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1. Directors of Pharmacy
2. Medical Directors NHS Boards

12 April 2021

Dear Healthcare Professional,

COVID-19 THERAPEUTIC ALERT - INHALED BUDESONIDE FOR ADULTS (50 YEARS AND OVER) WITH COVID-19

Please see the attached position statement on the interim results from the National Institute for Health Research (NIHR) supported PRINCIPLE trial shows that inhaled budesonide (typically used and licensed in the management of asthma) can reduce the recovery time for COVID-19 positive patients being managed within primary care. This is the first COVID-19 treatment for use in the UK within a community setting. I would be grateful if you could cascade this information to relevant colleagues.

Could all Directors of Pharmacy please forward this alert to:-

- Hospital Pharmacists
- Community Pharmacists

Please could Medical Directors forward this alert to:-

- General Practitioners
- Accident & Emergency Departments
- Directors of Public Health
- Consultants in Communicable Diseases
- Relevant Clinics
- Chief Executives of NHS Board

Thank you for your co-operation.

Yours sincerely

IRENE FAZAKERLEY
Pharmacy and Medicines Division

COVID-19 Therapeutic Alert

CEM/CMO/2021/011 12 April 2021

Inhaled Budesonide for Adults (50 Years and Over) with COVID-19

Recommendation

Inhaled budesonide is not currently being recommended as standard of care but can be considered (off-label) on a case-by-case basis for symptomatic COVID-19 positive patients aged 65 and over, or aged 50 or over with co-morbidities, in line with the published Interim Position Statement.

Supporting Evidence

After completing an interim analysis, the PRINCIPLE trial has reported that **inhaled budesonide (800 micrograms taken twice daily, for up to 14 days) can reduce recovery time by a median of 3 days in symptomatic COVID-19 positive patients aged 65 and over, or aged 50 or over with co-morbidities. A benefit in self-reported early sustained recovery at 28 days was also identified.**

The analysis has not established whether budesonide can reduce hospital admissions or reduce mortality.

The interim results from PRINCIPLE build on the findings of the STOIC trial Phase II study on inhaled budesonide. This study suggests that early administration of inhaled budesonide reduces the likelihood of needing urgent medical care and reduces time to recovery following early COVID-19 infection.

Eligibility

In summary, potentially eligible patients will:

- Have COVID-19 symptoms, with symptom onset within the last 14 days, AND
- Be COVID-19 positive, confirmed by a recent polymerase chain reaction (PCR) test, AND
- Be aged 65 or over, or aged 50 or over with one or more co-morbidities consistent with the long-term conditions referenced in the flu vaccine list

Please see the published Interim Position Statement for more details on the specific inclusion and exclusion criteria.

Action

Prescribers are asked to:

- Consider prescribing inhaled budesonide (off-label, on a case-by-case basis) for symptomatic COVID-19 positive patients in line with the published Interim Position Statement using the usual routes[1], where supply allows. Prescribers will be advised if there are any national supply restrictions.

- Note that the recommended product is the Pulmicort 400 Turbohaler (AstraZeneca UK Ltd), studied within the PRINCIPLE and STOIC trials. A single inhaler should be used for a maximum of 14 days (or until the inhaler is used up, if sooner) with two doses, twice a day (a total daily dose of 1,600 micrograms). Please see the Supply section below for details of alternative products.

- Note that supplementary information for patients is available here, including links to video resources.

- Report any suspected adverse drug reactions (ADRs) for patients receiving budesonide to the MHRA via the Yellow Card reporting site at: https://yellowcard.mhra.gov.uk/

Community pharmacies and dispensing practices are asked to:

- Use business as usual routes to order supplies of inhaled budesonide from wholesalers, maintaining stock levels to meet both routine use (i.e. the management of asthma) and prevailing demand for therapeutic use in the management of COVID-19. Pharmacies will be advised if there are any national supply restrictions.

- Ensure patients (or their representatives) are aware of how the inhaler should be used and signpost them to additional support. Supplementary information for patients is available here and includes links to video resources.

- Note that inhaled corticosteroids prescribed for use in the management of COVID-19 are currently subject to the usual applicable prescription charges in England, unless the patient is normally exempt. Prescriptions remain free of charge in Northern Ireland, Scotland and Wales.

