Budesonide CR capsules in the Management of Immune-Related Adverse Effects (irAEs)

A guide for members on the prescribing and monitoring of Budesonide when used in the management of ir-colitis caused by treatment with immune-checkpoint inhibitors.

It should be noted that this use is considered off-label use; relevant governance processes within each organisation should be followed to ensure the risks associated with this are mitigated.

British Oncology Pharmacy Association in Collaboration with The Immuno-Oncology Clinical Network

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1. Introduction

- Budesonide is an enteric-coated synthetic glucocorticoid. It is given orally after which it is absorbed in the distal small bowel, where it undergoes extended first-pass metabolism from cytochrome P450 3A4 in the liver, to compounds with negligible systemic glucocorticoid activity. It therefore has selective anti-inflammatory action within the gut, with minimal systemic side effects.

- Within the UK, budesonide is licensed the induction of remission in patients with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon. In addition, it is licensed for microscopic colitis and autoimmune hepatitis. Please refer to the SmPC for full licensing details.

- In parallel to this there is emerging evidence for its use in less severe cases of immune-related colitis, and specifically in microscopic colitis caused by checkpoint inhibitors.

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate budesonide. It is not a clinical guideline, but a consensus view of current use of budesonide when used for immune-related colitis. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance processes.

2. Prescribing and Monitoring Advice

2.1 Contraindications

- Hypersensitivity to budesonide
- Hypersensitivity to any of the excipients
- Hepatic cirrhosis
- Rare hereditary problem of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency

2.2 Precautions

Although systemic absorption of budesonide is low, there is a risk of side effects typical to systemic corticosteroid use. As with all steroid use it should therefore be used with caution in patients with the following conditions, although the risk is reduced compared to other oral/intravenous steroids

- Active infection
- Previous hepatitis B or TB infection
- Concurrent administration with other biological agents which will increase risk of serious infections
- Hypertension
- Diabetes mellitus
- Osteoporosis
- Glaucoma
- Peptic ulcer disease
- Depressive illness
- Previous steroid psychosis

Caution should also be exercised in the following scenarios

- Immunisations - Avoid live immunisations. Contact specialist for advice.
- In patients who have not previously had chicken pox/measles, care should be taken to avoid exposure to these infections
- Breastfeeding – budesonide is excreted in breast milk, although at very low concentrations and unlikely to be clinically significant.

2.3 Pregnancy Advice

- The available clinical experience is limited. Like all steroids, budesonide will cross the placenta but will do so at a lower level than other orally administered corticosteroid treatment.

2.4 Pre-treatment assessment

- Usually microscopic IR-colitis will have been confirmed by endoscopy +/- biopsy
- Confirmation of negative stool culture Full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs), glucose, HbA1C
- Blood pressure
- Full TB history, including family and travel history.
- Hepatitis A, B and C serology
- Urine pregnancy test for women of childbearing potential

2.5 Pharmaceutical form

- Hard gelatin capsules for oral administration.
- Each capsule contains budesonide 3mg as gastro-resistant, prolonged release granules.

2.6 Dosage

- 9mg orally once per day. Or if the patient prefers, they can take 3mg TDS.
- When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy.

2.7 Method of administration

- The capsules containing the gastro-resistant granules should be taken about half an hour before meals, swallowed whole with plenty of fluid (e.g. a glass of water).
- The capsule must not be chewed.

2.8 Therapeutic Drug Monitoring

There is no recommended therapeutic drug monitoring required.

2.9 Other monitoring

Blood Test	Advice
WBC ≤3 x 10^9/L	Withhold until discussed with specialist team
Neutrophils ≤1.0 x 10^9 /l	Withhold until discussed with specialist team
Liver function tests – specifically INR, albumin and bilirubin	Reduced liver function may affect the elimination of corticosteroids, causing lower elimination rate and higher systemic exposure. Use with caution if above the ULN.
GFR <10 mL/min	Dose as in normal renal function

2.10 Adverse effects

- The most common adverse effects of treatment with any oral corticosteroid are listed below and may all occur in patients treated with budesonide.
- However, due to the low systemic absorption of budesonide these should be considered less likely to happen then compared to other orally administered corticosteroid.
- This is not an exhaustive list, and clinicians should refer to SmPC related to oral budesonide

- NOTE: Because treatment with budesonide results in lower systemic steroid levels than conventional oral corticosteroid therapy. When patients are transferred from systemic corticosteroid treatment with higher systemic effect to budesonide they may have adrenocortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients, and their dose of systemic steroid should be reduced cautiously.

System	Common Adverse Effects
Immune system disorders	Anaphylactic reaction, Hypersensitivity reactions such as angioedema
Endocrine disorders	Cushingoid features, Growth retardation
Metabolism and nutrition disorders	Hypokalaemia
Psychiatric disorders	Behavioural changes such as nervousness, insomnia, mood swings and depression, anxiety, aggression
Nervous system disorders	Tremor, psychomotor hyperactivity
Eye disorders	Glaucoma, cataract including subcapsular cataract, blurred vision
Cardiac disorders	Palpitations
Gastrointestinal disorders	Dyspepsia
Skin and subcutaneous tissue disorders	Skin reactions (urticaria, exanthema), Ecchymosis

Musculoskeletal and connective tissue disorders	Muscle cramps
Reproductive system and breast disorders	Menstrual disorders

2.11 Drug interactions

- Budesonide is a substrate for CYP3A4 enzymes. Therefore, concomitant medications that inhibit or induce these enzymes should be avoided where possible.
- Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).
- The tables below list the most common interactions but is not exhaustive. The SmPC and other drug interactions resources should be further consulted.

