Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Budenofalk 3 mg gastro-resistant capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 3 mg budesonide
Excipients with known effect: Each capsule contains 240 mg sucrose and 12 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsules, hard (gastro-resistant capsules)
Capsule, hard, pink containing white gastro-resistant granules

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Crohn's disease

Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon

- Microscopic colitis
- Autoimmune hepatitis

4.2 Posology and method of administration

Posology

Crohn's disease

Induction of remission
The recommended daily dose is three capsules once daily in the morning or one capsule (containing 3 mg budesonide) three times daily (morning, midday and evening; corresponding to a total daily dose of 9 mg budesonide) if this is more convenient to the patient.

Duration of treatment
The duration of treatment in active Crohn's Disease should be limited to 8 weeks.

Microscopic colitis

Induction of remission
The recommended dose is three capsules once daily in the morning (corresponding to a daily dose of 9 mg budesonide).

Maintenance of remission
Maintenance therapy should only be initiated in patients with frequently recurring symptoms of microscopic colitis after successful induction treatment. A dosage regimen of two capsules once daily in the morning (6 mg budesonide) or of two capsules once daily in the morning alternating with one capsule daily in the morning (corresponding to an average daily dose of 4.5 mg budesonide) can be applied, according to the individual requirements of the patient. The lowest effective dose should be used.

Duration of treatment
The duration of treatment in active microscopic colitis should be limited to 8 weeks.

In maintenance therapy, the treatment effect should be evaluated regularly to assess if continued treatment is necessary, not later than 12 months after the initiation of maintenance treatment. Maintenance treatment should only be extended beyond a duration of 12 months if the benefits for the individual patient are considered to outweigh the risks.

Autoimmune hepatitis

Induction of remission
For the induction of remission (i.e. normalisation of elevated laboratory parameters) the recommended daily dose is one capsule (containing 3 mg budesonide) three times daily (morning, midday and evening; corresponding to a total daily dose of 9 mg budesonide).

Maintenance of remission
After achievement of remission the recommended daily dose is one capsule (containing 3 mg budesonide) twice daily (one capsule in the morning and one capsule in the evening; corresponding to a total daily dose of 6 mg budesonide).
If the transaminases ALAT and/or ASAT increase during maintenance treatment, the dose should be increased to 3 capsules per day (corresponding to a total daily dose of 9 mg budesonide) as described for induction of remission.
In patients tolerant to azathioprine, treatment for induction and maintenance of remission with budesonide should be combined with azathioprine.

Duration of treatment
For the induction of remission a total daily dose of 9 mg should be given until remission is achieved. Thereafter, for maintenance of remission a total daily dose of 6 mg budesonide should be given. Treatment for maintenance of remission in autoimmune hepatitis should be continued at least for 24 months. It might be terminated only if biochemical remission is constantly maintained and if no signs of inflammation are present in a liver biopsy.

Termination of treatment
The treatment with Budenofalk3mg should not be stopped abruptly, but withdrawn gradually (tapering doses). Gradual dose reduction over 2 weeks is recommended.

Paediatric population
Children under the age of 12
Budenofalk 3mg should not be taken by children younger than 12 years due to insufficient experience and possibly increased risk of adrenal suppression in this age group.

Adolescent patients aged 12 to 18 years
The safety and efficacy of Budenofalk 3mg in children aged 12 to 18 years have not yet been established. Currently available data in adolescent patients (12-18 years) with Crohn's disease or autoimmune hepatitis are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

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).

4.3 Contraindications

Budenofalk 3mg must not be used in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- hepatic cirrhosis

4.4 Special warnings and precautions for use

Treatment with Budenofalk 3mg results in lower systemic steroid levels than conventional oral glucocorticosteroid therapy. Transfer from other glucocorticosteroid therapy may result in symptoms relating to the change in systemic steroid levels. 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 glucocorticosteroids may have undesirable effects.

This medicine is not appropriate for patients suffering from Crohn's disease of the upper gastrointestinal tract.

Due to the preferential local mode of action of the compound beneficial effects for patients suffering from extraintestinal symptoms (e.g. of the eyes, skin, joints) cannot be expected.

Systemic effects of glucocorticosteroids may occur, particularly when prescribed at high doses and for prolonged periods. 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).

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 glucocorticosteroid 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 glucocorticosteroids 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. Glucocorticosteroids 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.

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

Patients with liver function disorders
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 budesonide in daily doses of 9 mg was safe and well tolerated. There is no evidence that a specific dose recommendation for patients with non-cirrhotic liver diseases or only slightly impaired liver function is necessary.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid 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 corticosteroids.

