Therapeutics Technical Advisory Group | Te Rōpū Haumanu Kowheori-19

Position Statement on Budesonide Use

Date: 1 April 2022

The Therapeutics Technical Advisory Group (Therapeutics TAG) was established by the Ministry of Health in August 2021 to provide expert advice on existing and emerging medicines for use in the management of COVID-19.

Inhaled budesonide for adults with COVID-19 in the community

This position statement on inhaled budesonide has been updated on 1 April 2022. Changes from the previous Position Statement are in red text.

The amendment narrows the recommended eligible population for inhaled budesonide to target those who are at highest risk of progression to requiring in-hospital treatment for COVID-19 disease. The document now also includes guidance for navigating challenges with turbuhaler use in certain communities.

Therapeutics Technical Advisory Group recommendations

The COVID-19 Therapeutics Technical Advisory Group (TAG) recommends the following:
Consider use of inhaled budesonide 800 mcg BD for up to 14 days in non-hospitalised patients with confirmed COVID-19, who can manage a turbuhaler device, and are:

- Within the first 14 days of symptom onset of COVID-19 illness
- AND are not taking other inhaled* or systemic corticosteroid
- AND are not eligible for antiviral or antibody therapy, or where use is contraindicated
- AND have not completed an effective course of vaccination[ł]
- AND are over 60 years old if Māori or Pasifika OR over 70 years old if other ethnicity
- AND have at least 2 other risk factors for severe COVID-19
    - *Other risk factors include: chronic kidney disease, obesity BMI >35, chronic lung disease, active cancer, uncontrolled hypertension, uncontrolled diabetes, significant cardiac disease, chronic liver disease, or immunocompromise.*

* Patients already using an inhaled corticosteroid for a different indication (either alone or in combination with long acting beta agonist [LABA]) should continue to use their regular medication. For example, if using regular long-term fluticasone for asthma, continue this and do not switch to budesonide.
Inhaled budesonide/formoterol (Symbicort®) should NOT be started in place of budesonide (Pulmicort) for this indication.

ł Incomplete vaccination course is considered to be receipt of:

- Fewer than 2 doses of vaccine
- OR only 2 doses of vaccine, with second dose < 7days or > 6months before symptom onset

Context of this recommendation

The benefits of inhaled budesonide in COVID-19 positive cases include:

- reduction in time to recovery
- reduced need for supplemental oxygen
- likely but modest reduction in risk of hospital presentations/admissions
- no safety concerns raised in COVID-19 budesonide studies
- inhaled therapy is familiar and accessible as community treatment.

The budesonide studies (PRINCIPLE [1] and STOIC [2]) were performed in largely unvaccinated populations during outbreaks involving older variants. The New Zealand population in 2022 represents a highly vaccinated and moderately boosted population which if taken together with the Omicron variant, translates to a lower absolute risk of hospitalisation in the fully vaccinated, therefore contributing to an overall lower benefit from inhaled budesonide. On this basis, the Therapeutics TAG are recommending inhaled budesonide to those at highest risk of COVID-19 disease progression to requiring in-hospital management.

Basis of the Therapeutics Technical Advisory Group recommendation

The Therapeutics TAG recommendation of inhaled budesonide use in COVID-19 is based on the following:

i) The two main RCTs which are the PRINCIPLE and STOIC studies

ii) Equity within the NZ population context

iii) Appraisal of other COVID-19 living guidelines including those of the Australian National COVID-19 Clinical Evidence Taskforce, Ontario COVID-19 Science Advisory Table working group and NICE guidelines

iv) Northern Region Clinical Practice Committee (NRCPC) report.

i) STOIC trial and PRINCIPLE trial

Members of the Therapeutics TAG have reviewed the literature on inhaled budesonide in COVID-19 positive people.

The STOIC trial found inhaled budesonide (compared with standard of care [SOC]) reduced COVID-19 related emergency assessments or hospital admissions and self-reported recovery time was shortened by 1 day compared with SOC.

The PRINCIPLE trial which is the largest budesonide trial to date found a shortened time to recovery in the budesonide group with a median benefit of 2.94 days compared to SOC (11.8 days vs 14.7 days, >99.9% probability of superiority) and a high likelihood of reduced risk of hospital admission or mortality (6.8% budesonide vs 8.8% SOC, probability of superiority of 96.3%).

There were no safety signals on inhaled budesonide in COVID-19 patients in either study.

