Request to Change Colour Classification (RAG): Budesonide 9mg MR oral tablets (Cortiment)

Details of request

Request received from:

Jon Kwok, Lead Gastro Pharmacist, Lancashire Teaching Hospitals NHS Foundation Trust

Proposed action:

Budesonide M/R 9mg tablets (Cortiment MMX) for:
Induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient.
Induction of remission in patients with active microscopic colitis (MC).

Current Colour Classification: Red
Proposed Colour Classification: Amber

Request rationale for proposal:

"Cortiment MMX is the only oral topical corticosteroid licensed to remission in patients with active mild to moderate UC. This patient cohort can be managed safely in primary care when a self-management care plan is agreed and put in place. Self-management care plan will be shared with relative general practice. Doses, course length and escalation plan are all included in the care plan with clear instructions. GP would be able to follow the plan to start, review or escalate treatment in primary care. The referral pathway will be included in the care plan so that patient could be referred back to secondary care if treatment failed.

General Practice is currently unable to prescribe this medicine, and patients end up contacting IBD flare line in secondary care and it subsequently delayed start of treatment.

Changing it to amber would allow GP to prescribe for patients who have previously responded to Cortiment without having to refer back to secondary care. Patients who do not live in hospital local area would benefit from picking up at their local pharmacy rather than attending hospital for the medicine.

Both Budenofalk and Entocort have similar indications and they are both classified as amber, hence the request of changing cortiment MMX colour classification.

Brand prescribing should be encouraged in oral budesonide to reduce risk of dispensing error. A wrong preparation could lead to treatment failure due to the different drug release mechanism and indication."

Review of Request

Background:

Budesonide 9mg MR tablets (Cortiment) received a Red RAG rating from LSCMMG in 2017 for the indication:

An alternative to oral/topical corticosteroids, where these treatments are judged to be unsuitable or will cause unacceptable side effects, for the induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA (aminosalicylate) treatment is not sufficient.

The summary of supporting evidence at the time stated:

- Cortiment® 9mg is the first oral formulation of budesonide to be licensed for UC and exerts its action topically in the colon.
- The CORE I and CORE II studies demonstrated a significantly higher rate of combined clinical and endoscopic remission for budesonide MMX 9mg compared to placebo.
- The CONTRIBUTE study showed budesonide MMX 9mg was significantly better than placebo at increasing the rate of combined clinical and endoscopic remission in patients refractory to 5-ASA treatment.
- Three phase III studies showed the safety profile of budesonide MMX 9mg to be favourable to oral systemic corticosteroids and similar to that observed in patients using placebo.
- Current treatments for UC are not sufficiently effective with response rates of 40-70% among patients with mild to moderate disease using mesalazine.
- No studies directly compared budesonide MMX 9mg to systemic oral corticosteroids precluding comparisons of efficacy between these treatments.
- The cost of using budesonide in place of other corticosteroid treatments would be approximately £9,298 to £14,748 depending on the choice of treatment used.

Updates to evidence since 2017:

- Budesonide 9mg MR tablets (Cortiment) has a **new licensed indication** of *"induction of remission in patients with active microscopic colitis (MC)*". (2020)
- Update to **SPC** special warnings and precautions for use: *Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare condition diseases such as Central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.*
- The **tariff price** (Feb 2023) and corresponding course cost remain the same: 30 x Cortiment® 9mg tablets = £75, therefore a 8-week course costs £140.
- NICE CG166 Ulcerative Colitis has been superseded by **NG130** (2019)
    - A time-limited course of oral corticosteroid is recommended if remission is not achieved with aminosalicylates or if they are not tolerated
- **British Society of Gastroenterology** consensus guidelines on the management of inflammatory bowel disease in adults (2019)
    - Although no adequately powered comparative trials between budesonide MMX and conventional corticosteroids have been conducted to date, budesonide MMX may be considered as an alternative to conventional corticosteroids in patients with mild-moderate UC and failure of response to 5-ASA therapy

- Budesonide has a lower rate of systemic adverse effects than conventional corticosteroids (33% vs 55%), and is not associated with adrenal suppression or a significant reduction in bone mineral density.