Others
Glucocorticosteroids may cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticosteroid treatment is recommended.

Concomitant treatment with ketoconazole or other CYP3A4 inhibitors should be avoided (see section 4.5).

Budenofalk 3mg capsules contain lactose and sucrose. Patients with rare hereditary problems of galactose or fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency or total lactase deficiency should not take this medicine.

In patients with autoimmune hepatitis serum levels of transaminases (ALAT, ASAT) should be evaluated at regular intervals to adapt the dose of budesonide adequately. During the first month of treatment, transaminase levels should be evaluated every two weeks, thereafter at least every 3 months.

4.5 Interaction with other medicinal products 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 corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. Ketoconazole 200 mg once daily p.o. 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 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, or – if budesonide binds stronger to CYP3A4 – the competing substance might be increased in plasma and a dose-adaption/reduction of this drug might be required.

Elevated plasma concentrations and enhanced effects of glucocorticosteroids have been reported in women also receiving oestrogens or oral contraceptives, but this has not been observed with oral low dose combination contraceptives.

Cimetidine at recommended doses in combination with budesonide has a small but insignificant effect on the 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 colestyramine, and with antacids cannot be ruled out. If given at the same time as Budenofalk 3mg, such interactions could result in a reduction in the effect of budesonide. Therefore these preparations should not be taken simultaneously, but at least two hours apart.

Because adrenal function may be suppressed by treatment with budesonide, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

4.6 Fertility, pregnancy and lactation

Pregnancy
Administration during pregnancy should be avoided unless there are compelling reasons for therapy with Budenofalk 3mg. There are few data of 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 effect, the maximal concentration of budesonide in plasma has to be expected to be higher in the treatment with Budenofalk 3mg compared to inhaled budesonide. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development (see section 5.3). The relevance of this to man has not been established.

Breast-feeding
Budesonide is excreted in human milk (data on excretion after inhalative use is available). However, only minor effects on the breast-fed child are anticipated after Budenofalk 3mg intake within the therapeutic range. A decision must be made whether to

discontinue breast-feeding or to discontinue/abstain from budesonide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effect of budesonide on human fertility. Fertility was unaffected following budesonide treatment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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)
very rare: (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	Frequency according to MedDRA convention	Adverse reaction
Metabolism and nutrition disorders	Common	Cushing's syndrome: e.g. with moon face, truncal obesity, reduced glucose tolerance, diabetes mellitus, hypertension, sodium retention with oedema, increased potassium excretion, inactivity or atrophy of the adrenal cortex, red striae, steroid acne, disturbance of sex hormone secretion (e.g. amenorrhoea, hirsutism, impotence)
	Very rare	Growth retardation in children
Eye disorders	Rare	Glaucoma, cataract, blurred vision (see also section 4.4)
Gastrointestinal disorders	Common	Dyspepsia, abdominal pain
	Uncommon	Duodenal or gastric ulcer
	Rare	Pancreatitis
	Very rare	Constipation
Immune system disorders	Common	Increased risk of infection
Musculoskeletal and connective tissue disorders	Common	Muscle and joint pain, muscle weakness and twitching, osteoporosis
	Rare	Osteonecrosis
Nervous system disorders	Common	Headache
	Very rare	Pseudotumor cerebri including papilloedema in adolescents

Psychiatric disorders	Common	Depression, irritability, euphoria
	Uncommon	Psychomotor hyperactivity, anxiety
	Rare	Aggression
Skin and subcutaneous tissue disorders	Common	Allergic exanthema, petechiae, delayed wound healing, contact dermatitis
	Rare	Ecchymosis
Vascular disorders	Very rare	Increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy)
General disorders and administration site conditions	Very rare	Fatigue, malaise

Most of the adverse events mentioned in this SmPC can also be expected for treatments with other glucocorticosteroids.

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

Clinical studies showed that the frequency of glucocorticosteroid-associated adverse events is lower with oral Budenofalk than with oral treatment of equivalent dosages of prednisolone.

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

Side effects in clinical studies with paediatric patients

Crohn's disease

In clinical trials with Budenofalk 3mg capsules in 82 paediatric patients with Crohn's disease adrenal suppression and headache were the most frequent undesirable effects. Side effects which are typical for glucocorticosteroids were reported as well as other rare reactions such as dizziness, nausea, vomiting, and hyperacusis (see also section 5.1).