Since these studies, a RCT of ciclesonide[3] (inhaled corticosteroid unavailable in NZ) demonstrated reduction in hospital presentation and admission (1% vs 4.5%, p=0.03) which is further supported by a Cochrane systematic review.[4] It is possible that the observed efficacy represents a class effect rather than evidence for this individual inhaled corticosteroid only but there is insufficient evidence currently to support this hypothesis.

ii) Recommendation within the NZ context

The PRINCIPLE study included those ≥ aged 65, or ≥ aged 50 with any of the following comorbidities: heart disease, hypertension, asthma or lung disease, diabetes, hepatic impairment, stroke or neurological problems, weakened immune system (e.g. receiving chemotherapy), and self-reported obesity or body-mass index of at least 35 kg/m^2. The Māori and Pasifika population have higher rates of comorbidities at younger age, and are disproportionately represented in hospitalisation for COVID-19. For these reasons, the age threshold recommended for the Māori and Pasifika population is lower than for other ethnicities.

The cost of one Pulmicort Turbuhaler® containing 200 doses of 400 micrograms of budesonide is listed by PHARMAC on the Online Pharmaceutical Schedule - September 2021 at $32.00. One device per patient would meet the proposed treatment plan.

Most patients with asthma requiring inhaled therapy in NZ will be on Symbicort® (based on the Asthma & Respiratory Foundation NZ Asthma guideline using Antiinflammatory Reliever [AIR]) rather than Pulmicort; therefore it is not anticipated that this recommendation will disadvantage current patients with asthma (or COPD).

iii) Australian National Covid-19 Clinical Evidence Taskforce and Ontario COVID-19 working group

https://covid19evidence.net.au/

The guideline for inhaled budesonide use has been updated by the Australian COVID-19 Taskforce in October 2021, to a Conditional recommendation of inhaled budesonide for the PRINCIPLE study population except for obesity.

https://covid19-sciencetable.ca/sciencebrief/evidence-based-use-of-therapeutics-for-ambulatory-patients-with-covid-19/

Recommendation from the Ontario COVID-19 Science Advisory Table working group: Inhaled budesonide 800 mcg twice daily for 14 days *may be considered* in patients with standard and higher risk of hospitalisation, especially if other community COVID-19 therapeutics are not available or contraindicated.

https://www.guidelines.co.uk/infection/nice-managing-covid-19-guideline/455939.article

The NICE guideline recommends the use of budesonide to treat COVID-19 only as part of a clinical trial. This may be a reflection of the larger number of alternative community therapeutics for COVID-19 in the United Kingdom, which is not the situation in NZ.

iv) Northern Region Clinical Practice Committee (NRCPC) report

The NRCPC report dated 30 August 2021 prepared by Dr Stephen Streat, Deputy Chair NRCPC was appraised by members of the Therapeutics TAG. The report reviewed the indications for inhaled budesonide in non-hospitalised COVID-19 patients, with respect to course of illness, need for hospital services (ED, hospitalisation, ICU and death), efficacy, safety and cost utility of this treatment. Whilst the Therapeutics TAG acknowledges the detailed report, the context at which the NRCPC recommendations were made have changed with the publication of the PRINCIPLE study, which was the main driver for the various guidelines changes listed in point (iii).

References

1) Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. Published online August 10, 2021. DOI:https://doi.org/10.1016/S0140-6736(21)01744-X

2) Ramakrishnan S, Micolau DV Jr, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC); a phase 2 open-label, randomized controlled trial. Lancet Respir Med. 2021; 9:763-72.

3) Clemency B, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA Intern Med. 2022 Jan 1;182(1):42-49.

4) Griesel M, Wagner C, Mikolajewska A, et al. Inhaled corticosteroids for the treatment of COVID-19. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD015125.

5) National COVID-19 Clinical Evidence Taskforce, Australia**.** Caring for people with COVID-19. Available at: https://covid19evidence.net.au/

6) COVID-19 Advisory for Ontario, Canada. Evidence-based use of therapeutics for ambulatory patients with COVID-19. Available at: https://covid19-sciencetable.ca/sciencebrief/evidence-based-use-of-therapeutics-for-ambulatory-patients-with-covid-19/

7) Ministry of Health, New Zealand. COVID-19 Data and Statistics. https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-case-demographics#ethnicity Accessed 25 October 2021.