Budenofalk® 3mg

Acute Crohn's disease
with involvement of the ileum and/or ascending colon

Collagenous colitis

Revised edition 2005

Dr. Falk Pharma Ex. 1026
IPR Petition - USP 8,771,729

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Product presentations, compositions and indications as referenced herein may differ from those in your country. Therefore, please contact Dr. Falk Pharma GmbH, Freiburg (Germany) or the local Falk partner.

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Summary of product characteristics
Budenofalk® 3mg

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Preface

Problems of glucocorticoid therapy in inflammatory bowel diseases

Etiology and pathogenesis of inflammatory bowel diseases – Crohn's disease and ulcerative colitis – are not definitely clarified till today. Therefore, a causal therapy of these diseases is not possible and the therapy is limited to symptomatic treatment of acute disease attacks as well as to relapse prophylaxis. Both, Crohn's disease and ulcerative colitis well respond to a therapy with glucocorticosteroids (GS). However, using glucocorticoids systemically, there is a potential danger of a high rate of side effects, especially during long-term therapy. Therefore, GS were developed, specifically designed for topical use which are characterized by a highly intrinsic activity and favourable physical-chemical properties. On the other hand, these properties are dependent on lipophilia, receptor binding affinity (RBA), distribution volume (V_D), clearance (Cl), protein binding, and metabolic stability of GS. In addition, a local release of the highly effective steroid at the site of inflammation is possible by a specific galenic formulation.

With Budenofalk® 3mg capsules (budesonide) such a drug is available with a favourable benefit/risk-ratio. Budesonide with a high topical activity has an extensive first-pass-metabolism in the liver and, therefore, it shows only a relatively low systemic bioavailability. Consequently, the systemic range of side effects of Budenofalk® 3mg capsules is substantial less in comparison with systemically acting glucocorticoids.

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1 Short information

Budenofalk® 3mg capsules contain budesonide as active ingredient, a glucocorticoid with high topical and low systemic effects leading to substantially reduced side effects. Each gastric juice-soluble Budenofalk® 3mg capsule contains about 350 gastric juice-resistant pellets with pH-modified release which pass the pylorus independent of the interdigestive phase III because of their small diameter of about 1 mm. Due to a lag-phase of 2 to 3 hours, the release of active drug occurs directly in the terminal ileum and colon, where budesonide develops its topical effect. The degree of the local effect is dependent on the availability and on the specific pharmacological properties of the glucocorticoid at the site of inflammation. These factors are very favourable for the topical therapy with budesonide compared to the conventional, systemically acting glucocorticoids. However, the duration of the specific glucocorticoid effect is dependent on the temporal availability of the steroid at the target tissue. Therefore, optimized therapeutical interactions may be obtained only by the provision of adequately effective steroid concentrations as continuously as possible in the target cells and target tissues. That will be achieved by multiple, over the day distributed dosages of budesonide (3 × 3 mg per day) of Budenofalk® 3mg capsules. Because of the first-pass effect with a high rate of metabolism in the liver of about 90%, the systemic bioavailability of budesonide is very low at about 10%. Accordingly, the rate of steroid-typical side effects is much lower than that observed with conventional, systemically active steroids.

The licensed indications for Budenofalk® 3mg capsules are the treatment of

- **acute Crohn's disease of mild to moderate activity with involvement of the ileum and/or ascending colon**
- **collagenous colitis**

The standard dosage is 3 × 1 capsule à 3 mg, corresponding to 9 mg of budesonide daily. This is in accordance with the recommendation of the consensus conference of the German Association for Digestive and Metabolic Diseases 2003 for "Treatment of Crohn's disease". Furthermore, this association recommended the change to the oral therapy of active Crohn's disease with budesonide in case of side effects induced by systemically acting steroids (SCHÖLMERICH 2003).

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2 Product profile of Budenofalk® 3mg capsules

Budenofalk® 3mg capsules are gastric juice-soluble hard gelatine capsules. Each hard capsule contains 3 mg budesonide distributed in about 350 gastric juice-resistant pellets with a diameter of about 1 mm for pH-modified release of the active substance (Figure 1).

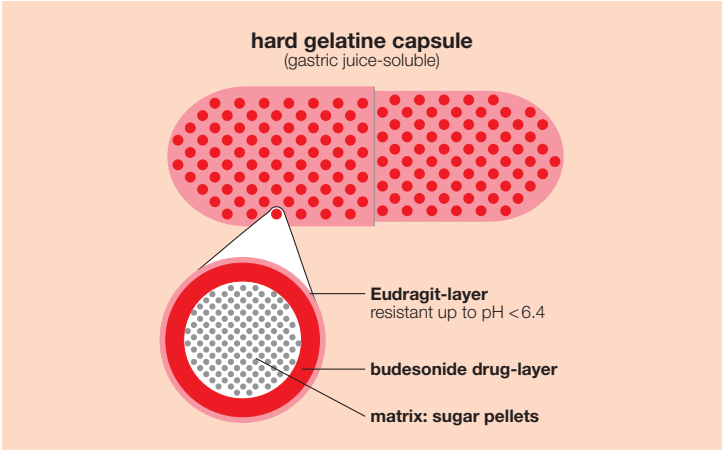

Figure 1: Budenofalk® 3mg capsule with pH-modified release of the active drug from the pellets (MÖLLMANN et al. 1996a).

The pellets, released in the stomach, are able to pass the pylorus due to their small diameter, independent of the interdigestive phase III. The pH-dependent (pH ≥ 6.4) release of the active drug occurs in the ileum and colon.
The mean passage time of the pellets to the terminal ileum is between 180 and 240 minutes.

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3 Chemical properties of budesonide

Budesonide is a non-halogenated glucocorticoid derived from 16α-hydroxy-prednisolone.

Chemical name: 16α,17α-butylidene dioxy-11β, 21-dihydroxy-1,4-pregnadiene-3,20-dione (IUPAC) 11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (WHO)

Molecular formula: $C_{25}H_{34}O_6$

Structural formula:

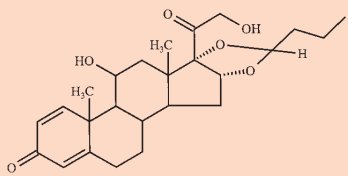

Figure 2: Chemical structure of budesonide.

Molecular weight: 430.54

Melting point: 221–232°C with degradation (Merck Index 10)

Solubility: High lipophilic substance: Solubility in ethanol 30 mg/ml, in chloroform 400 mg/ml, in water 0.01 mg/ml

Budesonide is a mixture of the two epimers 22R and 22S in the ratio of about 1:1 due to the introduction of an asymmetric acetal group into the budesonide molecule and due to a special manufacturing process. Both epimers have the same qualitative pharmacological effects, but the 22R-epimer is about two- to three-fold more active than the 22S-epimer (BRATTSAND et al. 1982b, ROTH et al. 1980, THALÉN & BRATTSAND 1979).

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4 Pharmacology

4.1 Pharmacodynamics

4.1.1 Mode of action

Budesonide has, as all glucocorticoids, a multiple profile of action. The main effect of the natural glucocorticoid hydrocortisone, as well as all synthetic modifications thereof, are mediated by specific cytoplasmatic glucocorticoid receptors within the target cell which range in the most body cells between 2000 and 30000 binding sites. By binding of the glucocorticoid to the intracellular glucocorticoid receptors after passive diffusion into the cell, a complex is formed which enters into the nucleus. There it binds to so-called glucocorticoid response elements (GRE) of the DNA in the region of specific genes. This binding induces the gene transcription and the synthesis of several proteins (e.g. inflammatory proteins). Moreover, the binding of the glucocorticoid-receptor-complex to the so-called negative GREs suppresses the expression of certain other genes, e.g. the inhibition of the propiomelanocortin gene expression within the adenohypophysis.

The binding of the glucocorticoid to its receptor results in inhibition of the production of both cytokine-induced and nuclear factor κB (NF-κB)-mediated inflammation factors. This results in a reduced release of arachidonic acid and an inhibition of the synthesis of leukotrienes, prostaglandins, and of the platelet activating factor (PAF) as well. Therefore, the reduced formation of leukotrienes and prostaglandins, known for being mediators of inflammation, is an especially important result of this reaction cascade.

The inhibitory properties are based upon a decrease of synthesis, a release of the specific messenger-RNAs (mRNAs) and on a shortened half-life of mRNAs which are responsible for the regulation of synthesis and for the release of cytokines from inflammatory cells. Therefore, this genomic, from the protein synthesis dependent main effect of glucocorticoids is responsible for an important part of their anti-inflammatory action (ANDUS & TARGAN 1994, EWE 1994, FUNDER 1993, HIRATA et al. 1987, HOCHHAUS et al. 1996, HUCHZERMEYER 1992, KAISER & KLEY 1992, MIESFELD 1990, MÜLLER & RENKAWITZ 1991, THALÉN & BRATTSAND 1979).

This represents the basic difference between budesonide as a glucocorticoid and other anti-inflammatory substances, for example 5-ASA/mesalazine and

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its derivatives, which are used in the treatment of inflammatory bowel disease which is schematically depicted in Figure 3.

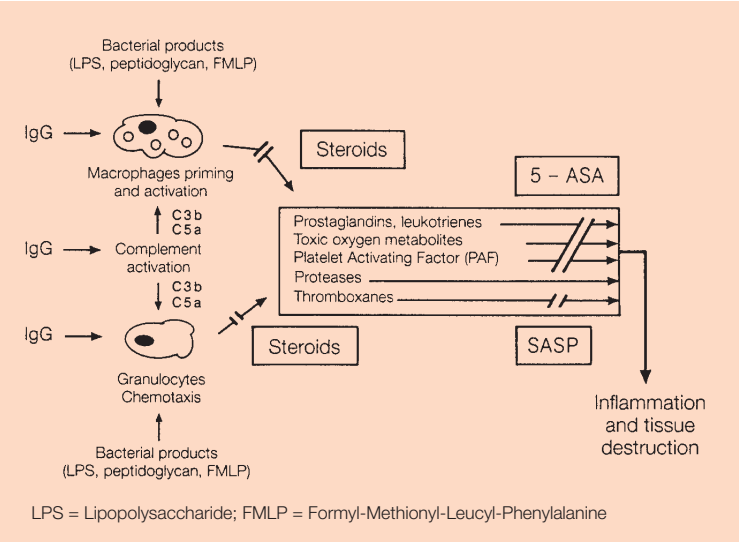

Figure 3: Possible inhibitory effects of glucocorticoids, mesalazine (5-ASA) and sulfasalazine (SASP) on different mediators of intestinal inflammation (according to SCHREIBER et al. 1992).