- **SMC** have accepted Cortiment for use within NHSScotland for the induction of remission in patients with active microscopic colitis, stating: Cortiment® offers a prolonged release formulation of budesonide for this indication. Other oral budesonide formulations are available at lower cost. (2022)

- **GMMMG** rejected an application to add Cortiment to their formulary (2018), the group agreed that they were unable to approve the application due to the lack of evidence base against standard therapy.

- **Pan Mersey APC** RAG rate Cortiment as 'Amber Recommended' for ulcerative colitis and microscopic colitis. Where the treatment course was previously recommended for the patient by a specialist, further course(s) may be initiated in primary care for symptom relapse where recommended as part of a treatment plan.

- Rosiou K et al. Sources of excess steroid prescriptions and clinical adverse outcomes associated with steroid excess in patients with inflammatory bowel disease: The Leeds IBD Steroids study, *Alimentary Pharmacology & Therapeutics,* 2022
  - Flares requiring the use of steroids should lead to reassessment of the overall IBD disease activity and treatment with a view to optimising maintenance treatment. Steroid prescriptions from primary care may not always be accompanied by appropriate disease reassessment or communicated to the secondary care team. Additionally, prescriptions for steroids may be given for inappropriate doses or durations. The interface between primary and secondary care at the time of IBD flares is therefore critical to understand but has not been robustly investigated since, to date, studies have mostly concentrated on examining primary care or secondary care only.
  - We examined appropriateness and timeliness of treatment escalation and avoidability of steroid excess in relation to prescription sources.
  - Of 2246 patients, 33% were exposed to steroids over 2 years. Primary care issued 28% of prescriptions. Secondary care prescriptions were more often of appropriate dose and duration (85% vs 41%, p< 0.001).
  - Prednisolone was prescribed in 88% of all steroid courses with the percentage being 11 and 1 for Budesonide and Budesonide MMX respectively.
  - Further flares occurred in 50% of patients prescribed steroids from primary care (vs 39%; p= 0.003).
  - Steroid excess was observed in 15%. Patients with steroid excess who received prescriptions from primary care that were not communicated to secondary care less often received timely treatment escalation (49% vs 66%, p= 0.042) and steroid excess was more often avoidable (73% vs 56%, p= 0.022).
  - Patients with steroid excess had higher risks of hospitalisation for IBD (OR = 12.33, 95% CI [8.89–17.11]), hospitalisation for infections (OR = 2.89, 95% CI [1.82–4.61]) and GP prescribed antibiotics (OR = 1.41, 95% CI [1.07–1.86]).
  - Conclusion: Patients commonly access steroids through primary care, but doses and durations are frequently inappropriate with patients more likely to flare. Steroid excess was associated with IBD admissions, admissions for infections and antibiotic prescriptions. Improved liaison between primary and secondary care is required to reduce steroid excess.

- Rosiou K et al. Comparative Outcomes of Budesonide MMX versus Prednisolone for Ulcerative Colitis: Results from a British Retrospective Multi-Centre Real-World Study, *Journal of Clinical Medicine*, 2021
  - During the COVID-19 pandemic many IBD units chose Budesonide MMX (Cortiment) as the first-line treatment for flares of ulcerative colitis (UC) in outpatients for its favourable side effect profile (As per guidance from the British Society of Gastroenterology). This retrospective study of all UC patients treated with oral steroids between 1 March 2019–30 June 2019 and 1 March 2020–30 June 2020 aimed to compare Cortiment with Prednisolone in routine clinical practice.
  - Included patients from the IBD units of three representative UK hospitals (Leeds Teaching Hospitals, Royal Wolverhampton Hospitals, and St George's Hospital, London); 221 patients, 94 in 2019 and 127 in 2020. All adult patients treated with oral steroids (Prednisolone or Cortiment) for a flare in UC were included in the study.
  - The proportion of patients prescribed Prednisolone fell significantly from 75.5% in 2019 to 29.9% in 2020, whereas the proportion of Cortiment prescriptions rose significantly from 24.5% to 70.1% (p < 0.001).