Autoimmune hepatitis

Safety data from the subset of a total of 42 paediatric patients in an autoimmune hepatitis clinical trial revealed that undesirable effects reported were not different and not more frequent compared to the adult population in this study (see also section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

To date, no cases of overdose with budesonide are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticosteroid ATC code: A07EA06

The exact mechanism of budesonide in the treatment of Crohn's disease is not fully understood. Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of Budenofalk 3mg capsules is

predominantly based on a local action in the gut. Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. At doses clinically equivalent to systemically acting glucocorticosteroids, budesonide gives significantly less HPA axis suppression and has a lower impact on inflammatory markers.

Budenofalk 3mg capsules show a dose-dependent influence on cortisol plasma levels which is at the recommended dose of 9 mg budesonide/day significantly smaller than that of clinically equivalent effective doses of systemic glucocorticosteroids.

Clinical efficacy and safety
Crohn's disease

Clinical study in adult patients with Crohn's disease
In a randomized, double-blind, double-dummy trial in patients with mild to moderate Crohn's disease (200 < CDAI < 400) affecting the terminal ileum and/or the ascending colon the efficacy of 9 mg budesonide in a single daily dose (9 mg OD) was compared to the treatment with 3 mg budesonide given three times daily (3 mg TID).
The primary efficacy endpoint was the proportion of patients in remission (CDAI < 150) at week 8.
A total of 471 patients were included in the study (full analysis set, FAS), 439 patients were in the per protocol (PP) analysis set. There were no relevant differences in the baseline characteristics in both treatment groups. At the confirmatory analysis, 71.3% of the patients were in remission in the 9 mg OD group and 75.1% in the 3 mg TID group (PP) ($p = 0.01975$) demonstrating the non-inferiority of 9 mg budesonide OD to 3 mg budesonide TID.
No drug-related serious adverse events were reported.

Clinical studies in paediatric patients with Crohn's disease
Two randomised controlled studies with Budenofalk 3mg capsules included patients in the age range of 8 to 19 years with mildly to moderately active Crohn's disease (PCDAI [paediatric CD activity index] 12.5-40) with ileal, ileocolonic or isolated colonic inflammation.

In one study a total of 33 patients were treated with 9 mg budesonide (3 mg TID) daily for 8 weeks followed by 6 mg budesonide daily during week 9 and 3 mg budesonide daily in week 10 or with prednisone (40 mg/d for two weeks, tapered to zero in steps of 5 mg/week). Remission (PCDAI ≤ 10) was achieved in 9/19 (47.3%) of the patients in the budesonide group (both at week 4 and 12) and 8/14 (57.1%, at week 4) and 7/14 (50%, at week 12) of the patients in the prednisone group.
A second study including 70 children with CD compared two dosing schedules of budesonide: Patients in group 1 were treated for 7 weeks with 9 mg /day budesonide (3 mg TID) followed by 6 mg/day budesonide (3 mg BID) for additional 3 weeks. In group 2, patients were treated for 4 weeks with 12 mg/d budesonide (3 mg TID and 3 mg OD) and thereafter for each of 3 weeks with 9 mg/d budesonide (3 mg TID) and 6 mg/day budesonide (3 mg BID), respectively. Mean decrease of PCDAI at week 7 was defined as primary efficacy end point. There was a relevant decrease in the PCDAI in both treatment groups. The decrease was more pronounced in group 2 but the difference between the groups did not reach statistical significance (n.s.).
Secondary efficacy endpoints: Improvement (defined as a decrease of PCDAI ≥ 10 points) was seen in 51.4% of the patients in group 1 and 74.3% of the patients in group 2 (n.s.); remission (PCDAI ≤ 12.5) was found in 42.9% of the patients in the first group versus 65.7% in the second group (n.s.).

Microscopic colitis

Clinical studies in induction of remission in collagenous colitis
Efficacy and safety of budesonide for induction of remission in collagenous colitis were evaluated in two prospective double-blind (DB), randomized, placebo-controlled, multicentre studies with patients with active collagenous colitis.
In one study, 30 patients were randomized to a treatment with 9 mg budesonide per day, 25 patients to a treatment with 3 g mesalazine per day, and 37 to placebo. The primary efficacy variable was the rate of patients in clinical remission, defined as ≤ 3 stools per day. 80% of the patients treated with budesonide, 44% of the patients treated with mesalazine and 59.5% of the patients in the placebo-group reached the primary endpoint (budesonide vs. placebo = 0.072). According to another definition of clinical remission taking into account also the stool consistency, i. e. a mean of < 3 stools per day and a mean of < 1 watery stool per day in the last 7 days prior to the last administration of the study drug, 80% of the patients in the budesonide group, 32.0% of the patients in the mesalazine group and 37.8% of the patients in the placebo group achieved remission (budesonide vs. placebo: $p < 0.0006$). Budesonide was safe and well tolerated. None of the adverse events in the budesonide group was considered drug related.
In another study 14 patients were randomized to a treatment with 9 mg budesonide per day and 14 were randomized to placebo. The primary efficacy variable was clinical response defined as a drop to ≤ 50 % of the disease activity at baseline with clinical disease activity defined as the numbers of stools during the last 7 days. 57.1% of patients in the budesonide group and 21.4% in the placebo group achieved clinical response ($p = 0.05$). Budesonide was safe and well tolerated. No serious adverse drug reactions occurred in the budesonide group.