In addition, non-genomic, non-nuclear pathways are involved in the glucocorticoid action which are induced via cytoplasmic (JOHNSON et al. 1982) and membrane-bound receptors as well as via non-specific, non-receptor mediated processes (EWE 1994, HOCHHAUS et al. 1996). These processes include the modulation of phosphorylation, effects on calcium influx into the cell, the decrease of ACTH secretion and, especially, a direct interaction with lipocortin (HIRATA et al. 1987) which is substantially involved in the regulation

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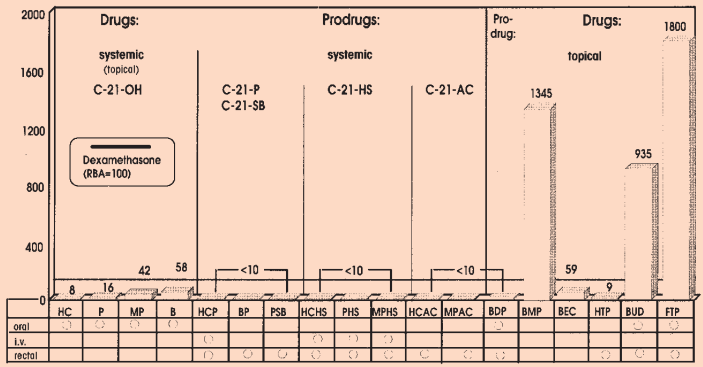
of leukotrienes and prostaglandins. These processes, which do not depend on protein synthesis, proceed very rapidly (HOCHHAUS et al. 1996).

4.1.2 Receptor affinity

The individual response of patients to glucocorticoid therapy, including a glucocorticoid resistance, may depend on receptor density and receptor affinity in particular. Therefore, the receptor binding affinity of several glucocorticoid derivatives is of particular importance for their therapeutical use (HOCHHAUS et al. 1996). Glucocorticoids for topical use may be classified by their receptor affinity (Figure 4). Comparative studies have shown that budesonide belongs to the glucocorticoids with a very high receptor affinity (BRATTSAND 1990, MÖLLMANN et al. 1993a 1996a). The topical activity is directly correlated with the receptor binding affinity, in other words, budesonide has a high topical activity (BRATTSAND 1990).



HC = hydrocortisone, P = prednisolone, MP = methylprednisolone, B = betamethasone, BUD = budesonide, HCP = hydrocortisone phosphate, PP = prednisolone phosphate, MPP = methylprednisolone phosphate, BP = betamethasone phosphate, HCHS = hydrocortisone hemisuccinate, PHS = prednisolone hemisuccinate, MPHS = methylprednisolone hemisuccinate = sodium succinate, PSB = prednisolone sulfobenzoate, FTP = fluticasone propionate, BDP = beclomethasone dipropionate

Figure 4: Relative receptor binding affinity (RBA) of different glucocorticoids to the human glucocorticoid receptor used in inflammatory bowel diseases (MÖLLMANN et al. 1996a, modified after WÜRTHWEIN et al. 1992).

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In addition, the receptor affinity of a glucocorticosteroid stays in direct relationship to its biological activity. Therefore, it is to assume that a glucocorticoid with a high receptor affinity, like budesonide, also has a high anti-inflammatory activity (DAHLBERG et al. 1984).

4.1.3 Anti-inflammatory effects of glucocorticoids in inflammatory bowel diseases

Since most cells are provided with glucocorticoid receptors, glucocorticoids affect the function of many different cell types. This is true for inflammatory cells, too, which are involved in the pathogenesis of inflammatory bowel diseases (Table 1). Therefore, the therapeutic effect is multifactorial and may not be explained by a single mechanism (ANDUS & TARGAN 1994). Glucocorticoids impair specific and non-specific immune reactions, they suppress early events of inflammation such as the release of inflammatory mediators, vasodilatation, increased vascular permeability, and leukocyte infiltration. Furthermore, they inhibit late inflammatory events such as fibroblast activation with collagen deposition and vascular proliferation. The local inflammatory response is characterized by a mixed infiltrate composed of lymphocytes, plasma cells, macrophages, eosinophils, mast cells, and neutrophils, all of them playing a role in inflammatory bowel diseases. Hence, their functions are influenced by glucocorticoids in a way that a multiple inhibition of inflammation stimulating processes results (Table 1) (ANDUS & TARGAN 1994, BRATTSAND 1990, 1993, FAUCI 1976, von HERBAY et al. 1990, KURITZKES & SHANAHAN 1991, MacDERMOTT 1986, SCHLEIMER 1990). A comparison of the immunopharmacology of glucocorticoids with 5-aminosalicylic acid for therapy of inflammatory bowel diseases was published recently (SCHÖLMERICH 2003).

In a number of experimental animal studies as well as in healthy volunteers and patients, the effects described for glucocorticoids on different inflammatory cells and mediators, which are responsible for the beginning and maintenance of inflammatory processes, were also investigated and demonstrated for budesonide (TROMM 2004).

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Cell type	Effects (↓ inhibition; ↑ increase)	
Lymphocytes	• Redistribution of lymphocytes from the intravascular compartment to lymphoid organs	
	• Proliferation of T-cells	↓
	• Proliferation and differentiation of B-cells	↓
	• Cytotoxicity	↓
	• Production of cytokines	↓
	• Apoptosis	↑
Monocytes/macrophages	• Redistribution of monocytes from the intravascular compartment to lymphoid organs	
	• Chemotaxis and phagocytosis	↓
	• Production of prostaglandins and leukotrienes	↓
	• Production of cytokines such as IL-1, IL-2, IL-6, IL-8, and TNF-α	↓
	• Secretion of proteinases	↓
Eosinophils	• Growth and differentiation	↓
	• Survival time	↓
	• Migration	↓
	• Chemotaxis	↓
Basophils/mast cells	• Growth and differentiation	↓
	• Proliferation and migration	↓
	• Secretion of histamine, LTC_4 and PAF	↓
Neutrophils	• Transmigration from the blood to the site of inflammation	↓
	• Activation and chemotaxis	↓
Endothelial cells	• Inhibition of increased vascular permeability	
	• Expression of adhesion molecules	↓
	• Cytokines	↓
→ **Multiple inhibition of inflammation stimulating processes**		

Table 1: Anti-inflammatory effect of glucocorticoids (modified according to ANDUS & TARGAN 1994, BRATTSAND 1990).

Studies in rats with experimentally induced bowel disease led to a nearly normal distribution of macrophages and a normalization of the number of dendritic cells following the administration of budesonide (van REES et al. 1993). Hyperemia and exsudative response were abolished by topical budesonide application (EKSTRÖM & ANDERSSON 2000). In a cell layer

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model, pathological epithelial changes induced by activated monocytes could be prevented by budesonide and analogs of this substance (ZAREIE et al. 1999).

In comparative studies, the effect of budesonide on the release of cytokines was compared in patients with Crohn's disease with that in healthy volunteers. The release of cytokines (TNF-α, IL-1β from monocytes) was strongly inhibited by budesonide, both, in healthy volunteers and in patients. The inhibitory effect of budesonide was shown to be about 20-fold higher than that of dexamethasone. Thus, budesonide was shown to be a potent anti-inflammatory substance (HOWALDT et al. 1993).

During administration of budesonide, a markedly decreased release of histamine from basophils and a reduced IgE-dependent release of histamine from human leukocytes were found in in vitro studies (BERGSTRAND et al. 1984, 1986).

At treatment of patients with ulcerative colitis, budesonide was shown to inhibit both, the release of LTB_4 from human macrophages and the secretion of cytotoxic proteinases from eosinophils (WATKINSON 1988).

4.1.4 Relation of topical to systemic action

In the treatment of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, the relation between topical and systemic action is of essential importance because it is directly correlated to the relation of the desired therapeutic effect to adverse events. Although the conventional, systemically acting glucocorticoids are approved drugs in the treatment of acute attacks of inflammatory bowel diseases since many years, their long-term use is strongly limited due to a relatively high rate of adverse events (e.g. Cushing syndrome, osteoporosis, osteonecrosis, hypertension, diabetes mellitus, cataract, and depressions). Therefore, glucocorticoids like budesonide with a low systemic bioavailability and simultaneously with a high local anti-inflammatory effect were developed for the treatment of inflammatory bowel diseases in order to create a most beneficial ratio between a desired, local therapeutic effect and undesired, systemic adverse events.

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4.1.4.1 Topical action of budesonide

The "modern" glucocorticoids, designed for topical use, can generate a 100-fold or even higher intrinsic activity compared to systemically acting "classic" primary glucocorticoids (MÖLLMANN et al. 1996a; see also Figure 4). These specific properties have been well documented, especially for budesonide as a representative of this group (BRATTSAND 1990, CHANOINE 1988).

Budesonide is not administered as a so-called prodrug, but in a biologically active form as a C-21 alcohol and, it immediately exerts its full intrinsic activity in the target organ. Due to its chemical structure as C-16,17α-acetonide, budesonide is highly lipophilic, has a relatively high receptor binding affinity (e.g. eleven times higher than that of dexamethasone; see Figure 4), and thus shows high topical activity combined with high extrahepatic metabolic stability (BRATTSAND 1990, MÖLLMANN et al. 1996a, RYRFELDT et al. 1982).

In an animal model, the topical activity of budesonide and thus its local, anti-inflammatory effect was demonstrated in experimentally induced bowel inflammations in rats and rabbits (FABIA et al. 1993, 1994, GUSTAFSSON & PERSSON 1994, van REES et al. 1993).

In an acetic acid-induced colitis model in the rat, in which the experimentally induced colitis showed morphological similarities to human ulcerative colitis, a comparable good effect of a local and systemic application of budesonide was observed. However, this effect was achieved by markedly different doses. The local, intrarectal dose of budesonide was only 10^{-5} M, corresponding to 0.17 mg/kg BW. With regard to the first-pass effect after rectal administration with a systemic bioavailability of 15%, this corresponds to a dose of only 0.03 mg/kg BW. The local, rectal treatment with a 4.5-fold lower budesonide dose which caused a reduction of the colitis of 76%, was shown to be as effective as the systemic parenteral treatment (80%) with a budesonide dose of 0.75 mg/kg BW. The local effect of budesonide may be definitely deduced from these results. The lower influence on body weight as well as on the weight of adrenal glands, spleen and thymus under local budesonide application confirms the very low systemic effect of this form of application (FABIA et al. 1993, 1994).

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The vasoconstriction test is very often used to prove the topical activity of a glucocorticoid because MILLER & MUNRO (1980) have shown a good correlation between the achieved vasoconstriction and its clinical efficacy. The high-potent glucocorticoids designed for topical use cause a strong vasoconstriction and are simultaneously the most effective inhibitors of inflammation, while corticosteroids with a low vasoconstriction action conversely exert the lowest anti-inflammatory effects (McKENZIE & STOUGHTON 1962).