- Report any suspected adverse drug reactions (ADRs) for patients receiving budesonide to the MHRA via the Yellow Card reporting site at: https://yellowcard.mhra.gov.uk/

- Support COVID-19 specific supply and reporting arrangements in line with any supplementary national (country-specific) guidance provided.

[1] FP10 (England) / HS21 (Northern Ireland) / GP10 (Scotland) / WP10 (Wales)

Supply

Additional supplies of the Pulmicort 400 Turbohaler (AstraZeneca UK Ltd) are now available to be ordered through business as usual routes from wholesalers.

In the case of limited supplies, the following alternatives may be considered in the order of preference set out below (noting that additional guidance may need to be provided to help patients to achieve the correct total daily dose of 1,600mcg):

- Lower dose strength Pulmicort Turbohaler (200 micrograms) (100 doses per inhaler)
- Budelin Novolizer 200 micrograms per actuation inhalation powder (Mylan) (100 doses per inhaler)
- Easyhaler Budesonide 400micrograms / dose dry powder inhaler (Orion Pharma (UK) Ltd) (100 doses per inhaler)
- Easyhaler Budesonide 200micrograms / dose dry powder inhaler (Orion Pharma (UK) Ltd) (200 doses per inhaler)

Product Details

The Interim Position Statement has been informed by the PRINCIPLE trial protocol and the Summary of Product Characteristics (SmPC) for inhaled budesonide.

Inhaled budesonide has a local anti-inflammatory effect and is used in the treatment of asthma.

The use of inhaled budesonide in the management of COVID-19 under the published Interim Position Statement is off-label, which should be explained to the patient as part of shared decision making. Further guidance on the prescribing of off-label medicines can be found below:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities

Distribution

General Practice
NHS 111
Community Pharmacies
ICS /STP and Clinical Commissioning Group Pharmacy Leads
NHS Trusts (NHS boards in Scotland and Wales)
Regional Medical Directors
Regional Chief Pharmacists
Lead/Senior Pharmacists and Regional Procurement Pharmacy Leads
Trust/Hospital Medical Directors and Chief Pharmacists to circulate to medical, pharmacy and nursing staff managing COVID-19 patients

Enquiries

England

Enquiries from general practice and community pharmacy should in the first instance be directed to the local clinical commissioning group.

Enquiries from NHS trusts in England should in the first instance be directed to the trust pharmacy team who will escalate issues to the Regional Chief Pharmacist and national teams if required.

Further information can also be requested from the dedicated email address: england.spoc-c19therapeutics@nhs.net.

Northern Ireland

Enquiries from general practice and community pharmacy should in the first instance be directed to your local HSCB office.

Enquiries from hospitals in Northern Ireland should in the first instance be directed to your hospital pharmacy team who will escalate issues to the Regional Pharmaceutical Procurement Service or Pharmaceutical Directorate at the Department of Health if required Further information can be obtained by contacting RPHPS.Admin@northerntrust.hscni.net

Scotland

Enquiries in Scotland should in the first instance be directed to the Health Board Director of Pharmacy who will escalate issues to either NHS National Procurement or the Scottish Government's Medicines Policy Team if required. Contact should be made using the following emails: nss.nhssmedicineshortages@nhs.scot or medicines.policy@gov.scot

Wales

Enquiries in Wales should in the first instance be directed to the health board's Chief Pharmacist who will escalate issues to the Pharmacy and Prescribing Team at Welsh Government if required. Enquiries to the Welsh Government should be directed to: COVID-19.Pharmacy.Prescribing@gov.wales.

Department of Health & Social Care | The Scottish Government Riaghaltas na h-Alba | Llywodraeth Cymru Welsh Government | Department of Health | An Roinn Sláinte | Männystrie O Poustie | NHS

Interim Position Statement

Interim Position Statement: Inhaled budesonide for adults (50 years and over) with COVID-19

12 April 2021

Interim position

The PRINCIPLE trial has reported a 3-day median benefit in self-reported recovery for patients with COVID-19 in the community setting who received inhaled budesonide. The impact on hospitalisation rates or mortality has not been established, but the evaluation is ongoing, so recommendations may change as more data become available. At this point in time, inhaled budesonide is not being recommended for routine use, but can be considered to be prescribed by healthcare professionals on a case-by-case basis using the information described in this Interim Position Statement and the interim results from the PRINCIPLE trial (pre-print). This is an off-label use of a licensed medicine, the meaning of which should be discussed with the patient.