Clinical study in maintenance of remission in collagenous colitis

Clinical efficacy and safety of budesonide in the maintenance of remission in collagenous colitis were evaluated in a prospective double-blind (DB), randomized, placebo-controlled, multicentre study with patients with quiescent collagenous colitis. The primary endpoint was the proportion of patients in clinical remission over 52 weeks. Remission was defined as a mean of < 3 stools/day, thereof a mean of < 1 watery stool/day during the week prior to the final visit and with no relapse during the 1-year course. Relapse was defined as a mean of ≥ 3 stools/day thereof a mean of ≥ 1 watery stool/day during the previous week. 92 patients were randomised to treatment in the DB phase (44 budesonide, 48 placebo) and took at least one dose of the study medication (full analysis set, FAS). The posology was 6 mg budesonide/day alternating with 3 mg budesonide/day (corresponding to an average daily dose of 4.5 mg budesonide). In the final analysis, significantly more patients in the budesonide group (61.4%) compared to patients in the placebo group (16.7%) reached the primary endpoint, demonstrating the superiority of budesonide over placebo ($p < 0.001$).

Clinical study in induction of remission in lymphocytic colitis

Clinical efficacy and safety of budesonide in the induction of remission in lymphocytic colitis were evaluated in a prospective, double-blind (DB), double-dummy, randomized, placebo-controlled, multicentre study with patients with active lymphocytic colitis. The primary endpoint was the rate of clinical remission, defined as a maximum of 21 stools, thereof not more than 6 watery stools in the last 7 days prior to the last visit. 57 patients were randomised (each 19 patients in the budesonide group, mesalazine-group and placebo-group) and took at least one dose of the study medication (budesonide: 9 mg OD; mesalazine: 3 g OD). The treatment duration was 8 weeks. In the confirmatory analysis, significantly more patients in the budesonide group (78.9%) compared to patients in the placebo-group (42.1%) reached the primary endpoint, showing the superiority of budesonide over placebo ($p = 0.010$). 63.2% of the patients in the mesalazine group reached remission ($p = 0.097$).

Autoimmune hepatitis

Clinical study in adult patients with autoimmune hepatitis

In a prospective, double-blind, randomised, multicentre trial, 207 patients with autoimmune hepatitis (AIH) without cirrhosis were treated with initial daily doses of 9 mg/d budesonide (n = 102) for up to 6 months or 40 mg/d prednisone (tapered to 10 mg/d, n = 105). Upon biochemical remission, the budesonide dose was reduced to 6 mg/d. Patients also received 1-2 mg/kg/d azathioprine throughout the study. The composite primary endpoint was complete biochemical remission (i.e. normal serum levels of aspartate- and alanine-aminotransferase) without occurrence of predefined steroid-specific side effects at 6 months. This primary endpoint was achieved in 47% of the patients in the budesonide group and 18% of the patients in the prednisone group ($p < 0.001$). Regarding secondary efficacy variables, at 6 months, complete biochemical remission occurred in 60% and 39% of the patients in the budesonide group and in the prednisone group, respectively ($p = 0.001$). 72% and 47% of the patients in the budesonide group and in the prednisone group, respectively, did not develop steroid-specific side-effects ($p < 0.001$). The mean decrease in IgG and γ-globulin concentrations and the decrease in the rates of patients with elevated IgG and γ - globulin concentrations did not show any differences between treatment groups. An open-label, follow-up treatment of additional 6 months was offered to all patients after the controlled, double-blind phase. A total of 176 patients proceeded to this open-label phase and received 6 mg/d budesonide in combination with 1-2 mg/kg/d azathioprine. Rates of patients with biochemical remission and rates of patients with complete response (not statistically significant) were still higher in the original budesonide group (complete response rate 60% and biochemical remission 68.2% at the end of the open label phase) than in the original prednisone group (complete response rate 49% and biochemical remission 50.6% at the end of the open label phase).

