AUSTRALIAN PRODUCT INFORMATION

BUDENOFALK® (BUDESONIDE) CAPSULES

1. NAME OF THE MEDICINE

BUDENOFALK capsules
Budesonide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BUDENOFALK capsules contain 3 mg of budesonide within enteric-coated (gastro-resistant) granules as the active ingredient.

Excipients of known effect: Sugars (as lactose monohydrate and sucrose).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

BUDENOFALK capsules are presented as pink opaque, oblong hard gelatin capsules.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BUDENOFALK capsules are indicated for:

Induction of remission in patients with mild to moderately active Crohn's disease affecting the ileum and/or the ascending colon (see Section 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and the elderly:
For acute Crohn's disease (for 8 weeks):

- 9 mg budesonide once daily in the morning, or
- 3 mg budesonide 3 times daily (morning, midday and evening)

Safety and Efficacy of BUDENOFALK capsules have been assessed for up to 8 weeks in adults. Continuous treatment beyond 8 weeks is not recommended. Patients may receive episodic treatment.

At discontinuation
At the end of treatment, the dosage should be tapered gradually, to avoid the possibility of insufficient function of the cortex of the suprarenal gland.

In the first week of tapering, the dosage should be reduced to two capsules daily, one in the morning, one in the evening. In the second week of tapering, only one capsule should be taken in the morning. After two weeks of gradual dose reduction, treatment can be discontinued.

Method of administration
The BUDENOFALK capsules may be taken whole, without chewing or crushing, about 30 minutes before meals with sufficient water. Patients with difficulty swallowing the capsules may open the capsule and administer the enteric-coated granules without chewing or crushing and with plenty of liquid.

Due to the enteric coating on the granules inside the BUDENOFALK capsules and not on the capsule shell itself, the dissolution of budesonide is unchanged whether the patient administers the capsule whole or opens the capsules and then swallows the granules.

Furthermore, there are no data on the effects of crushing the granules before dosing on the pharmacokinetics of budesonide nor on the safety and efficacy of the compound and is therefore not recommended.

4.3 CONTRAINDICATIONS

BUDENOFALK capsules are contraindicated in patients with the following:

- hypersensitivity to budesonide or any of the ingredients
- hepatic cirrhosis

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Treatment with BUDENOFALK capsules does not appear useful in patients with Crohn´s disease affecting the upper gastro-intestinal tract. Extraintestinal symptoms, e.g. involving the skin, eyes or joints, are unlikely to respond to BUDENOFALK capsules because of its local action.

Treatment with BUDENOFALK capsules results in lower systemic glucocorticoid levels than systemic glucocorticoid therapy. Particular care is needed in patients who are transferred from systemically acting glucocorticoid treatment with higher systemic effect to BUDENOFALK capsules. These patients may have adrenocortical suppression at the time of initiation of treatment with BUDENOFALK capsules. Therefore, monitoring of adrenocortical function may be considered in these patients and their dose of systemic glucocorticoid should be reduced cautiously.

Caution is required in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataracts, family history of diabetes, family history of glaucoma, or any other condition in which glucocorticoids may have undesirable effects.

Systemic effects of glucocorticoids may occur, particularly when prescribed at high doses. for prolonged periods and for those agents which are highly absorbed systemically. Such effects may include Cushing’s syndrome, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma and a wide range of psychiatric/behavioural effects (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Glucocorticoids may cause suppression of the HPA axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticoid treatment is recommended.

As with all glucocorticoids, some degree of adrenal suppression may occur in particularly sensitive patients, therefore, monitoring of haematological and adrenal function is strongly advised.

Infection: Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The risk of deterioration of bacterial, fungal, amoebic and viral infections during glucocorticoid treatment should be carefully considered. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked, and therefore may reach an advanced stage before being recognised.

Chickenpox: Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. If the patient is a child, parents must be given the above advice. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic glucocorticoids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Glucocorticoids should not be stopped and the dose may need to be increased.

Measles: Patients with compromised immunity who have come into contact with measles should, wherever possible, receive normal immunoglobulin as soon as possible after exposure.

Live vaccines: Live vaccines should not be given to individuals with chronic corticosteroid use. The antibody response to other vaccines may be diminished.

Visual disturbance: Visual disturbance may be reported with systemic and topical glucocorticoid 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 diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical glucocorticoids.

Others:
BUDENOFALK capsules contain lactose and sucrose. Patients with rare hereditary problems of galactose or fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency, the Lapp lactase deficiency or the congenital lactase deficiency should not take this medicine.