In the cutaneous vasoconstriction test, budesonide was shown to be markedly more effective than most other glucocorticoids following topical application to healthy volunteers. For example, budesonide acted 1.6 times to 3 times stronger than beclomethasone dipropionate (JOHANSSON et al. 1982a, 1982b) and about 1000 times stronger than prednisolone and hydrocortisone (JOHANSSON et al. 1982a). Using the vasoconstriction test, it was demonstrated in other investigations that budesonide has a higher topical anti-inflammatory effect than dexamethasone, betamethasone, flunisolide, desonide, hydrocortisone butyrate, fluocinolone acetonide, and triamcinolone acetonide (BRATTSAND et al. 1982a, 1982b, GRUVSTAD & BENGTSSON 1980, JOHANSSON et al. 1982a, 1982b, THALÉN et al. 1989). It was also shown by these studies that budesonide causes a markedly lower suppression of plasma cortisol than prednisolone or hydrocortisone.

In addition to the chemical structure, the galenical preparation of a glucocorticoid is of importance for its topical action. Following an oral administration of a budesonide formulation with modified release, it has been shown that the intestinal inflammation in a hamster model with experimentally induced ileitis was more effectively reduced than following an oral administration of pure budesonide. These results demonstrate that the release of the active agent at the site of inflammation has a marked influence on the efficacy of budesonide. They further demonstrate that the topical rather than the systemic action is responsible for its anti-inflammatory effect (BOYD et al. 1994).

With Budenofalk® 3mg capsules, a galenic preparation with pH-modified drug release is available, especially developed for oral therapy of inflammatory bowel diseases of the ileum and colon. Due to the largely local release of budesonide at the site of pathological processes in the terminal ileum

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and colon, optimal concentrations of the active substance can be achieved which realize a highly local effect by the specific properties of budesonide (MÖLLMANN et al. 1996a).

4.1.4.2 Systemic action of budesonide

Following oral administration, the classic glucocorticoids were shown to have a high systemic bioavailability. In contrast to those, the systemic bioavailability (10%) of budesonide is comparatively low (Figure 5, HOCHHAUS et al. 1996, MÖLLMANN et al. 1996a, b, RYRFELDT et al. 1982).

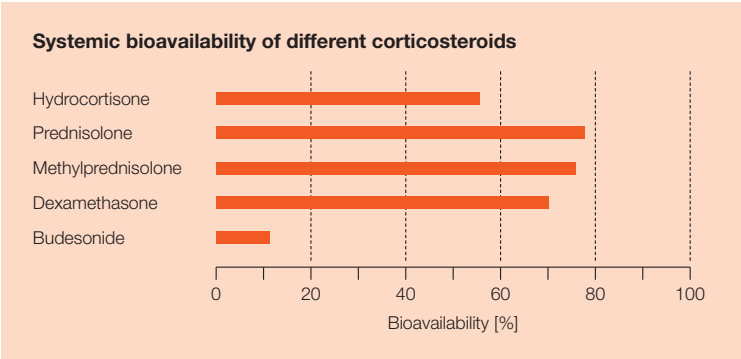

Figure 5: Systemic bioavailability of different glucocorticoids following oral administration (BRATTSAND 1990).

This can be illustrated by a comparison of the pharmacodynamic potential of the absorbed portion of budesonide with that of the classic glucocorticoid methylprednisolone (Figure 6). As shown, the systemic effects on lymphocytes after oral administration of 1–3 mg budesonide as pH-modified release capsules are equivalent to the effects of 0.2–0.4 mg methylprednisolone after intravenous injection. However, the pharmacological effect of budesonide is equivalent to a systemic dose of 20–60 mg methylprednisolone (MÖLLMANN et al. 1996a).

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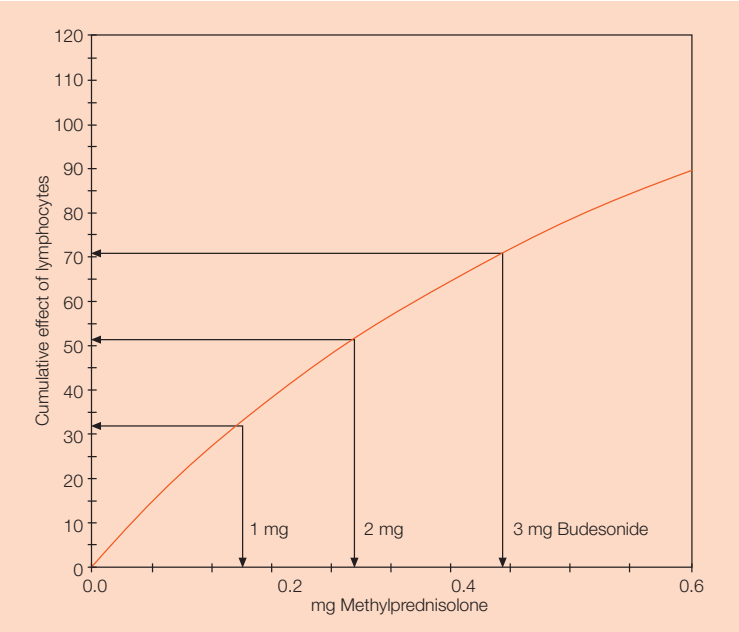

Figure 6: Comparison of the systemic effect of budesonide on lymphocytes with the effect of equivalent doses of methylprednisolone (MÖLLMANN et al. 1996a).

In addition, the total number of leukocytes as well as the plasma cortisol concentrations were distinctly less influenced following oral administration of budesonide than following oral administration of beclomethasone dipropionate (JOHANSSON et al. 1982a).

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The low systemic bioavailability is based upon the high first-pass effect during the first liver passage by which budesonide is metabolized about 90% to physiologically largely ineffective metabolites (see 4.2.4 Metabolism and elimination, Figure 12).

Using the influence of budesonide on the kinetics of granulocytes and lymphocytes, pharmacodynamic investigations of systemic effects of Budenofalk® 3mg capsules have shown that the duration of action of budesonide is limited to about 8 hours following oral administration of the capsules (Figure 7) (MÖLLMANN et al. 1996a).

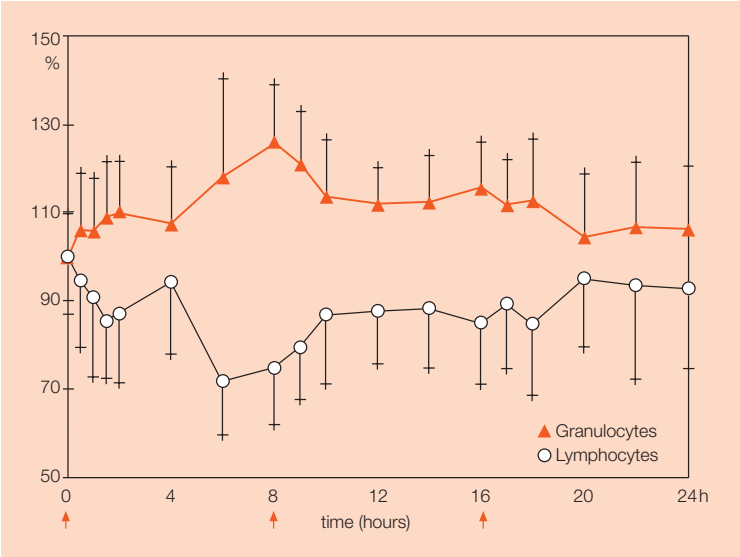

Figure 7: Effect/time profiles of lymphocytes and granulocytes following oral administration of Budenofalk® 3mg capsules in 8-h intervals (arrow-markings) (MÖLLMANN et al. 1996a).

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The pharmacokinetic features of budesonide obtained from these pharmacological investigations are of importance to provide therapeutic dosage schedules for multiple application. As a practical consequence, lower doses of budesonide in form of Budenofalk® 3mg capsules should be administered in regular intervals in divided daily doses for the treatment of acute Crohn's disease (with involvement of the ileum and/or ascending colon) in order to achieve adequate levels of action at the intestinal mucosa, thereby minimizing the systemic side effects (DERENDORF et al. 1993, 1996, MÖLLMANN et al. 1996a).

The comparatively low rate of side effects can be explained by its relatively low systemic bioavailability of only 10% as shown in all pharmacological investigations (DERENDORF et al. 1993, MÖLLMANN et al. 1996a, 1996b) (see also chapter 6 "Clinical experience").

4.1.5 Influence on gastrointestinal nervous tissue

Inflammatory bowel diseases are accompanied by structural changes of enteral nerves, which do not only refer to the inflamed bowel parts. In a rat with an experimentally induced colitis, a reduced release of ^{3}H-noradrenaline from the myenteric plexus was determined which could be compensated by budesonide (JACOBSON et al. 1993). In this study, the MPO-activity (activity of the myeloperoxidase) was not influenced by budesonide.

However, another study revealed normalization of the MPO-activity by the use of budesonide in an animal model (acetic acid-induced colitis in a rat) (FABIA et al. 1994).

4.1.6 Effect on small intestine structure and mucosa associated cells

In 11 patients with active Crohn's disease, ileocoloscopies were performed before treatment with 9 mg budesonide or prednisolone in decreasing doses and after a 6 months therapy. Lymphocytes of the lamina propria were isolated from the biopsy material, the mucosa's architecture was determined by microdissection, and the gastrointestinal function was checked, too. It was concluded that the therapy with budesonide and prednisolone led to a remarkable reduction of CD4/CD25^{+} T-cells in the lamina propria, whereas no

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shift of the CD4/CD8-relation could be determined (STALLMACH et al. 1998). Furthermore, an increase of villi height was observed which is possibly due to the reduction of active $CD4^+$ cells in the lamina propria.

Human intestinal eosinophils of patients with gastrointestinal allergy or ulcerative colitis were responsive to budesonide administration. In mucosal samples, the spontaneous and IgE mediated secretory activity of eosinophils was inhibited (RAITHEL et al. 1999, RAITHEL 2003).

4.1.7 Immunosuppressive effect on the gastrointestinal immune system

Patients with the necessity of bowel resection due to colorectal carcinomas were chosen for a further study. Colon mucosa was taken from a macroscopic and histologically normal colon part at least 5 cm away from the sick bowel region and processed in culture medium within 30 minutes after dissection. The immune function was measured in vitro by determination of the DNA synthesis, the ornithine-decarboxylase-activity (ODC) and the TNFα-secretion. Budesonide and methylprednisolone revealed comparable suppressive effects on the DNA-synthesis, the ODC- and the TNFα-secretion. Added IL-2 did not abolish the antiproliferative effect of both substances (ELITSUR et al. 1998).

4.1.8 Anti-diarrheal effect

In several animal studies, the positive influence of glucocorticoids on various impaired ion transport systems have been demonstrated (HUA et al. 1999; SANDLE 1991; THIESEN et al. 1997). Budesonide increased bicarbonate biliary secretion in rat cholangiocytes and the activity of Na^+/H^+ pumps (ALVARO et al. 2000).

