Therapeutic Technical Advisory Group | Te Rōpū Haumanu Kowheori-19

Position Statement on Budesonide Use

Date: 29 October 2021

The Therapeutics Technical Advisory Group (Therapeutics TAG) was convened 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 managed isolation and the community

Therapeutic Technical Advisory Group recommendations

The COVID-19 Therapeutics Technical Advisory Group 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 are:

- Within the first 14 days of symptom onset of COVID-19 illness
- AND are not taking other inhaled[ł] or systemic corticosteroid
- AND are either:
    - 65 years or older, OR
    - any age with any of the following comorbidities:
        - Diabetes
        - Heart disease and/or hypertension
        - Asthma or lung disease
        - Immunocompromised
        - Mild hepatic impairment
        - Stroke or other neurological problem
        - Obesity

* Inhaled budesonide/formoterol (Symbicort®) should NOT be started in place of budesonide (Pulmicort) for this indication.
ł 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.

Context of this recommendation

Data from the current Northern region COVID-19 outbreak indicates hospitalisation rates around 10%; therefore 90% of the COVID-19 positive patients will be managed in the MIQs or community outreach program. A significant proportion of these will be anticipated to be symptomatic and may present to primary care or hospital. As the number of COVID-19 cases grow, the need for effective and accessible

treatment in the community that can reduce illness duration and utilisation of hospital-based healthcare services is a priority.

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.

Basis of the Therapeutics Technical Advisory Group recommendation

The Therapeutics Technical Advisory Group 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 and Ontario COVID-19 Science Advisory Table working group

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

i) STOIC trial and PRINCIPLE trial

Members of the Therapeutics Technical Advisory Group 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.

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/m2.

The Therapeutics Technical Advisory Group recommends the removal of the age criteria of 50 years for patients with co-morbidities for the NZ population in acknowledgment that at-risk populations such as Maori and Pasifika people often develop these co-morbidities at younger ages than the PRINCIPLE study population in the UK who were predominantly European. In addition, the current NZ outbreak has seen a large proportion of those infected to be of a younger age bracket. Demographics of COVID-19 infection in NZ by age group: 20-29 age group 22.9%, 30-39 age group 18.6%, 40-49 age group 13.3% i.e. those between the ages of 20-49 years make up 55% of COVID positive cases. COVID-19 infection by ethnicity: 18% Māori, 22.6% Pacific people and 36.9% European. These figures support the recommendation of removing age as a qualifying criterion when at least one comorbidity is present.

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 asthma (or COPD) patients.

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: “Though current evidence does not support inhaled corticosteroids having any effect on disease course or serious disease outcomes, inhaled budesonide 800 mcg twice daily for 14 days may be considered in selected patients, as it may reduce patient-reported symptoms and time to recovery”.

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

4) 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/

5) 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.