribing committee.

The secretary gave the group a brief background around biosimilar medicines since this was the first biosimilar product to be reviewed by NTAG. It was noted that biosimilar medicines are not the same as generics. Generic medicines are developed to be *identical* to the reference product whereas a biosimilar medicine is a medicine that is developed to be *highly similar* to the reference product in terms of efficacy, safety and biological activity. Although the active substance of a biosimilar and its reference medicine are essentially the same biological substance, the characteristics of biologic drugs cannot be reproduced exactly due to their complex nature and production methods. Like the reference medicine, the biosimilar will have a degree of natural variability, and minor quality differences are expected to be observed between a biosimilar and its reference product.

To gain approval in the EU, such variability and any differences between the biosimilar and its reference medicine must have been shown not to affect safety or effectiveness. The European Medicines Agency (EMA) demands an extensive comparability exercise is performed through a stepwise process that begins with structural, physicochemical and biological analysis, non-clinical, then pharmacokinetic and pharmacodynamic studies, followed by clinical safety and efficacy trials.

Infliximab was first authorised in the EU in 1999 under the brand name of Remicade® (MSD), and is approved for the following indications: Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, Psoriasis, Adult Crohn's disease, Paediatric Crohn's disease, Adult ulcerative colitis and Paediatric ulcerative colitis.

In September 2013, the EMA approved a biosimilar formulation of infliximab known as CT-P13, which was subsequently marketed under two different brand names: Inflectra® (Hospira), and Remsima®▼ (Napp). Despite two separate marketing authorisations, Inflectra® and Remsima® are essentially the same biosimilar product (CT-P13), and are both manufactured by Celltrion. The licensed therapeutic indications, dosing regimen, pharmaceutical form, strength and composition for both biosimilar products are identical to those of the originator infliximab (Remicade®). Both biosimilars were launched in the UK in February 2015, after the patent for Remicade® expired.

In extensive product characterisation exercises all major physicochemical characteristics and biological activities of CT-P13 were comparable to those of Remicade®.

The clinical program demonstrating biosimilarity between CT-P13 (marketed as Inflectra® and Remsima®), and the reference product infliximab (Remicade®) consisted of a phase III efficacy and safety study in patients with active rheumatoid arthritis (PLANETRA), and a phase I pharmacokinetic study in patients with ankylosing spondylitis (PLANETAS). Both studies were randomised, double-blind, multi-centre, parallel-group trials lasting 54-weeks. Patients who completed each of the studies had the option to continue on an open-label, 48-week extension phase, in which they either continued on CT-P13, or were switched from Remicade® to CT-P13.

The studies showed that up to 54 weeks there were no clinically meaningful differences in the efficacy, safety or pharmacokinetic profile between CT-P13 and Remicade® in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Preliminary data from 48-week open-label extensions showed that patients who switched from Remicade® to CT-P13, efficacy was sustained, and comparable to those maintained on CT-P13.

Overall, the type and incidence of treatment-emergent adverse events observed in the clinical studies was generally similar between the two treatment groups and were in line with the well-characterised safety profile of Remicade®.

Although clinical studies were only performed in patients with RA and AS, 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 CT-P13 approval to all other indications for which the reference product Remicade® is approved, including ulcerative colitis, Crohn's disease, psoriatic arthritis and psoriasis.

Both Inflectra® and Remsima® have a NHS list price of £377.66 per 100 mg vial, which is 10% lower than the list price of Remicade® (£419.62 per 100 mg vial). However, the actual cost of Remicade® and the biosimilar products differs substantially from list prices due to locally negotiated procurement discounts. Based on the CMU contract price, Inflectra® and Remsima® would be cost saving in all indications compared with Remicade® at its current price. The exact level of cost savings depends on the price difference, together with the number of patients treated with each product and any differences in dosing and scheduling for the licensed indications.

In order to facilitate the safe introduction of infliximab biosimilars to the NHS, brand name prescribing, identification, recording and traceability needs to be in place. Brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and/or administration. In addition, for each patient, a traceable record of the brand, batch number, and other vital details of the product used should be made.