In humans, modulatory effects of glucocorticoids on secretory processes could be shown, too, e.g. an inhibition of mucosal eosinophil secretion in mucosal samples of patients with gastrointestinal allergy or ulcerative colitis (RAITHEL et al. 1999, 2001). Clinically, budesonide was applied successfully in patients with irinotecan and 5-FU induced diarrhea (LENFERS et al. 1999, REICHARDT 2004) and Crohn's disease patients with high ileostomal output

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after ileostomy (ECKER et al. 2003). In a controlled trial, budesonide showed a low preventive effect on irinotecan-induced diarrhea (KARTHAUS et al. 2003).

SCHEURLEN et al. (1993, 1998) discussed an increased number of colonic sodium pump sites as possible reason for the rapid improvement in diarrheal symptoms after local steroid treatment. BAJOR et al. (2003) showed in patients with collagenous colitis (CC) that the clinical effect of budesonide in CC may be linked to a reduced bile acid load of the colon, caused by an increased active absorption of bile acids.

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4.2 Pharmacokinetics

4.2.1 Analytical methods

The pharmacokinetic properties of budesonide were investigated in animal experiments, as well as in healthy volunteers, and in patients with Crohn's disease using a direct radioimmunoassay (RIA)-method and a more specific, selective high pressure liquid chromatography/RIA (HPLC/RIA)-method (AHERNE et al. 1982, MÖLLMANN et al. 1996b, RYRFELDT et al. 1979). While the RIA-method determines the total content of budesonide and its metabolites, the unmetabolized budesonide is ascertained by the HPLC/RIA-method. Comparable pharmacokinetic data were also obtained using a combination of liquid chromatography and mass spectroscopy (DIMOVA et al. 2003, LINDBERG et al. 1992).

4.2.2 Absorption, plasma concentrations and bioavailability

As compared to prednisolone in rats, budesonide was shown to be better absorbed into ileal tissue and better retained (50-fold) after topical application, resulting in a greater intestinal selectivity (MILLER-LARSSON et al. 2001). In man, budesonide is rapidly and nearly completely absorbed from the intestine after oral administration (MÖLLMANN & HOCHHAUS 1995, MÖLLMANN et al. 1996b, RYRFELDT et al. 1982).

The intestinal mucosa contains a number of transport proteins, of which especially the P-glycoprotein plays an important role in the bioavailability of glucocorticoids. Glucocorticoid resistance, which occurs in about 20% of Crohn's patients, may be explained by a polymorphism of the MDR-1 gene, which codes for the P-glycoprotein. It has recently been shown that budesonide is also a substrate of the P-glycoprotein. Hence P-glycoprotein, in addition to CYP 3A, plays a decisive role in the pharmacokinetics and pharmacodynamics of budesonide (DILGER 2004).

Analyzing the absorption of budesonide, the galenic formulation has to be considered. One has to distinguish between

- gastric soluble tablets with immediate budesonide release and
- pH-modified release from Budenofalk® 3mg capsules due to the Eudragit L coating which enables the budesonide release at the site of inflammation in patients with Crohn's disease.

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4.2.2.1 Pharmacokinetics of Budenofalk® 3mg capsules in healthy volunteers and Crohn's disease patients

In pharmacokinetic studies, gastric juice-soluble budesonide 3 mg **tablets** with immediate release (dose: 3 × 3 mg budesonide in 8-h-intervals) showed a rapid absorption and an immediate increase of budesonide plasma concentrations with T_{max}-values after about 1.5, 10 and 18 h (Figure 8, Table 2). In comparison, when Budenofalk® 3mg **capsules** with gastric juice-resistant pellets with a pH-modified budesonide release pattern were administered at daily budesonide doses of 3 × 1 mg, 3 × 2 mg or 3 × 3 mg, respectively, the budesonide release occurred with a lag time (t_{lag}) of 2–4 hours (Figure 9, Table 2). Under steady state conditions T_{max}-values occurred at about 5, 14 and 23 h after administration of 3 × 1 Budenofalk® 3mg **capsules** in healthy volunteers and in patients with Crohn's disease (Figures 9, 10; Table 2, MÖLLMANN & HOCHHAUS 1995, MÖLLMANN et al. 1996b, TROMM et al. 1993b).

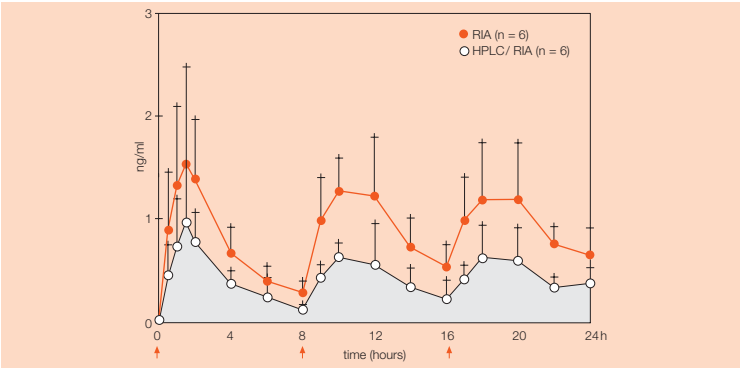

Figure 8: Concentration/time curve after oral administration of 3 × 3 mg budesonide in 8-h intervals (arrow-markings) in form of non-gastric juice resistant budesonide 3 mg **tablets**; determined by RIA and HPLC/RIA in healthy volunteers (MÖLLMANN et al. 1996b).

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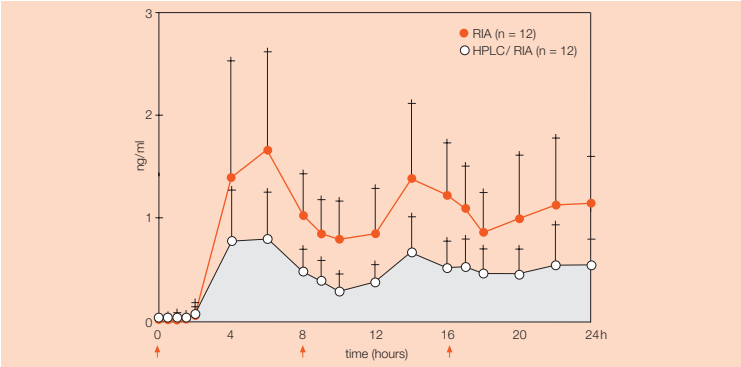

Figure 9: Concentration/time curve after oral administration of 3 × 3 mg budesonide in 8-h intervals (arrow-markings) in form of pH-modified budesonide release **capsules** (Budenofalk® 3mg capsules); determined by RIA and HPLC/RIA in healthy volunteers (MÖLLMANN et al. 1996b).

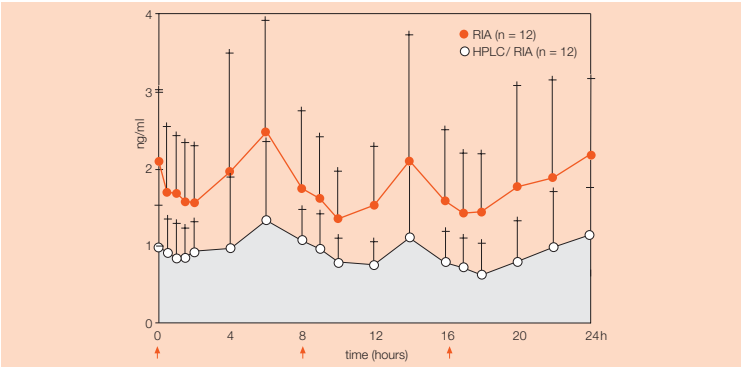

Figure 10: Concentration/time curve after oral administration of 3 × 3 mg budesonide in 8-h intervals (arrow-markings) in form of pH-modified budesonide release **capsules** (Budenofalk® 3mg capsules); determined by RIA and HPLC/RIA under steady state conditions in patients with Crohn's disease (MÖLLMANN et al. 1996b).

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T_{max}-values of budesonide 3 mg **tablets** with immediate release significantly differed from those of Budenofalk® 3mg **capsules** with pH-modified release, indicating the particular features of Budenofalk® 3mg **capsules** with regard to their specific topical use in acute Crohn's disease. The pharmacokinetic data determined by the HPLC/RIA-method are summarized in Table 2 for both, budesonide **tablets** and Budenofalk® 3mg **capsules**, after administration at 8-h intervals (MÖLLMANN et al. 1996b).

		Healthy volunteers				**Patients with Crohn's diseases at steady state**	
Parameters		**Budesonide 3×3 mg tablets (n = 6)**		**Budesonide 3×3 mg capsules (n = 12)**		**Budesonide 3×3 mg capsules (n = 12)**	
		MV	SD	MV	SD	MV	SD
$t_{1/2}$	[h]	1.5	0.71	2.6	1.3	4.33	2.13
k_e	[l/h]	0.45	0.20	0.33	0.16	0.18	0.06
MRT	[h]	3.4	1.3	7.9	2.3		
$AUC_{0-8\,h}$	[ng · h/ml]	3.05	1.46	3.64	1.80	8.04	5.48
$AUC_{8-16\,h}$	[ng · h/ml]	3.30	1.39	3.70	1.19	6.70	4.02
AUC_{16-24h}	[ng · h/ml]	3.56	1.62	3.97	2.08	6.34	4.32
AUC_{∞}	[ng · h/ml]	10.74	4.73	13.49	4.94		
AUC_{∞}/D	[ng · h/ml · mg]	1.19	0.53	1.50	0.55		
Cl/f	[l/min]	16.3	6.5	12.5	4.4	10.76	8.02
T-Lag	[h]	0.00	0.00	2.5	1.3		
$T_{max\,1}$	[h]	1.6	0.4	5.8	1.6	4.96	1.89
$T_{max\,2}$	[h]	10.2	1.0	14.7	1.5	14.45	1.63
$T_{max\,3}$	[h]	18.2	1.0	23.5	0.9	23.09	1.38
C_{max1}	[ng/ml]	1.07	0.55	1.03	0.45	1.55	1.09
C_{max2}	[ng/ml]	0.76	0.30	0.82	0.33	1.36	1.53
C_{max3}	[ng/ml]	0.73	0.32	0.70	0.38	1.39	1.12
C_{max1-3}/D	[ng/ml · mg]	0.28	0.12	0.29	0.09	0.50	0.45

MV = mean values; SD = standard deviations; k_e = elimination rate; MRT = mean residence time; AUC = area under the curve; D = dose; Cl/f = clearance total dose/AUC_{∞}; T-Lag = time-lag

Table 2: Pharmacokinetic data determined by the HPLC/RIA-method after administration of 3 × 3 mg budesonide in form of gastric-juice soluble **tablets** or pH-modified release **capsules** in 8-h intervals (MÖLLMANN et al. 1996b).