Clinical study in paediatric patients with autoimmune hepatitis

The safety and efficacy of budesonide in 46 paediatric patients (11 males and 35 females) aged 9 to 18 years were studied as a subset of patients of the above mentioned clinical study. 19 paediatric patients were treated with budesonide and 27 received the active control (prednisone) for induction of remission with a daily dose of 9 mg budesonide. After 6 months in the study, 42 paediatric patients continued for a further 6 months on open label, follow up treatment with budesonide. The rate of complete responders (defined as biochemical response, i.e. normalisation of liver transaminases (ASAT, ALAT) and lack of steroid-specific side-effects) in patients aged ≤ 18 years was considerably lower compared to adult patients. There was no significant difference seen between the treatment groups. After follow up treatment with budesonide for a further 6 months, the rate of paediatric patients with complete response was still slightly lower compared to adult patients but the difference between the age groups was much smaller. There was no significant difference in the rate of complete responders between those originally treated with prednisone and those treated continuously with budesonide.

5.2 Pharmacokinetic properties

Absorption

Budenofalk 3mg capsules, which contain gastric juice resistant granules, have – due to the specific coating of the granules - a lag phase of 2-3 hours. In healthy volunteers, as well as in patients with Crohn's disease, mean maximal budesonide plasma concentrations of 1-2 ng/ml were seen at about 5 hours following an oral dose of Budenofalk 3mg capsules at a single dose of 3 mg, taken before meals. The maximal release therefore occurs in the terminal ileum and caecum, the main area of inflammation in Crohn's disease.

In ileostomy patients release of budesonide from Budenofalk 3mg is comparable to healthy subjects or Crohn's disease patients. In ileostomy patients it was demonstrated that about 30-40% of released budesonide is still found in the ileostomy bag, indicating that a substantial amount of budesonide from Budenofalk3mg will be transferred normally into the colon. 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 between 85 and 90%.

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

Elimination
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
A relevant proportion of budesonide is metabolised in the liver. The systemic exposure of budesonide might be increased in patients with impaired hepatic functions due to a decrease in budesonide metabolism by CYP3A4. This is dependent on the type and severity of liver disease.

Paediatric patients
Pharmacokinetics of budesonide were evaluated in 12 paediatric patients with Crohn's disease (age: 5 to 15 years). Following multiple dose administration of budesonide (3 x 3 mg of budesonide for one week) mean AUC of budesonide during the dosing interval was about 7 ng h/ml, and C_{max} about 2 ng/ml. Disposition of oral budesonide (3 mg, single dose) in paediatric patients was similar to that in adults.

5.3 Preclinical safety data

Preclinical data in acute, subchronic and chronic toxicological studies with budesonide showed atrophies of the thymus gland and adrenal cortex and a reduction especially of lymphocytes. These effects were less pronounced or at the same magnitude as observed with other glucocorticosteroids. Like with other glucocorticosteroids, and in dependence of the dose and duration and in dependence of the diseases these steroid effects might also be of relevance in man.

Budesonide had no mutagenic effects in a number of *in vitro* and *in vivo* tests.

A slightly increased number of basophilic hepatic foci were observed in chronic rat studies with budesonide, and in carcinogenicity studies an increased incidence of primary hepatocellular neoplasms, astrocytomas (in male rats) and mammary tumours (female rats) were observed. These tumours are probably due to the specific steroid receptor action, increased metabolic burden on the liver and anabolic effects, effects which are also known from other glucocorticosteroids in rat studies and therefore represent a class effect. No similar effects have ever been observed in man for budesonide, neither in clinical trials nor from spontaneous reports.

In general, preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development. But the relevance to man has not been established (see also section 4.6.).

The active substance budesonide shows an environmental risk for the aquatic environment, especially to fish.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules contents
Ammonio methacrylate copolymer (type A) (Eudragit RL)
Ammonio methacrylate copolymer (type B) (Eudragit RS)
Lactose monohydrate
Maize starch
Methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit L 100)
Methacrylic acid-methyl methacrylate copolymer (1:2) (Eudragit S 100)
Povidone K25
Purified water*
Sucrose
Talc
Triethyl citrate

* intermediate excipient

Capsule shell:
Black iron oxide (E 172)
Erythrosine (E 127)
Gelatin
Purified water
Red iron oxide (E 172)
Sodium laurilsulphate
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC/PVDC blister strips.
Pack sizes: 10, 50, 90, 100 or 120 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Dr. Falk Pharma GmbH
Leinenweberstrasse 5
79108 Freiburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA0573/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6April 2001Date of last renewal: 4 January 2009

10 DATE OF REVISION OF THE TEXT

January 2020