It was noted that NICE has updated its position and process for providing guidance and advice on biosimilar medicines within the NHS. These products will usually be considered in the context of a Multiple Technology Appraisal (MTA) in parallel with their reference products in the indication under consideration. In line with this NICE have issued a draft recommendation on the use of infliximab in ulcerative colitis. The Committee concluded that its recommendations for infliximab could apply both to the reference product and to its biosimilars.

The Scottish Medicine Consortium (SMC) has accepted Inflectra® and Remsima® for restricted use within NHS Scotland for the treatment of rheumatoid arthritis; adult and paediatric Crohn's disease and ulcerative colitis; adult ankylosing spondylitis; psoriatic arthritis and psoriasis in with the reference product Remicade.

The All Wales Medicines Strategy Group (AWMSG) has recommended Inflectra® and Remsima® as an option for restricted use within NHS Wales. Both products should be prescribed within its licensed indications in accordance with NICE or AWMSG guidance for Remicade®, the reference product.

The group approved the use of infliximab biosimilars as an option where the originator product (Remicade®) would normally be prescribed. It was agreed that this recommendation would apply to new patients.

It was proposed that if localities are considering a managed therapeutic switch programme that this should be carried out after discussion and agreement with local Trusts and Specialists, ensuring that a full discussion with the patient is carried out prior to any switch.

If this approach is taken by localities it was felt that a co-ordinated approach via regional contracting to ensure consistency throughout the NTAG region may be useful. The group noted that further real world data on the safety and efficacy of switching from one product to another in GI indications is expected in due course. It was however noted that Remicade® itself had undergone over 40 changes in the manufacturing process since its original authorisation which meant that it could potentially be classed as biosimilar version of itself.

ACTION Secretary to draft decision summary as above

5) Appraisal: Teriparatide (Forsteo®) for the treatment of bisphosphonate-induced atypical fractures.

The appraisal report concerning the use of off-label teriparatide was introduced by the secretary. This appraisal was referred to NTAG by CCGs.

Bisphosphonates have been shown to be effective in the treatment of osteoporosis; numerous large clinical trials have demonstrated their efficacy in reducing bone turnover, increasing bone mineral density and reducing vertebral and non-vertebral fracture risk in patients with osteoporosis. However, since 2005, there have been increasing concerns regarding the potential risk of an unusual type of femur fracture amongst patients on bisphosphonate therapy. They are thought to be atypical in that they involve the strongest part of the femur (namely the subtrochanteric and diaphyseal region) and are characterised by features distinctly different from 'typical' osteoporotic femur fractures.

Whilst clear, robust causality has not yet been established, several regulatory authorities worldwide have issued safety advice regarding the risk of atypical fractures with long term bisphosphonate treatment. In the UK, the MHRA published a Drug Safety Update in 2011 reporting the findings of a European review. Recommendations included:

- Checking the contra-lateral femur in patients who present with a femoral shaft fracture, as atypical femoral fractures are often bilateral.
- Considering discontinuing bisphosphonate therapy in those with a suspected atypical femoral fracture.
- Counselling patients to report any thigh, hip, or groin pain that they experience during bisphosphonate treatment.
- Periodically reviewing the need for continued treatment, particularly after five or more years of use. The optimal duration of bisphosphonate treatment for osteoporosis has not yet been established

Femoral fractures are common in the general population. In adolescents and young adults, fractures more commonly occur towards the lower, stronger end of the bone as a result of violent traumatic injuries. In elderly patients, however, femoral fractures tend to occur more commonly in the weaker bone region towards the femoral neck. In contrast, atypical fractures tend to occur lower down in the subtrochanteric and femoral shaft regions due to low impact trauma or even in the absence of any trauma.

Atypical fractures are often associated with a prodromal period of thigh pain, circumferential cortical thickening, and cortical stress lesions. A complete transverse or oblique fracture subsequently develops. Atypical femoral fractures can have a large impact on quality of life and have been associated with poor healing, which may be due to the prolonged presence of bisphosphonates even when discontinued.