Concomitant treatment with ketoconazole or other CYP3A4 inhibitors should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in hepatic impairment
Based on the experience with patients suffering from late-stage primary biliary cirrhosis (PBC) with hepatic cirrhosis an increased systemic availability of budesonide in all patients with severely impaired hepatic function is to be expected. However, in patients with liver disease without hepatic cirrhosis, in daily doses of 9 mg (3 x 3 mg) of budesonide was found to be safe and well tolerated. There are currently no data to support a specific dose recommendation for patients with non-cirrhotic liver diseases or only slightly impaired liver function is necessary.

Use in the elderly
The experience in elderly with BUDENOFALK capsules is limited.

Paediatric use
BUDENOFALK capsules are not recommended for use in children or adolescents. Long term effects, including on height and bone density have not been assessed.

Effects on laboratory tests
As adrenal function may be suppressed by treatment with glucocorticoid, including budesonide, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic interactions

Cardiac glycosides:
The action of the glycoside can be potentiated by potassium deficiency.

Saluretics:
Potassium excretion can be enhanced.

Pharmacokinetic interactions

Cytochrome P450:

- *CYP3A4 inhibitors:*
  Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects, in which case patients should be monitored for systemic glucocorticoid side-effects. Ketoconazole 200 mg orally once daily increased the plasma concentrations of budesonide (3 mg single dose) approximately 6-fold during concomitant administration. When ketoconazole was administered 12 hours after budesonide, the concentrations increased approximately 3-fold. As there are not enough data to give dose recommendations, the combination should be avoided.
  Other potent inhibitors of CYP3A4 such as ritonavir, itraconazole, clarithromycin, and grapefruit juice are also likely to cause a marked increase of the plasma concentrations of budesonide. Therefore concomitant intake of budesonide should be avoided.
- *CYP3A4 inducers:*
  Compounds or drugs such as carbamazepine and rifampicin, which induce CYP3A4, might reduce the systemic but also the local exposure of budesonide at the gut mucosa. An adjustment of the budesonide dose (using e.g. budesonide 3mg capsules) might be necessary.
- *CYP3A4 substrates:*
  Compounds or drugs which are metabolized by CYP3A4 might be in competition with budesonide. This might lead to an increased budesonide plasma concentration if the competing substance has a stronger affinity to CYP3A4. Conversely, if budesonide has a stronger affinity to CYP3A4, the plasma concentrations of the competing substance might be increased and a dose-adjustment of this drug might be required.
  Elevated plasma concentrations and enhanced effects of glucocorticoids have been reported in women also receiving oestrogens or oral contraceptives, but although this has not been observed with oral low dose combination contraceptives.
  Cimetidine, when administered at recommended doses in combination with budesonide has a small but insignificant effect on pharmacokinetics of budesonide. Omeprazole has no effect on the pharmacokinetics of budesonide.

Steroid-binding compounds:
In theory, potential interactions with steroid-binding synthetic resins such as cholestyramine, and with antacids cannot be ruled out. If given at the same time as BUDENOFALK capsules, such interactions could result in a reduction in the effect of budesonide. Therefore, these preparations should be administered at least two hours apart.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effect of budesonide on human fertility. Subcutaneous administration of budesonide to rats at doses up to 20 µg/kg/day did not affect fertility.

Use in pregnancy
(Category B3)

Administration during pregnancy should be avoided unless there are compelling reasons for therapy with BUDENOFALK capsules.

There are few data on pregnancy outcomes after oral administration of budesonide in humans. Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effects, the maximal concentration of budesonide in plasma is expected to be higher with oral budesonide compared to inhaled budesonide.

In pregnant animals, administration of budesonide, like other glucocorticoids, has been shown to cause foetal death and abnormalities of foetal development (reductions in foetal/pup growth and litter size, skeletal and visceral abnormalities). The relevance of these findings to humans has not been established.

Use in lactation

Budesonide is excreted in human milk. However, only minor effects on the breast-fed infant are anticipated after BUDENOFALK capsule intake within the therapeutic range. A decision should be made whether to discontinue breastfeeding or to discontinue BUDENOFALK capsules, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

BUDENOFALK capsules are generally well tolerated. In clinical studies most adverse events were of mild to moderate intensity and of a non-serious character.