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The concentration/time curve after oral intake of 3 × 3 mg budesonide per day indicates that the daily dose of 9 mg budesonide should be administered to patients with Crohn's disease in three divided doses in order to achieve local concentrations at the intestinal mucosa as constant as possible, thereby warranting therapeutically acting drug levels for about 24 hours (DERENDORF et al. 1993, MÖLLMANN et al. 1996a, 1996b).

Pharmacokinetic parameters such as clearance (Cl/f), maximum plasma concentration (C_{max}), AUC values and half-life elimination ($t_{1/2}$), which were determined in healthy volunteers and patients with Crohn's disease, indicate a linear pharmacokinetic and a low systemic bioavailability of budesonide from pH-modified release capsules (Budenofalk® 3mg capsules). As the determined pharmacokinetic parameters and especially the maximum plasma concentrations after oral administration of Budenofalk® 3mg capsules (3 × 3 mg budesonide/day) to healthy volunteers and patients with Crohn's disease under permanent therapy (at steady-state conditions) did not differ, neither dose accumulation nor disease relevant changes of the pharmacokinetic characteristics of budesonide are expected, referring to absorption, distribution and elimination.

Therefore, the therapeutic aim of a disease adapted medication and an as low as possible systemic substance drain is achieved most likely with Budenofalk® 3mg capsules. These characteristics of Budenofalk® 3mg capsules with pH-modified substance release makes them highly suitable for safe and specific treatment of patients with acute Crohn's disease if the ileum and/or colon ascendens is concerned (MÖLLMANN et al. 1996b).

4.2.2.2 Influence of food intake on the pharmacokinetics of Budenofalk® 3mg capsules

The simultaneous intake of the Budenofalk® 3mg capsules with food results in a time delay of t_{max} of approximately 2–3 hrs (Figure 11). This effect, also found for other pellet formulations (HARDY et al. 1991), is probably due to the delayed passage from stomach induced by food.

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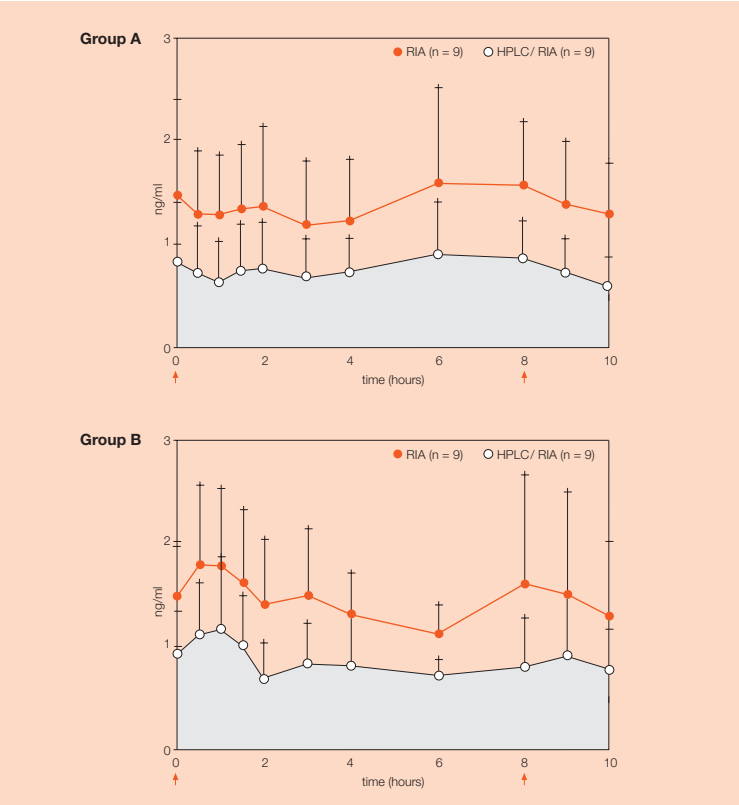

Figure 11: The mean serum concentrations (± standard deviations) of budesonide at steady state (RIA- and HPLC/RIA-results) after application of 3 × 1 Budenofalk® 3mg capsule (= 9 mg budesonide) daily show the delay of t_{max} in ileostomy patients with simultaneous intake of food (group B) compared to patients with fasting administration (group A). The arrows show the intake of Budenofalk® 3mg capsules on day 8.

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4.2.2.3 Distribution of budesonide in the intestine

In a pharmacokinetic/pharmacodynamic study in ileostomy patients, it was shown under steady-state conditions that substantial amounts of unchanged substance from the Budenofalk® 3mg capsules reached the distal intestinal segments, and thus the site of inflammation in patients with Crohn's disease (MÖLLMANN et al. 1995).

In this open, parallel group study with crossover design, 18 ileostomy patients were enrolled who were in remission or had mild disease activity. They randomly received either fasting (n = 9) or during daily meals (n = 9) one of the Budenofalk® 3mg capsules three times daily in 8-h intervals for 7 days. 25 to 37% of the total dose could be recovered as unchanged budesonide in the ileostoma bag using RIA and HPLC/RIA. Therefore, this part of substance was not absorbed until then and thus is available to act in the colon. The concentrations of budesonide determined in both treatment groups are considered adequate to saturate completely the receptors at the site of action and thus to induce the maximum of possible effects at the site of inflammation in patients with Crohn's disease.

The pharmacokinetics of Budenofalk® 3mg capsules were very similar in this patient group to the pharmacokinetic parameters determined in patients with Crohn's disease, and the bioavailability did not differ significantly. Thus, especially the results regarding the drug concentration at the site of inflammation may be related to the treatment of patients with Crohn's disease (MÖLLMANN et al. 1995). PEÑA et al. (2004) found reasonable concentrations of budesonide after application of 3 × 3 mg budesonide or 1 × 9 mg budesonide (Budenofalk® 3mg capsules) even in the rectal mucosa of patients with ulcerative colitis.

4.2.2.4 Divided doses vs. single dose application

The concentration/time curve after oral doses of 3 × 3 mg budesonide per day indicates that the daily dose of 9 mg budesonide should be administered to patients with Crohn's disease in three divided doses in order to achieve local concentrations at the intestinal mucosa as constant as possible, thereby warranting therapeutically acting drug levels for about 24 hours (DERENDORF

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et al.1993, MÖLLMANN et al. 1996a, 1996b). Therefore, studies in Crohn's disease patients were performed with divided doses of Budenofalk® 3mg capsules.

However, KOLKMAN et al. (2004) and PEÑA et al. (2004) studied the differences between a divided dose of 3 × 3 mg budesonide (Budenofalk® 3 mg capsules, n = 8) and a single dose of 1 × 9 mg daily (n = 7) in patients with mild to moderately active left-sided ulcerative colitis (UC). Under steady state conditions they found higher budesonide serum concentrations after administration of 1 × 9 mg of budesonide. Though under both dosage regimes local concentrations of budesonide in the intestinal mucosa were reasonable in the sigmoid and even in the rectum. In this pilot trial the efficacy of a single daily dose of 9 mg was better than a divided dose of 3 × 3 mg budesonide daily.

4.2.3 Distribution and binding

For budesonide, a distribution volume of about 300 l (2–4 l/kg BW) was determined from pharmacokinetic studies in healthy volunteers. This high distribution volume, compared to other glucocorticoids (prednisolone = 30–44 l; methylprednisolone = 1–1.5 l/kg BW; hydrocortisone = 0.3–0.7 l/kg BW; triamcinolone = 99.5–148 l/kg BW), indicates a high tissue affinity and binding. According to in vitro investigations, about 90% of the absorbed budesonide binds to plasma proteins, especially to albumin (RYRFELDT et al. 1982).

4.2.4 Metabolism and elimination

Budesonide is predominantly metabolized in the liver. After oral administration, approximately 90% of the absorbed drug undergoes an extensive first-pass metabolism, which is responsible for the low systemic bioavailability of only 10–11% (DAHLBERG et al. 1984, EDSBÄCKER et al. 1983, MÖLLMANN et al. 1996a, RYRFELDT et al. 1982). In the pharmacokinetic studies on oral budesonide formulations, bioavailability of budesonide was also 10–11% for all formulations and dosages used in these studies (MÖLLMANN et al. 1996b).

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16α-hydroxyprednisolone and 6β-hydroxybudesonide (Figure 12) arise as the major metabolites of this biotransformation by isoenzymes of the cytochrome-P450 system in the liver. They have a very low receptor affinity and they are pharmacologically nearly inactive (JÖNSSON et al. 1995, MÖLLMANN et al. 1996a, RYRFELDT et al. 1982).

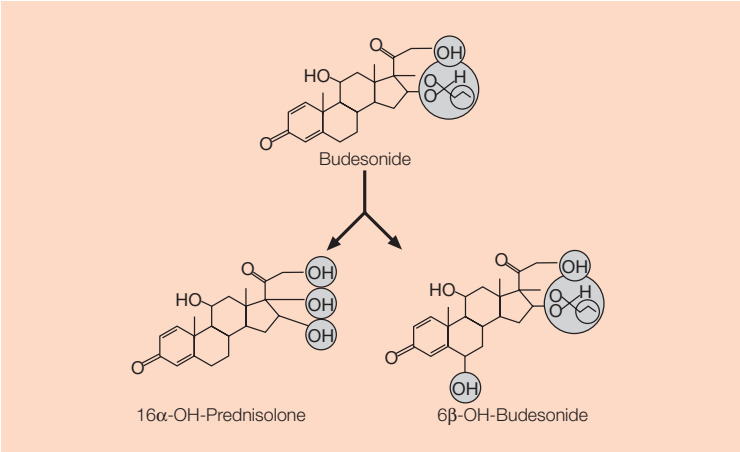

Figure 12: Biotransformation of budesonide to 16α-hydroxyprednisolone and 6β-hydroxy-budesonide in the liver.

According to the results of a pharmacokinetic study, budesonide has a relatively short elimination half-life of about 2 h and a high plasma clearance of 83.7 l/h which illustrate the rapid systemic elimination of budesonide (RYRFELDT et al. 1982).

The recovery rate of budesonide after oral administration to healthy volunteers was 45% in urine and 29.6% in feces in the first 96 hours (RYRFELDT et al. 1982).

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Investigations for the elimination rate of budesonide from Budenofalk® 3mg **capsules** showed a mean elimination rate of 0.33 ± 0.16 l/h, following oral administration of 3 × 3 mg budesonide/day. The elimination half-life, calculated from these values, is 2.6 ± 1.3 h; the mean residence time is 7.9 ± 2.3 h.

A markedly lower mean residence time of 3.4 h was obtained for budesonide **tablets**, which is related to the immediate release of budesonide from the tablets. In addition, the release of budesonide is delayed by 2 to 4 hours from the Budenofalk® 3mg **capsules** and its longer residence time indicate that the pellets, incorporated in the hard capsules, reach the terminal ileum and the colon (MÖLLMANN et al. 1996b).