The exact incidence of atypical fractures remains unknown. One estimate suggests that they may affect up to 5 in 10,000 people taking bisphosphonates, whilst a Swedish study found an incidence of 55 per 100,000 person years.

Treatment strategies include discontinuation of the bisphosphonate and/or switching to a difference osteoporosis treatment, avoid weight bearing, pharmacological approaches, and surgical interventions. There are no clear guidelines on the treatment of atypical fractures.

Whether patients, especially those with incomplete fractures or no pain, should be treated conservatively or surgically remains controversial.

Teriparatide (Forsteo®, Eli Lilly) is a synthetic polypeptide consisting of the 1-34 amino acid N-terminal region of human parathyroid hormone (HPH). It is administered once daily by subcutaneous injection for a maximum of 24 months. NICE recommends teriparatide as an option for the secondary prevention of osteoporotic fractures in post-menopausal women who can't take bisphosphonates or strontium ranelate. It also recommends teriparatide as an alternative treatment in women who have fractures along with falling bone density when taking alendronate, risedronate, or etidronate for one year.

The aim of using teriparatide is to optimise recovery of atypical fracture, minimise risk of contra-lateral fracture, and other fragility fractures.

However there is little published evidence for the efficacy of teriparatide in atypical fractures and no large, robust trials have been performed. Clinical use is therefore primarily guided by prior plausibility, expert opinion, and case reports. Concurrent pharmacological or surgical treatments, reported outcomes, time to teriparatide initiation, and treatment duration varied between reports. Overall, the results of published case reports and other small studies appear positive but are difficult to interpret. The optimal regimen and precise place in therapy of teriparatide remain uncertain.

There is no specific safety data on the use of teriparatide in the treatment of bisphosphonate-induced atypical fracture, though those affected will likely closely match the licensed population, for which safety is already established. The most commonly reported adverse effects are nausea, limb pain, headache and dizziness. There are concerns that long term use of teriparatide may be associated with an increased risk of osteosarcoma. Treatment is therefore limited to a maximum of 24 months.

Teriparatide is a high-cost PbR-excluded drug. One maximum length course of 20 micrograms per day for two years costs ~£6,525.12 per patient. Patients need to be suitably trained in order to self-administer it.

Using a rough estimation, there are approximately six atypical fractures caused by bisphosphonates in the NTAG region per year. Treating these fractures with teriparatide would equate to £39,150.72, spread over two years. The concurrent need for surgical intervention and other pharmacological treatments remains unknown.

The group therefore agreed that teriparatide should not be recommended due to the lack of available data showing efficacy.

However the group were mindful of the fact that treating these patients can be difficult; there are no guidelines and in some cases surgery may not be the best option. It was felt that for those difficult to treat patients an option must be available to ask for funding to support drug treatment. It was agreed that this would be via individual funding request mechanisms.

The group also noted that a randomised placebo controlled trial is currently recruiting, with an estimated completion date of December 2019.

ACTION Secretary to draft decision summary as above

6) Work Plan

It was noted that a re-review of the 2012 NETAG recommendation on Orthotic functional electrical stimulation for drop foot of neurological origin was due to be discussed at the September meeting. It was also agreed that certolizumab for active psoriatic arthritis would be discussed as no NICE TA was expected. Certolizumab for severe axial spondyloarthritis was now going to be reviewed by NICE so this would be removed from the work plan.
The final appraisal for discussion at the September meeting would therefore be the sequential use of biologics for the management of psoriatic arthritis.

ACTION: Secretary to add the above items to the agenda for the September meeting.

7) AOB

The Chair informed the group that a draft annual report had been written and was available; this had been discussed at the CCG forums meeting at the end of May which he had attended to present the report. The report was well received.
As the group had not yet had an opportunity to comment on the report it was agreed that it would be sent out to the group via email for comments prior to it being published on the website.

ACTION: Secretary to email draft annual report to membership for comments.

The date of the next meeting was noted to be 8th September 2015, Meeting Room 4, The Durham Centre.

Minutes produced by B Reddy, Professional Secretary to NTAG, 19th June 2015.