- A significantly higher proportion of patients in the Cortiment group had rectal therapy added compared to the Prednisolone group (51.7% vs. 15.7%, p < 0.001), whereas there was no difference observed between the two groups in the alterations in mesalazine use (p = 0.492), in-hospital admissions (p = 0.829), or commencement of biologics (p = 0.562). The mean bowel frequency at four weeks of treatment was significantly higher for the group of patients who were prescribed Cortiment in 2020 compared to those prescribed prednisolone in 2019 (MPred2019 = 3.42 vs. MCorti2020 = 6.18, p < 0.001), and there was a statistically significant difference observed in the pMAYO score (MPred2019 = 3.11 vs. MCorti2020 = 4.93, p < 0.001) as well. Moreover, 60.6% of the patients in the Prednisolone group had improvement in their symptoms at week four of treatment compared to 39.3% in the Cortiment group (p = 0.014). Finally, no statistically significant differences were observed between the two groups with regards to rectal bleeding and physician global assessment at four weeks of treatment (p = 0.11 and p = 0.12, respectively) and physician global assessment at end of treatment (p = 0.231), whereas 94.2% of the patients in the prednisolone group had <50% of bleeding at end of treatment compared to 74.5% in the Cortiment group (p = 0.015).
- This study demonstrates the change in the pattern of prescribing steroids in 2020 that resulted in increased use of Cortiment and was associated with worse disease outcomes at four weeks of treatment.
- The registration studies for Cortiment assessed the efficacy for the treatment of mild to moderate UC. Yet, in routine clinical practice, Cortiment is often used in patients already established on immunosuppressive therapies and, therefore, by definition, in cases classed as moderate to severe UC.

- Danese S et al. A multicentre prospective cohort study assessing the effectiveness of budesonide MMX (CortimentMMX) for active, mild-to-moderate ulcerative colitis, *United European Gastroenterology Journal,* 2019
- Multicentre observational prospective cohort study conducted in Europe and Canada. Effectiveness, safety, and tolerability of CortimentMMX in a real-life setting of patients treated for mild-to-moderate UC was investigated.
- The primary endpoint was the clinical benefit of Cortiment MMX in routine practice (improvement 3 points in the clinical sub-scores of the Ulcerative Colitis Disease Activity Index, UCDAI).
- Data from 326 patients with mild-to-moderate UC were analysed for the primary endpoint. Clinical benefit was achieved in 60.1% (196/326) of patients at the end of CortimentMMX treatment. Clinical remission (UCDAI clinical subscore 1), full symptoms resolution (rectal bleeding (RB) ¼ 0 and stool frequency (SF) ¼ 0) and symptoms resolution (RB ¼ 0 þ SF 1) at the end of the CortimentMMX treatment were achieved in 51.8%, 45.1% and 63.2% of patients, respectively. The median time to symptoms resolution was 30 days (range 29.0–36.0 days). Fifty patients (14.3%) had to discontinue CortimentMMX due to adverse events; 17.5% of patients (n ¼ 61) reported at least one adverse event related to the study drug.

Summary for consideration

- LSCMMG approved Budesonide M/R 9mg tablets (Cortiment MMX) for use in L&SC in 2017 with a Red classification for mild-moderate UC
- No other oral budesonide products have a LSCMMG RAG rating for UC
- Amending the RAG rating to Amber would require consideration of the level of Amber rating (0, 1 shared care, or 2 shared care and enhanced service), taking into consideration that prescribing would require GPs to “start, review or escalate treatment in primary care”
- Prescribing by brand is required
- The cost has remained static since the initial review
- A new indication for this preparation had been licensed since the initial review and the applicant has asked that this also be considered for Amber RAG rating; SMC have approved use for this indication in Scotland
- GMMMG rejected an application to include Cortiment in its formulary in 2018
- Pan Mersey have Cortiment as ‘Amber Recommended’ for both licensed indications
- Recent real-world data suggests that the communication between primary and secondary care in the management of IBD with steroids is vital for patient outcomes.