In patients with liver diseases, as e.g. primary biliary cirrhosis (PBC), the stage of the disease should be considered. Plasma clearance of budesonide may be markedly decreased in late stage PBC with an increased risk of portal vein thrombosis (GRÜNHAGE et al. 2002, HEMPFLING et al. 2003). Comparing patients in PBC stage I/II ($n = 12$) and those in stage IV ($n = 7$), patients in stage IV showed significantly higher peak plasma concentrations ($p < 0.05$) and area under the curve ($p < 0.01$) after a single dose of 3 mg budesonide. The same was true at steady state conditions after 3 weeks of treatment. The higher levels of budesonide in PBC stage IV patients lead to a significant decrease in plasma cortisol and reduction of urinary cortisol excretion. Two patients developed portal vein thrombosis (PVT).

Also in patients with severe autoimmune hepatitis in the cirrhotic stage (Child A), budesonide is metabolized to less degree (GEIER et al. 2003, SCHÜLER et al. 1995a, 1995b).

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5 Toxicology

5.1 Acute toxicity

Budesonide has a low acute toxicity comparable to that of the reference corticoids beclomethasone dipropionate and fluocinolone acetonide. Following oral administration to mice and rats, the LD_{50} of budesonide was > 800 mg/kg BW or > 400 mg/kg BW, respectively, and was 35–100 mg/kg BW or 15 mg/kg BW, respectively, following subcutaneous administration (RICHTER 1992).

5.2 Subchronic toxicity

Determining the subchronic toxicity, significant systemic effects were observed in mice after oral administration of the high dose of 700 µg/kg BW which disappeared following a dose reduction to 200 µg/kg BW. But this dose was still toxic to rats. The non-toxic dose in rats was less than 50 µg/kg BW (RICHTER 1992).

5.3 Chronic toxicity

Following subcutaneous application, a dose of 5 µg budesonide/kg BW was shown to be the non-toxic range in chronic toxicity test in rats. No effects occurred at a dose of 0.1 µg/kg BW (RICHTER 1992). After a long-term treatment with budesonide at daily doses of 10, 50 and 200 µg/kg BW, a reduction of survival was observed in male rats, but no signs of carcinogenicity were observed. The addition of 50 µg budesonide/kg BW per day to the drinking-water resulted in an increased rate of hepatic tumors in rats, as known for other glucocorticoids. This indicates a typical species-specific as well as a substance group-specific effect. There is no evidence that high doses of budesonide may induce tumors in human (RYRFELDT et al. 1992).

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5.4 Local effect and tolerability

Topical applications of budesonide ointment and cream on intact or abraded skin of rabbits or pigs (the latter in comparison to fluocinolone acetonide or placebo) showed only weak reddenings, especially on abraded skin. The difference to intact skin was significant. During the search of possible contact hypersensibilization (guinea pig maximizing test), neither budesonide nor placebo nor the reference steroids hydrocortisone and fluocinolone acetonide showed a delayed contact hypersensibilization. After extended studies on 300 healthy volunteers, the conclusion is drawn that neither budesonide ointment nor budesonide cream had skin irritating or light sensibilizing effects.

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5.5 Teratogenicity

Subcutaneously applied doses of budesonide larger than 100 µg/kg BW are considered teratogenic in rats, but concentrations below 20 µg/kg BW are considered non-teratogenic. Compared to the reference glucocorticoid triamcinolone acetonide, budesonide was shown to be less fetotoxic and teratogenic.

During the breeding period or during pregnancy of rats and rabbits, budesonide caused a reduction of the conception rate and an increase of fetal losses and malformations at subcutaneous administration of the substance at daily doses of 20 or 80 µg/kg BW. However, such systemic effect of budesonide is unlikely at a topical use in the gut due to its high first-pass metabolism as well as due to the essentially lower therapeutic dose in human.

In rabbits, even the lowest dose of 5 µg/kg BW, administered subcutaneously, was shown to be teratogenic. However, a comparison with the reference glucocorticoid fluocinolone acetonide was not possible in this case, because even the lowest dose of this substance resulted in a spontaneous abortion at the end of the pregnancy period (KIHLSTRÖM & LUNDBERG 1987, RICHTER 1992).

Investigations of fertility and general reproduction characteristics have shown that the lowest budesonide dose of 5 µg/kg BW did not affect the prenatal viability or the viability of the offspring at delivery or during lactation. However, at medium doses (20 µg/kg BW) and higher doses (80 µg/kg BW) marked effects were observed which were similarly observed in a dose-dependent manner for the peri- and postnatal development of the rats (RICHTER 1992). In pregnant rats, a decrease of food intake and a dose-dependent reduction of body weight were observed under budesonide. Also the offspring showed a reduced birth-weight due to intrauterine growth retardation. Fetal malformations occurred at a dose of 25.8 µg/kg BW. Skeletal anomalies such as retarded ossification of the cranium and spinal column (KIHLSTRÖM & LUNDBERG 1987) have decisively been observed.

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5.6 Mutagenicity

There was no evidence of mutagenic potential of budesonide, investigated in different standard tests on the mutagenicity (Ames® test, micronucleus test in mice, sex-linked recessive lethal test in *Drosophila melanogaster*, and chromosomal aberration test in human lymphocytes).

5.7 Cancerogenic effect

The addition of 50 µg/kg budesonide per day to the drinking-water of rats resulted in an increased rate of hepatic tumors, as known for other glucocorticoids (species-specific and substance group-specific effect; RYRFELDT et al. 1992).

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6 Clinical experience

in acute Crohn's disease with involvement of the ileum and/or ascending colon

The treatment of inflammatory bowel diseases with glucocorticoids such as budesonide is therapeutic standard nowadays and summarized by GOMOLLÓN et al. (1999), KANE et al. (2002), PAPI et al. (2000), SANDBORN & FEAGAN (2003). In these indications, the predominant topical and low systemic activity of budesonide is a special advantage.

Topical treatment with glucocorticoids in suppositories, enemas or foam preparations is only possible if the distal bowel parts are inflamed. Upper bowel regions cannot be reached with suppositories, enema or foam preparations. Therefore, the development of oral gastric juice-resistant preparations offers new therapeutic opportunities. Various studies on the non-halogenated corticoid budesonide with a low systemic effect in patients with Crohn's disease are summarized in several reviews (PAPI et al. 2000, KANE et al. 2002, YANG & LICHTENSTEIN 2002).

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6.1 Open, uncontrolled studies

6.1.1 Pilot study

In a first pilot study, Budenofalk® 3mg capsules were initially administered for 6 weeks at a dosage of 3 × 3 mg budesonide/day in 9 patients with active Crohn's disease (CDAI > 200 and duration of disease after diagnosis > 6 months). The mean duration of disease after primary diagnosis was 7.2 years. Two of these patients had a resection of the terminal ileum. All 9 patients responded well to the study medication, and the mean CDAI (BEST et al. 1976, 1979) significantly decreased in the course of treatment (Table 3).

Duration of therapy	CDAI	Number of patients
Beginning	278 ± 63	9
after 2 weeks	114 ± 109	9
after 4 weeks	96 ± 94	9
after 6 weeks	28 ± 42	6

Table 3: Decrease of disease activity (CDAI) during therapy with Budenofalk® 3mg capsules in the course of the study.

Three patients had to stop therapy in the sixth week due to high fever with arthritis and erythema nodosum, abscess with simultaneous development of conglomerate tumor, or development of a conglomerate tumor, respectively. In another patient, the treatment was stopped after termination of the pilot study due to primary manifestation of gastric Crohn's disease. In the remaining 5 patients, the therapy was continued for further 6 weeks at a reduced dose (3 × 2 mg pH-modified release 1 mg budesonide capsules per day), without recurrence of an acute attack. Two of these patients still received 3 × 1 capsule of 1 mg budesonide per day for further 12 weeks. No relapse was observed. Only in one patient a slight buffalo hump developed (ROTH et al. 1993).

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6.1.2 Multicentric clinical studies

In an open clinical trial, 81 patients with active Crohn's disease, including patients with involvement of the distal colon and rectum, received 3 × 3 mg budesonide/day as Budenofalk® 3mg capsules for 6 weeks. Subsequently, the therapy was continued in 35 of the patients for further 6 weeks with 3 × 2 mg budesonide (pH-modified release 1 mg capsules).

An initial induction of remission was found in 54.3% of the patients. Patients with a CDAI-baseline of < 300 did respond to therapy in a distinctly higher part (61%) than patients with a baseline of ≥ 300 (36.4%). 71.4% of participating patients furtheron remained in remission during the subsequent treatment period with 3 × 2 mg budesonide (pH-modified release 1 mg capsules). The percentage was very similar in the two subgroups (Table 4) (ANDUS et al. 1994, CAESAR et al. 1995, 1997c).

Therapeutic schedule	**3×3 mg budesonide for 6 weeks**	**3×2 mg budesonide for further 6 weeks**
Total		
Patients (n)	n = 81	n = 35
Remission rate (%)	54,3 %	71,4 %
CDAI ≥ 300		
Patients (n)	n = 22	n = 7
Remission rate (%)	36,4 %	71,4 %
CDAI < 300		
Patients (n)	n = 59	n = 28
Remission rate (%)	61,0 %	71,4 %

Table 4: Remission rates in patients with active Crohn's disease under therapy with oral budesonide (Budenofalk® 3mg capsules and pH-modified release 1 mg capsules).

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6.2 Dose-finding for the use of Budenofalk® 3mg capsules in active Crohn's disease

In the clinical studies on active treatment of Crohn's disease described till now, a dosage of 3 × 1 Budenofalk® 3mg capsule per day (= 9 mg budesonide) was used. Budenofalk® 3mg capsules were shown to be as effective as 6-methylprednisolone (GROSS et al. 1996) or prednisone (BAR-MEIR et al. 1998) at this dosage. The rates of therapeutic success achieved by Budenofalk® 3mg capsules corresponded to those achieved with another formulation of budesonide with modified delivery at the same daily dose (CAMPIERI et al. 1997, GREENBERG et al. 1994, RUTGEERTS et al. 1994). Patients with involvement of the distal colon and rectum were also included in the study with Budenofalk® 3mg capsules (see also Figure 17 in section 6.4). However, this indication is not licensed till now.

In a three-armed, randomized, double-blind, multicentric, parallel group study, the daily dose of 9 mg budesonide was investigated in comparison with 6 mg and 18 mg in a total of 318 patients with active Crohn's disease without steroid pretreatment (stratum 1) or in steroid-dependent patients with active or postactive Crohn's disease with steroid pretreatment (stratum 2) (CAESAR et al. 1996, 1997a, SCHÖLMERICH 1997, HERFARTH et al. 2004). Patients with involvement of the terminal ileum as well as patients with ileocolitis and involvement of the distal colon, were taken into account for inclusion into both strata in this study, too.