In two clinical trials involving 256 patients with acute Crohn’s disease, budesonide was well tolerated. The table below shows the adverse events that occurred in at least 10% of patients in any of the two clinical trials included:

Table 1

Adverse event	**BUC-23/CDA**		**BUC-52/CDA**		
	BUDENOFALK Capsules (3 mg TID) **(n = 100)** n (%)	**Prednisone** **(n = 101)** n (%)	**BUDENOFALK Capsules (9mg QD)** **(n = 77)** n (%)	**BUDENOFALK Capsules (3 mg TID)** **(n = 79)** n (%)	**SALOFALK Tablets (1.5 g TID)** **(n = 153)** n (%)
Abdominal pain	21 (21%)	16 (15.8%)	2 (2.6%)	1 (1.3%)-	8 (5.2%)
Epigastric pain / upper abdominal pain	4 (4%)	10 (9.9%)	-	-	-
Headache	-	-	8 (10.4%)	6 (7.6%)	19 (12.4%)
Viral infection	-	-	8 (10.4%)	3 (3.8%)	5 (3.3%)
Diarrhoea/soft stools	12 (12%)	7 (6.9%)	-	-	-

QD, once daily; TID, three times daily

Post-marketing adverse effects
The following undesirable effects and frequencies of BUDENOFALK capsules have been spontaneously reported.

The following frequency conventions are used in the evaluation of undesirable effects:
Very common: (≥1/10); Common: (≥1/100 to <1/10); Uncommon: (≥1/1,000 to <1/100); Rare: (≥1/10,000 to <1/1,000) and Very rare: (<1/10,000), not known (cannot be estimated from the available data).

Common (≥1/100 to <1/10):
- Depression, irritability, euphoria
- Muscle and joint pain, muscle weakness and twitching, osteoporosis
- Dyspepsia

Uncommon (≥1/1,000 to <1/100):
- Psychomotor hyperactivity, anxiety
- Duodenal or gastric ulcer

Rare (≥1/10,000 to <1/1,000):
- Aggression
- Glaucoma, cataract, blurred vision
- Pancreatitis
- Osteonecrosis
- Ecchymosis

Very rare (< 1/10,000), including isolated reports:
- *Metabolism and nutritional disorders:* oedema of legs, Cushing's syndrome
- *Nervous system disorders:* Pseudotumor cerebri (including papilloedema) in adolescents
- *Gastrointestinal disorders: Constipation*
- *General disorders: tiredness, malaise*

Some of the undesired effects were reported after long-term use.

Occasionally side effects may occur which are typical for systemic glucocorticoids. These side effects depend on the dosage, the period of treatment, concomitant or previous treatment with other glucocorticoids and the individual sensitivity.

Clinical studies showed that the frequency of glucocorticoid associated side effects is lower with BUDENOFALK capsules (approx. by half) than with oral treatment of equivalent dosages of oral prednisolone.

Systemically acting glucocorticoids

Immune system disorders:
Interference with the immune response (e.g. increase in risk of infections).

An exacerbation or the reappearance of extraintestinal manifestations (especially affecting skin and joints) can occur on switching a patient from systemically acting glucocorticoids to the locally acting budesonide.

Metabolism and nutrition disorders:
Cushing's syndrome: moon-face, truncal obesity, reduced glucose tolerance, diabetes mellitus, sodium retention with oedema formation, increased excretion of potassium, inactivity or atrophy of the adrenal cortex, growth retardation in children, disturbance of sex hormone secretion (e.g. amenorrhoea, hirsutism, impotence)

Psychiatric disorders:
Depression, irritability, euphoria.
In addition, a wide range of other psychiatric/behavioural effects may occur.

Eyes disorders:
Glaucoma, cataract

Vascular disorders:
Hypertension, increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy)

Gastro intestinal disorders:
Stomach complaints, gastroduodenal ulcer, pancreatitis

Skin and subcutaneous tissue disorders:
Allergic exanthema, red striae, petechiae, ecchymosis, steroid acne, delayed wound healing, contact dermatitis

Musculoskeletal, connective tissue and bone disorders:
Aseptic necrosis of bone (femur and head of the humerus)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute overdose with BUDENOFALK capsules is unlikely to result in clinical problems. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action
The exact mechanism of action of budesonide in the treatment of Crohn's disease is not fully understood. The anti-inflammatory effects of budesonide, such as inhibition of the release of inflammatory mediators and suppression of the cellular immunological response, may be important. The intrinsic potency of budesonide, measured by its affinity to the glucocorticoid receptor, is about 15 times higher than the potency of prednisolone.