Drug	**Interaction**
Carbamazepine	Reduce systemic exposure to budesonide
Clarithromycin	increase systemic exposure to budesonide
Cholestyramine	May reduce Budesonide uptake, in common with other drugs.
Erythromycin	increase systemic exposure to budesonide
Diltiazem	increase systemic exposure to budesonide
Grapefruit juice	increase systemic exposure to budesonide – avoid
HIV protease inhibitors	increase systemic exposure to budesonide – avoid
Itraconazole	increase systemic exposure to budesonide – avoid
Ketoconazole	increase systemic exposure to budesonide – avoid
Oestrogens and contraceptive steroids	Raised plasma concentrations of and enhanced effects of corticosteroids have been reported in women also treated with oestrogens and contraceptive steroids. However, a low-dose combination oral contraceptive that more than doubled the plasma concentration of oral prednisolone, had no significant effect on the plasma concentration of oral budesonide.
Phenobarbital	Reduce systemic exposure to budesonide
Phenytoin	Reduce systemic exposure to budesonide
Rifabutin	Reduce systemic exposure to budesonide
Rifampicin	Reduce systemic exposure to budesonide
St. John's Wort	Reduce systemic exposure to budesonide
Verapamil	increase systemic exposure to budesonide

Additive toxicity

- Concomitant administration of drugs which increase the risk of immunosuppression or myelosuppression should be avoided where clinically appropriate.

- If treatment with another immunosuppressive or myelosuppressive drug is unavoidable, supportive care to reduce the risk of opportunistic infections can be considered with careful considerations of risk-benefit profile.

2.12 Advice to patients

- The capsules containing the gastro-resistant granules should be taken about half an hour before meals, swallowed whole with plenty of fluid (e.g. a glass of water).
- The capsule must not be chewed.
- Avoid grapefruit juice whilst taking these capsules
- Do not stop taking without advice from the specialist team who prescribed them for you.

Appendix 1 Example Patient Information Leaflet

What is Budesonide?

Budesonide belongs to a group of medicines called 'corticosteroids' sometimes referred to as 'steroids'. These are medicines used to reduce inflammation.

Steroids are useful when there is inflammation within the body, as they 'calm down' the immune system to reduce inflammation. This is helpful when you experience side-effects with checkpoint inhibitors.

In your case it is likely that treatment has caused inflammation in your bowels and budesonide will be working to reduce this inflammation.

One advantage that it has over other oral steroid treatment, is that only a very small amount gets absorbed into your bloods stream, meaning there is a reduced likelihood of harmful side effects.

How is budesonide taken?

Budesonide is taken as on oral capsule. The usual dose is three capsules taken with a whole glass of water. Although you can choose to take one capsule three times a day if you would prefer.

How long will budesonide be prescribed for?

How long you take it for will depend on how you respond to it, and whether your symptoms improve. You may be advised to take it for several weeks.

Do not stop taking it without advice from the specialist team that prescribed it for you.

When the decision is made to for you to stop taking it, you may be advised to reduce the dose slowly.

Does budesonide have any side-effects?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you have an allergic reaction, see a doctor straight away. The signs may include raised lumps on your skin (weals), or swelling of your face, lips, mouth, tongue or throat. This may make it difficult to breathe.

The following are common side effects

(may affect up to 1 in 10 people)

- Heartburn.
- Muscle cramps.
- Pounding heart beat (palpitations).
- Rash or itchy skin.

• Heavy or irregular periods in women.

• Low levels of potassium in the blood which may cause muscle weakness, thirst or 'pins and needles'.

• Cushingoid features such as a rounded face, acne, weight gain and bruising more easily.

• Behavioural changes such as feeling nervous, difficulty sleeping, mood swings and depression.

For rarer side-effects please also read the patient information leaflet that will be in the box with your budesonide capsules

It is important to tell your doctor of any side effects or unusual symptoms that you are experiencing.

Can I still be vaccinated?

It is advisable to avoid live vaccinations during treatment with budesonide. Vaccines that are inactivated (not live) are safe to receive.

Is it safe to become pregnant while on budesonide?

You may have already had these conversations with your oncology team before starting immunotherapy. It is important that you do not plan a pregnancy if you are on budesonide and should use effective contraception whilst on treatment.

Can I take other medicines whilst I am taking budesonide?

You should always check with your oncology team or pharmacist if you are started on any new medicines, including anything you may buy over the counter, or as a herbal supplement. Please avoid grapefruit juice.

Who can I contact for further information?

If you have any queries about budesonide the best people to speak to is the team who you are under for treatment of your cancer, the team of specialists who have prescribed the budesonide for you, or your pharmacist.

3. References

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5. Document control

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