The eligibility and exclusion criteria for this Interim Position Statement have been drawn from those used in the PRINCIPLE trial and the Summary of Product Characteristics (SmPC) for inhaled budesonide. Healthcare professionals are encouraged to check the SmPC carefully.

Key messages from PRINCIPLE trial

- The trial included people in the community with COVID-19 at higher risk of complications from COVID-19 who are either 65 years or over or 50-64 years with comorbidities.
- Time to first self-reported recovery was shorter in the budesonide group (n=751) compared to usual care (n=1028) with an estimated median benefit of 3 days in patients with a positive SARS-CoV-2 test.
- There was no statistically significant improvement in COVID-19-related hospitalisation or deaths within 28 days of follow-up.
- There was benefit in self-reported early sustained recovery at 28 days.
- 79.7% of participants randomised to budesonide reported taking budesonide for at least 7 days.
- Results from the STOIC trial have been published, reporting a benefit from using inhaled budesonide in the community for people with COVID-19 within a smaller phase 2 trial.

Implementation

Eligibility criteria

Patients are eligible to be considered for treatment with inhaled budesonide when **all** of the following criteria are met:

- Patients with onset of symptoms[1] of COVID-19 within the past 14 days, and symptoms are ongoing.
- COVID-19 confirmed by PCR test within the past 14 days.
- 65 years and over OR 50-64 years with a comorbidity consistent with a long-term health condition from the flu list[2].

Exclusion criteria

Budesonide should not be administered in the following circumstances:

- Known hypersensitivity to budesonide or other inhaled corticosteroids.
- Patient admitted to hospital with COVID-19 before onset of treatment with budesonide.
- Almost recovered (generally much improved and symptoms now mild or almost absent).
- Any known contraindication to inhaled corticosteroids (as per SmPC: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Lactose, the excipient in the product, contains small amount of milk proteins and can therefore cause allergic reactions).
- Patient currently prescribed inhaled or systemic corticosteroids.
- Unable to use an inhaler (even with assistance or reasonable adjustments).

Dose

The PRINCIPLE trial used inhaled budesonide (Pulmicort Turbohaler® 400 micrograms), 800 micrograms twice daily for up to 14 days or until all doses of the inhaler are used (whichever comes first). Supplementary information for patients on the use of a budesonide inhaler is available here.

The following alternative devices for delivering budesonide may be considered[3]:

1. Pulmicort Turbohaler® 200 micrograms
2. Budelin Novolizer® 200 micrograms
3. Easyhaler Budesonide® 400 micrograms
4. Easyhaler Budesonide® 200 micrograms

Healthcare professionals should consider whether the use of inhaled budesonide should be continued if admission to hospital is required due to deteriorating symptoms of COVID-19.

[1] Symptoms listed within the PRINCIPLE trial protocol include, but are not limited to: shortness of breath, general feeling of being unwell, muscle pain, diarrhoea and vomiting

[2] https://www.nhs.uk/conditions/vaccinations/flu-influenza-vaccine/), which differs from the PRINCIPLE trial eligibility criteria.

[3] The device used should be best suited to the patient

Co-administration

Largely, there is no restriction to concomitant medications using inhaled budesonide. The SmPC states that concomitant treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A inhibitors may increase systemic budesonide levels, but that this is of little clinical significance for a short-term treatment of 14 days.

Safety reporting

Any suspected adverse drug reactions (ADRs) for patients receiving budesonide should be reported directly to the MHRA via the Yellow Card reporting site at: https://yellowcard.mhra.gov.uk/

Marketing authorisation

The use of inhaled budesonide in COVID-19 is off-label.

Governance

Off-label use of medication

There is no licensed alternative for this indication. The use of inhaled budesonide to treat COVID-19 is off-label. Prescribers should follow the principles of personalised care (including a shared decision making approach with the patient) to prescribe inhaled budesonide. Guidance on the prescribing of off-label medicines can be found here:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities

Effective from

This Interim Position Statement will be in effect from the date of publication.

Position review date

This is an Interim Position Statement based on pre-publication evidence. Further data from the PRINCIPLE trial is expected when the full cohort of patients completes their 28-day follow-up period. Published data from other trials may also require this Interim Position Statement to be reviewed. The full process of policy production has been abridged. Development of a clinical commissioning policy would replace this Interim Position Statement.