Data from clinical pharmacology studies and other controlled clinical trials strongly indicate that the mode of action of orally administered budesonide is predominantly based on a local action in the mucosa of the intestine and the colon due to its metabolism (by cytochrome P450 3A4) to pharmaceutically nearly inactive metabolites in the intestinal mucosa and in the liver. Doses of comparable clinical efficacy show that compared to prednisolone, BUDENOFALK capsules have a significantly lower influence on the hypothalamo-pituitary-adrenal (HPA) axis. At the recommended dosages, BUDENOFALK has significantly less effects on morning cortisol plasma levels, 24-hour cortisol plasma levels (AUC0-24) and 24-hour cortisol urine levels, than 20-40 mg prednisolone daily.

CLINICAL TRIALS
In a multicentre, randomised, controlled study (BUC-23/CDA) the efficacy and safety of BUDENOFALK enteric capsules given at a dose of 3 mg TID was compared with a decreasing dose of prednisone (from 40mg daily, reducing to 5 mg daily) over 8 weeks.

The Crohn's Disease Activity Index (CDAI) was the main clinical assessment for determining efficacy. The CDAI is a validated index based on subjective aspects rated by the patient (frequency of liquid or very soft stools, abdominal pain rating and general well-being) and objective observations (number of extra-intestinal symptoms, need for anti-diarrhoeal drugs, presence of abdominal mass, body weight and haematocrit).
The primary analysis was of a composite of selected steroid-related side effects and CDAI score. Three types of responder were assessed. These were defined as:

- "R1" responder – response without the occurrence of either "moon face" or "acne" (considered to be the main steroid-induced ADRs)
- "R2" responder – response associated with the occurrence of at least one steroid-induced ADR
- "R0" responder – overall response (R1 or R2 response).

The overall response rate (R0) did not take differences in steroid side effects into consideration and included all patients with a CDAI < 150 at end of study and, in patients with a baseline CDAI < 210, a decrease in CDAI of ≥ 60.

Table 2

Clinical remission rates after 8 weeks of study treatment (ITT and PP analysis sets; study BUC-23/CDA) in adult patients with active Crohn's disease

Analysis set/Remission category	BUDENOFALK Capsules n (%)	Prednisone n (%)	Treatment comparison [a] (p-value)
ITT analysis set	N=100	N=101	
R1 remission (primary variable)	30 (30.0%)	14 (13.9%)	0.004
R2 remission	21 (21.0%)	39 (38.6%)	n.a.
R0 remission	51 (51.0%)	53 (52.5%)	n.a.
PP analysis set	N=84	N=87	
R1 remission (primary variable)	28 (33.3%)	12 (13.8%)	0.002
R2 remission	19 (22.6%)	36 (41.4%)	n.a.
R0 remission	47 (56.0%)	48 (55.2%)	n.a.

[a] Fisher's exact test, 1-sided

In a double-blind, randomised, multicentre study (BUC-52/CDA) the efficacy and safety of a 8 weeks treatment with BUDENOFALK capsules 9 mg/day (3 mg capsules three times daily or 3 x 3 mg capsules once daily) was compared to SALOFALK tablets 4.5g/day (3 x 500 mg tablets three times daily) in the therapy of active Crohn's disease.

The primary efficacy variable was clinical remission of Crohn's disease defined as CDAI score of ≤ 150 from baseline at the final visit (week 8) or at the withdrawal visit. Results showed that BUDENOFALK capsules are non-inferior to mesalazine in the treatment of active Crohn's disease (non-inferiority margin -10%). No significant difference in remission rate was observed for the 2 budesonide dosage regimens (budesonide 3 mg three times daily compared to budesonide 9 mg once daily).

Table 3

Clinical remission rates at the final visit (Week 8) or withdrawal visit: Comparison of BUDENOFALK Capsules versus SALOFALK (mesalazine) Tablets (LOCF; ITT and PP analysis sets; study BUC-52/CDA) in adult patients with active Crohn's disease

	Total BUDENOFALK Capsules (3 mg TID) Group n (%)	**SALOFALK Tablets (1.5 g TID) Group** n (%)	**Difference in proportions:** (95% CI), p-value [a]
ITT	107 (69.48%) (n=154)	95 (62.09%) (n=153)	7.39% [b] (–3.19% to 17.97%) p=0.0013 [a]
PP	97 (72.39%) (n=134)	82 (68.91%) (n=119)	3.48% [b] (–7.77% to 14.73%) p=0.0139 [a]

[a] Farrington-Manning χ^2 test for shifted hypotheses, non-inferiority margin = -10%, 1-sided overall p-value of 3-stage group sequential design.