The patients randomly received 3 × 2 mg (6 mg) pH-modified release 1 mg capsules, or 3 × 3 mg (9 mg) or 3 × 6 mg (18 mg) budesonide daily in form of Budenofalk® 3mg capsules for 12 weeks. 6 mg per day were chosen as the lowest dose because, on the one hand, a daily dose of 3 mg for acute treatment of Crohn's disease had been shown to be not more effective than placebo (GREENBERG et al. 1994) and, on the other hand, no satisfactory therapeutic results could be achieved by this dose in the relapse prophylaxis, too (GROSS et al. 1998, LÖFBERG et al. 1994, SCHÖLMERICH & ANDUS 1995).

The main objective of this dose-finding study was to achieve remission in patients with active Crohn's disease (stratum 1) or to shift patients with active or postactive Crohn's disease from a treatment with systemically acting glucocorticoids to the locally acting budesonide (stratum 2). The main target parameter was the response rate after 6-weeks monotherapy with

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Budenofalk® 3mg capsules. Responders were defined as patients with a CDAI < 150, and non-responders as patients with discontinuation of therapy before the 2nd follow-up after 6 weeks, or with a CDAI ≥ 150 at the 2nd follow-up, respectively. A further aspect was the tolerability, especially the incidence of steroid-induced side effects.

The response rates after 6-weeks therapy with pH-modified release 1 mg budesonide capsules and Budenofalk® 3mg capsules (Table 5) and the course of CDAI in patients of stratum 1 (Table 6), are summarized in the following tables.

Analysis	**Budesonide 6 mg/d (3×2 mg)**	**Budesonide 9 mg/d (3×3 mg)**	**Budesonide 18 mg/d (3×6 mg)**
Intention-to-treat (n = 310)	46.7 %	55.6 %	63.2 %
Per-protocol (n = 238)	43.5 %	57.8 %	65.9 %

Table 5: Response rates in patients with Crohn's disease after 6-weeks therapy with pH-modified release 1 mg capsules and Budenofalk® 3mg capsules at three different dose schedules.

	Budesonide 6 mg/d (3×2 mg) (n = 39)			**Budesonide 9 mg/d (3×3 mg) (n = 33)**			**Budesonide 18 mg/d (3×6 mg) (n = 32)**		
Course of CDAI	I	II	Δ	I	II	Δ	I	II	Δ
	257.2	202.2	55.0	267.8	139.8	128.0	238.5	115.9	122.6

Δ = mean decrease of CDAI

Table 6: Decrease of mean CDAI in patients with active Crohn's disease in stratum 1 (without steroid pretreatment) from the beginning of the study (I) to the 2nd follow-up after 6 weeks (II) under treatment with pH-modified release 1 mg capsules and Budenofalk® 3mg capsules in three different dose schedules (intention-to-treat analysis).

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The results show a dose-dependent effect in the three treatment groups. The response rate using 9 mg budesonide per day corresponds to the results of previous budesonide studies, and is distinctly higher than using 6 mg/day. At 18 mg/day, a further increase of the response rate could be achieved, but the difference between 9 and 18 mg/day was smaller than that between 6 and 9 mg/day. However, it seems to be essential that the CDAI could be decreased in both groups for about the same number of points (128 or 122.6 points, respectively) to CDAI values of 139.8 or 115.9, respectively, thus remaining under the limiting value of 150 points (Table 6). In the group with 6 mg/day, the CDAI only decreased by an average of 55 points to 202.2, thereby distinctly remaining above the limiting value of 150 points.

Particularities with regard to severity, duration and localization, as well as the presence of extraintestinal manifestations were shown by a subgroup analysis as can be seen from Table 7.

The results of the subgroup analysis show the following therapeutic particularities with regard to treatment effects with budesonide pH-modified release capsules at different dosages:

- For patients in stratum 1 with exclusive localization of the inflammation in the ileum and/or cecum/colon ascendens, the highest response rates of 60 or 59%, respectively, were reached in the groups with 9 and 18 mg/day compared to only 30% in the group with 6 mg/day. Although, the patients with distal affection of the colon showed a higher response rate under therapy with 18 mg/day (73%) than the group with 9 mg/day (46%), a combined analysis of this study and previous studies (see section 6.4) on Budenofalk® 3mg capsules showed that also patients with distal affection can be treated successfully with 9 mg/day.
- The response rate of patients with an active state of Crohn's disease distinctively depends on the presence of extraintestinal manifestations according to the results of this trial. Almost no dose dependent response between the dose of 6 and 18 mg budesonide/day (6 mg: 46%; 9 mg: 50%; 18 mg: 50%) was shown for patients without extraintestinal manifestations, whereas for patients with the presence of at least one extraintestinal manifestation the response was dose dependent: 24% at the dose of 6 mg/day; 58% at the dose of 9 mg/day and 73% at the dose of 18 mg/day.

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Subgroup	Budesonide 6 mg/d	Budesonide 9 mg/d	Budesonide 18 mg/d
Stratum 1	36 % (n = 39)	55 % (n = 33)	66 % (n = 32)
Stratum 2	53 % (n = 66)	56 % (n = 66)	62 % (n = 74)
Disease duration ≥ 8 years	46 % (n = 46)	52 % (n = 48)	59 % (n = 49)
Disease duration < 8 years	51 % (n = 55)	60 % (n = 48)	67 % (n = 55)
Severity of Crohn's disease at baseline of study			
CDAI ≥ 300	0 % (n = 12)	24 % (n = 17)	42 % (n = 12)
150 ≤ CDAI < 300	46 % (n = 52)	54 % (n = 41)	60 % (n = 50)
only localized at ileum and/or cecum/colon ascendens	51 % (n = 55)	71 % (n = 51)	60 % (n = 53)
localized at colon transv. up to sigma and/or rectum, anus	38 % (n = 47)	40 % (n = 48)	66 % (n = 53)
Stratum 1:			
only localized at ileum and/or cecum/colon ascendens	30 % (n = 20)	60 % (n = 20)	59 % (n = 17)
localized at colon transv. up to sigma and/or rectum, anus	31 % (n = 16)	46 % (n = 13)	73 % (n = 15)
Stratum 1:			
Patients with at least one extraintestinal manifestation at baseline	24 % (n = 17)	58 % (n = 19)	73 % (n = 22)
Patients without extraintestinal manifestation at baseline	46 % (n = 22)	50 % (n = 14)	50 % (n = 10)
Stratum 2:			
CDAI ≥ 150 at baseline	40 % (n = 25)	32 % (n = 25)	47 % (n = 30)
CDAI < 150 at baseline	63 % (n = 40)	71 % (n = 41)	73 % (n = 44)

Table 7: Results of a subgroup analysis with regard to the response rates after 6-weeks therapy with pH-modified release 1 mg capsules or Budenofalk® 3mg capsules at different dosages in patients with Crohn's disease (intention-to-treat analysis).

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In this context it is remarkable that at doses of 9 mg/day and at higher doses the response rate of patients with extraintestinal manifestations seems to be better as for patients without any extraintestinal manifestations. This result is also proved by additional studies (see Table 8).

- In the patients with steroid pretreatment (stratum 2), being in remission at the start of the study, remission could be maintained in more than 70% of cases during the therapy with Budenofalk® 3mg capsules both, with 9 mg/day and 18 mg/day. Because the time until a relapse was also comparable in both groups (39 vs. 34 days), a dose of 9 mg/day is probably adequate for maintenance of remission following the change from systemic steroids to Budenofalk® 3mg capsules (still not licensed indication at present).
- The severity of disease at the beginning of therapy decisively influences the therapeutic success. Patients with Crohn's disease with involvement of the ileum and/or ascending colon and with a CDAI between 150 and 300 may be successfully treated with Budenofalk® 3mg capsules at a dose of 3 × 3 mg budesonide per day (= 9 mg budesonide/day). However, in patients with a CDAI ≥ 300 at the beginning of the study, the response rate was distinctly lower. 42% of these patients could be maintained in remission with 18 mg budesonide per day given as Budenofalk® 3mg capsules. In addition, the response rate was the highest under 18 mg/day in patients with a disease history longer than 8 years.

The conclusion of this dose-finding study on Budenofalk® 3mg capsules in the treatment of patients with active or postactive Crohn's disease with regard to the ratio of desired therapeutic effects to adverse events is:

- A daily dose of 6 mg budesonide is not adequately effective, neither for the treatment of acute Crohn's disease nor for maintenance of remission.
- 3 × 3 mg/day pH-modified release budesonide per day is the optimal dose to treat patients with moderately active Crohn's disease confined to the ileum and right colon. However, in patients with higher disease activity or disease affecting the transverse colon to the rectum 3 × 6 mg budesonide per day might be more effective during the first 6 weeks of therapy. However, this daily dose is not licensed till now.

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- A daily dose of 9 mg budesonide (3 × 1 Budenofalk® 3mg capsule) is very effective in the treatment of acute Crohn's disease with involvement of the ileum and/or ascending colon and postactive Crohn's disease (not yet licensed), and yields the best benefit/risk ratio among the dosages which have been evaluated. A dose of 9 mg budesonide/day is sufficient in patients with postactive Crohn's disease in order to change successfully from a therapy with conventional, systemically acting steroids. Thus, 3 × 3 mg budesonide (Budenofalk® 3mg capsules) per day represents the optimal dose in the treatment of acute Crohn's disease with involvement of the ileum and/or ascending colon (HERFARTH et al. 2004).

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6.3 Comparison of Budenofalk® 3mg capsules with 6-methylprednisolone and prednisone

In a comparative clinical study in 67 patients with active Crohn's disease, the efficacy and the rate of side effects of Budenofalk® 3mg capsules (n = 34) were compared with 6-methylprednisolone (n = 33). Patients with a CDAI > 150 were included in the study. Patients with involvement of the distal colon and the rectum (indications not licensed till now) were not excluded from this study. The primary aim of the study was to achieve remission of Crohn's disease (CDAI < 150), or to decrease the CDAI by at least 60 points in course of the 8-weeks treatment. The patients orally received either 3 × 1 Budenofalk® 3mg capsule per day or 6-methylprednisolone, according to the established weekly schedule of reduction 48-32-24-20-16-12-8 mg per day.

At the end of the 8-weeks treatment period, 55.9% of patients of the budesonide group and 72.9% of patients of the 6-methylprednisolone group were in remission. The difference between the groups was statistically not significant (Figure 13).