[b] Difference in proportions = proportion of patients in BUDENOFALK Capsule Group - proportion of patients in the SALOFALK Tablet group

n (%): number (percent) of patients in remission

Table 4

Clinical remission rates at the final visit (Week 8) or withdrawal visit: Comparison of BUDENOFALK Capsule regimens (LOCF; ITT and PP analysis sets; study BUC-52/CDA) in adult patients with active Crohn's disease

	BUDENOFALK Capsules (3 mg TID) Group n (%)	**BUDENOFALK Capsules (9 mg QD) Group** n (%)	**All patients** n (%)	**Difference in proportions: BUDENOFALK Capsules 9 mg QD vs. BUDENOFALK 3 mg TID Group** (95% CI), p-value [a]
ITT	56 (71.79%) (n=78)	51 (67.11%) (n=76)	107 (69.48%) (n=154)	–4.69% [b] (–19.23% to 9.85%) p=0.5275 [a]
PP	50 (75.76%) (n=66)	47 (69.12%) (n=68)	97 (72.39%) (n=134)	–6.64% [b] (–21.72% to 8.44%) p=0.3901 [a]

[a] 2-sided χ^2 test

[b] Difference in proportions = proportion of budesonide 9 mg QD - proportion of budesonide 3 mg TID

n (%): number (percent) of patients in remission

TID, three times daily; QD, once daily

Results of the studies show that BUDENOFALK 3 mg capsules are well tolerated in patients with active Crohn's disease (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

BUDENOFALK capsules are made from hard gelatin, which dissolves quickly in the stomach releasing the individual gastric juice-resistant granules, containing a total of 3 mg of budesonide in each capsule. There is a lag phase of 2 - 3 hours due to the delayed release of budesonide owing to the enteric coating on the granules.

In healthy volunteers, as well as in patients with Crohn's disease, mean maximal budesonide plasma concentrations of 1-2 ng/ml were seen about 5 hours following a single 3mg oral dose of BUDENOFALK capsules, taken before a meal. The maximal release therefore occurs in the terminal ileum and caecum, the main area of inflammation in Crohn's disease.

In ileostomy patients, the release of budesonide from BUDENOFALK enteric capsules is comparable to healthy subjects or Crohn's disease patients.

Concomitant intake of food may delay release of granules from stomach by 2–3 hours, prolonging the lag phase to about 4–6 hours, without change in absorption rates.

Distribution
Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85–90 %.

Biotransformation
Budesonide undergoes extensive biotransformation in the intestinal mucosa and in the liver (approximately 90%) to metabolites of low glucocorticoid activity. The glucocorticoid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide.

Metabolism
Budesonide is principally metabolised via cytochrome P450 (CYP) 3A4 in the intestinal mucosa and in the liver.

Excretion
The average elimination half-life is about 3–4 hours. The systemic availability in healthy volunteers, as well as in fasting patients with Crohn's disease, is about 9–13 %. The clearance rate is about 10–15 L/min for budesonide, determined by HPLC-based methods.

Specific patient populations (liver diseases)
Dependent on the type and severity of liver diseases and the fact that budesonide is metabolised by CYP3A4 in the liver, the metabolism of budesonide may be decreased in patients with liver diseases. Therefore, the systemic exposure of budesonide may be increased in patients with impaired hepatic function. With improving liver function and disease, metabolism of budesonide will normalize.

The bioavailability of budesonide (AUC) has been found to be significantly higher in patients with primary biliary cholangitis (PBC) who had liver cirrhosis (PBC Stage IV) compared to PBC patients without cirrhosis (PBC Stage I/II), following repeated daily administration of the daily dose of BUDENOFALK capsules (3 x 3 mg) once daily,

BUDENOFALK capsules
The mean peak plasma concentration of budesonide after a single BUDENOFALK 9 mg dose (3 x 3 mg capsules) was 1.73 ± 1.40 ng/mL at a median T_{max} of 5.00 hours. For the metabolite 6-β-hydroxy-budesonide, the mean plasma concentration and T_{max} were similar to budesonide (2.80 ± 1.26 ng/mL, and 5.5 hours, respectively). Higher concentrations were observed for the major metabolite 16-α-hydroxyprednisolone: the mean C_{max} of 23.11 ng/ml occurred after a median T_{max} of 5.45 hours. Of the BUDENOFALK 9 mg dose, 11.58% could be recovered in urine in form of 16-α-hydroxyprednisolone and 1.46% in form of 6-β-hydroxy-budesonide.

Pharmacokinetic data are summarised in the following table for the single 9 mg dose of BUDENOFALK capsules (3 x 3 mg budesonide) in 18 healthy subjects:

Table 5

Pharmacokinetic Parameters	Single 9 mg dose of BUDENOFALK capsules (3 x 3 mg capsules once daily)		
	Budesonide Mean* [SD]	16-α-hydroxy-prednisolone Mean* [SD]	6-β-hydroxy-budesonide Mean* [SD]
C_{max} [ng/mL]	1.73 [1.40]	23.11 [15.39]	2.80 [1.26]
t_{max} [hr]	5.00^ [2.15]	5.45^ [1.54]	5.50^ [1.71]
$t_{1/2}$ [hr]	3.37 [1.70]	2.97 [1.58]	5.37 [2.22]
$AUC_{(\infty)}$ [hr*ng/mL]	10.25 [6.03]	119.23 [59.10]	25.46 [10.66]
AUC_{last} [hr*ng/mL]	8.25 [6.18]	105.50 [60.62]	22.66 [8.83]

* Geometric means
^ nonparametric evaluation, median

Pharmacokinetic data are summarised in the following table for BUDENOFALK 3 mg capsules (3 x 3 mg budesonide three times daily) in 12 healthy subjects:

Table 6

	BUDENOFALK capsules (3 mg three times daily)	
	Budesonide Mean [SD]	Budesonide and metabolites Mean [SD]
C_{max} 1 [ng/mL]	1.03 [0.45]	1.89 [1.03]
C_{max} 2 [ng/mL]	0.82 [0.33]	1.82 [0.51]
C_{max} 3 [ng/mL]	0.70 [0.38]	0.55 [0.18]
t_{max} 1 [hr]	5.8 [1.6]	5.2 [1.6]
t_{max} 2 [hr]	14.7 [1.5]	15.1 [1.5]
t_{max} 3 [hr]	23.5 [0.9]	23.0 [1.3]
$t_{1/2}$ [hr]	2.6 [1.3]	3.0 [0.7]
$AUC_{(\infty)}$ [hr*ng/mL]	13.5 [4.9]	29.0 [9.1]

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Budesonide had no genotoxic effects in a battery of *in vitro* and *in vivo* tests.

Carcinogenicity
The carcinogenic potential of budesonide has been assessed in mice and rats at respective oral doses up to 200 and 50 µg/kg/day. No oncogenic effect was noted in mice. One study showed an increased incidence of malignant gliomas in male Sprague-Dawley rats given budesonide 50 µg/kg/day. However, this was not confirmed in further studies in male Sprague-Dawley and Fischer rats. In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. However, this was also observed in rats treated with prednisolone and triamcinolone acetonide, thus indicating a class effect of glucocorticoids in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BUDENOFALK capsules contain the following excipients: sugar spheres (sucrose), lactose monohydrate, povidone, methacrylic acid copolymer, ammonio methacrylate copolymer, triethyl citrate, purified talc, gelatin, erythrosine, sodium lauryl sulfate, titanium dioxide, iron oxide red and iron oxide black.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

BUDENOFALK capsules are supplied in blister strips with aluminum foil backing.

Cartons of 9, 10, 50 and 90.*

*Not all pack sizes may be available.

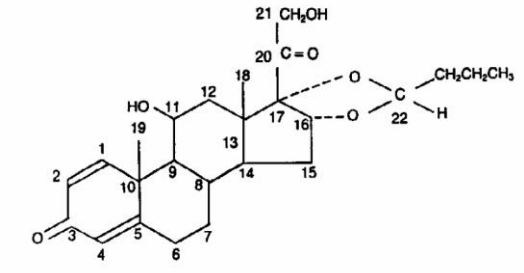
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Budesonide is a white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in alcohol.

Chemical structure



Budesonide
Proper name: Budesonide

Chemical name: 16α,17α-butylidene dioxy-11ß, 21-dihydroxy-1,4-pregnadiene-3 ,20-dione

$C_{25}H_{34}O_6$ = 430.5

CAS number: 51333-22-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Dr Falk Pharma Australia Pty Ltd
Suite 205, 9 Help Street
Chatswood, NSW 2067

9. DATE OF FIRST APPROVAL

12 June 2012

10. DATE OF REVISION

27 February 2025

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Update to sponsor address
1, 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3,6.5	Minor editorial changes