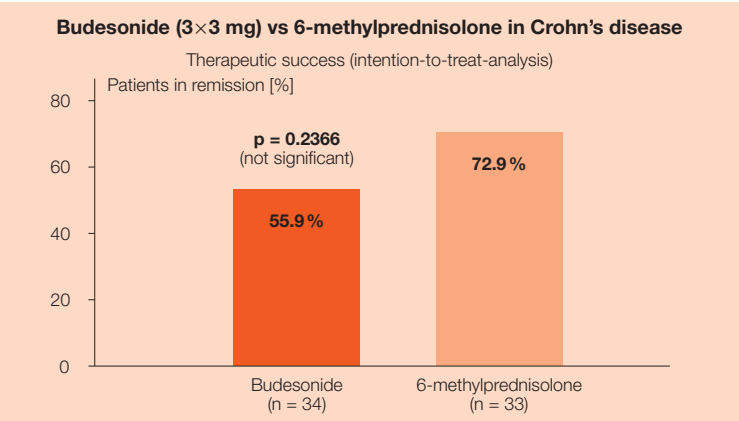

Figure 13: Remission rate after 8-weeks administration of Budenofalk® 3mg capsules or 6-methylprednisolone in patients with active Crohn's disease (GROSS et al. 1996).

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An analysis of remission rates showed comparable response rates for the two treatment groups, independent of the localization of Crohn's disease or the presence of extraintestinal manifestations. In both groups, the remission rates tended to be higher in patients with a baseline CDAI < 300 than in patients with highly active disease (CDAI ≥ 300) (Table 8).

Budesonide (3×3 mg) vs 6-methylprednisolone in Crohn's disease

Factors of response rate		Budesonide n (%)	6-methylprednisolone n (%)
Total		**34 (100 %)**	**33 (100 %)**
Localization			
only ileum and/or cecum and/or colon ascendens		4 out of 6 (67 %)	10 out of 13 (77 %)
colon transversum and/or colon descendens and/or sigma and/or rectum		15 out of 25 (60 %)	14 out of 20 (70 %)
Extraintestinal manifestations	**yes**	11 out of 18 (61 %)	11 out of 14 (79 %)
	no	8 out of 16 (50 %)	13 out of 19 (69 %)
CDAI	**≥ 300**	4 out of 10 (40 %)	6 out of 10 (60 %)
	< 300	15 out of 24 (63 %)	18 out of 23 (78 %)

Table 8: Analysis of remission rates according to the parameters localization and extraintestinal manifestation of Crohn's disease under treatment with Budenofalk® 3mg capsules or 6-methylprednisolone (GROSS et al. 1996).

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In the budesonide group, the total rate of adverse events was 60.0% compared to 81.8% in the 6-methylprednisolone group (no significant difference; Figure 14). But regarding the steroid-typical side effects, there was a highly significant difference between the two groups (p = 0.0015): Budenofalk® 3mg capsules only 28.6% compared to 6-methylprednisolone at 69.7% (GROSS et al. 1996) (see also section 9.5).

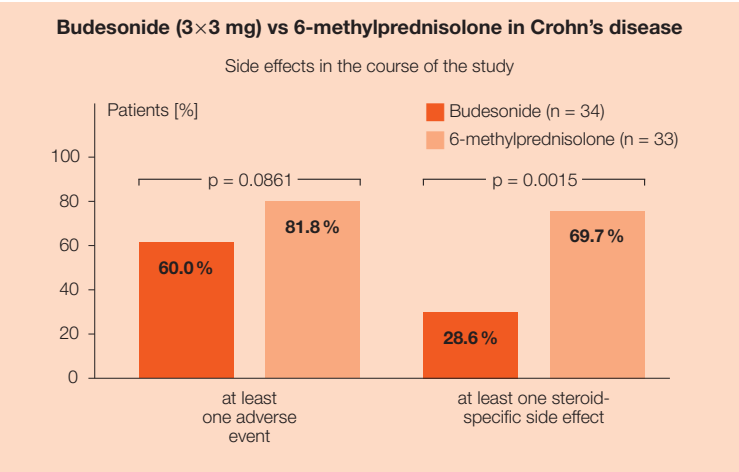

Figure 14: Total rate of adverse events and glucocorticoid specific side effects after a 8-weeks treatment course with Budenofalk® 3mg capsules or 6-methylprednisolone in patients with active Crohn's disease (GROSS et al. 1996).

In an additional double-blinded, controlled, randomized, comparative, multi-centre study, the efficacy and tolerability of orally administered budesonide (Budenofalk® 3mg capsules) was compared with prednisone in 201 patients with active Crohn's disease, using a double-dummy technique (BAR-MEIR et al. 1998).

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The patients randomly received either 3 × 1 capsule containing 3 mg budesonide distributed over the day (n = 100) or initially 8 tablets containing 5 mg prednisone daily as a single morning dose (n = 101) for 8 weeks. The daily dose of prednisone was continuously reduced during the treatment period to 1 × 5 mg at week 8. In order to maintain the double-blind design of the study, the patients received a corresponding placebo medication of prednisone tablets or budesonide capsules, respectively, in addition to their verum medication, using a double-dummy technique.

Every 2 weeks and after termination of the study (after week 8), a control examination was conducted, including the documentation with regard to changes in clinical profile, a physical examination, including steroid-type adverse reactions, blood and urine tests as well as a calculation of CDAI (Crohn's Disease Activity Index) according to Best (BEST et al. 1976, 1979). In addition, quality of life questionnaires were collected after termination of the study which had been issued after week 6.

The treatment effect on the total score of CDAI, calculated from 8 single items (BEST et al. 1979), was considered to be the primary efficacy parameter. All patients with a CDAI < 150 at the end of the study and in whom, in case of a baseline CDAI < 210, the decrease of CDAI was ≥ 60 points were defined as responders. Responders, fulfilling these criteria without occurrence of steroid-induced adverse reactions, were defined as R1-responders. Patients, fulfilling these criteria associated with the occurrence of at least one steroid-induced adverse reaction, were defined as R2-responders. All patients, being either R1-responders or R2-responders, were allocated to the group R0 which thus included all patients with a successful treatment, whether a steroid-induced adverse event had occurred or not.

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Figure 15 shows the development of the total CDAI-score during the course of the study in patients treated with either budesonide or prednisone.

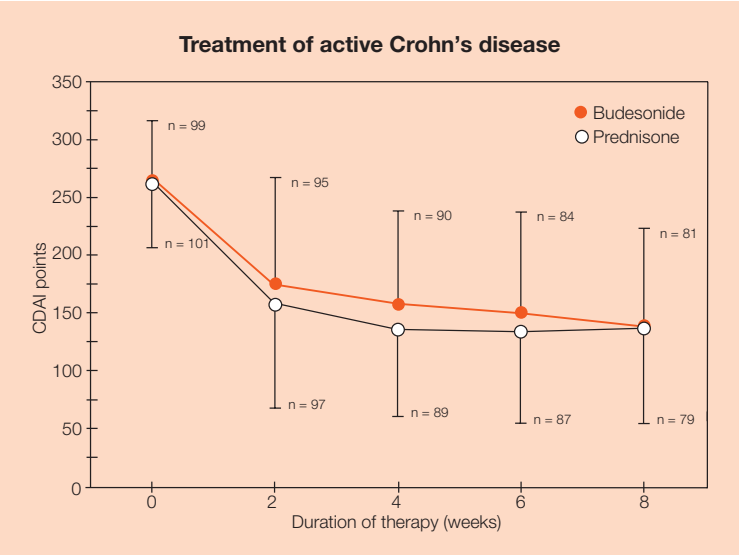

Figure 15: Therapy of active Crohn's disease with 3 × 3 mg budesonide or prednisone for 8 weeks (BAR-MEIR et al. 1998).

After termination of the study, the overall responder rate (R0) was slightly, but statistically insignificantly higher in the prednisone group (52.5%) than in the budesonide group (51%) (Figure 16).

The rate of R1-responders, i.e. patients with complete remission without occurrence of steroid-specific adverse events, was significantly higher in the budesonide group (30.0%) than in the prednisone group (13.9%) (Figure 16).

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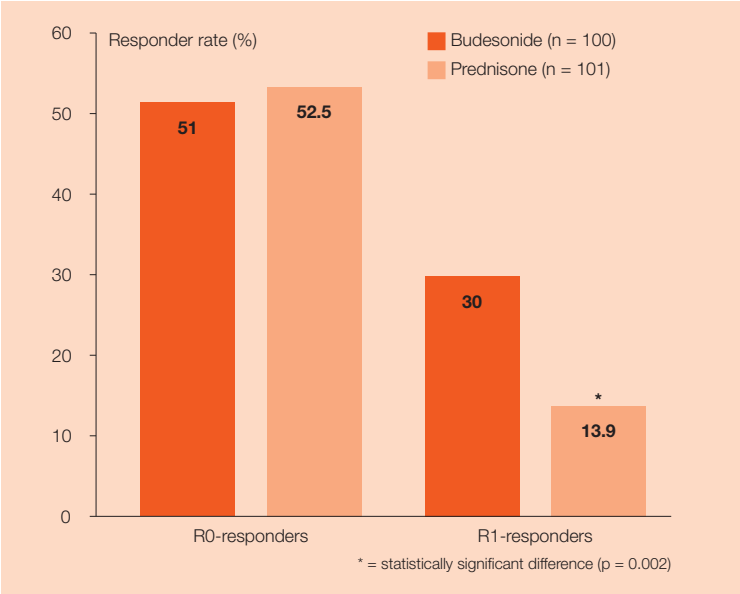

Figure 16: Responder rates after 8 weeks oral treatment of 201 patients with active Crohn's disease with Budenofalk® 3mg capsules (n = 100) or prednisone tablets (n = 101). R0-responders = total number of patients being in remission after 8 weeks, whether a steroid-specific adverse event had occurred or not. R1-responders = number of patients being in remission after 8 weeks without occurrence of steroid-specific adverse events in course of the study (BAR-MEIR et al. 1998).

The mean period until reaching a CDAI < 150, was 24 ± 13.2 days in the budesonide group and was 21 ± 11.7 days in the prednisone group. The number of patients reaching this CDAI-value within the first two study weeks, was markedly higher in the prednisone group (40 patients) than in the budesonide group (28 patients).

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The overall study results with regard to improvement of CDAI showed an efficacy of budesonide comparable to that of prednisone. Regarding the occurrence of important steroid type adverse events (in particular moon face and steroid acne), a prominent advantage in favour of budesonide could be shown. That is also valid for the overall safety profile of budesonide with regard to the overall rate of adverse events and changes of laboratory parameters.

Similar to the already mentioned studies, the response rate of patients with extraintestinal manifestations tend to be higher (54.5%; n = 12) at the dose of 3 × 3 mg budesonide/day compared to the response rate of patients without extraintestinal manifestations (50%; n = 39).

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6.4 Remission rates of acute Crohn's disease treated with Budenofalk® 3mg capsules

The combined analysis of remission rates from 4 clinical studies, in which patients with active Crohn's disease were treated with 3 × 1 Budenofalk® 3mg capsule per day, showed comparable response rates regarding the localization of Crohn's disease and the occurrence of extraintestinal manifestations in subgroups (Figures 17 and 18). Regarding localization of Crohn's disease, only the small group with disease affecting the upper gastrointestinal tract obviously showed a lower response rate.

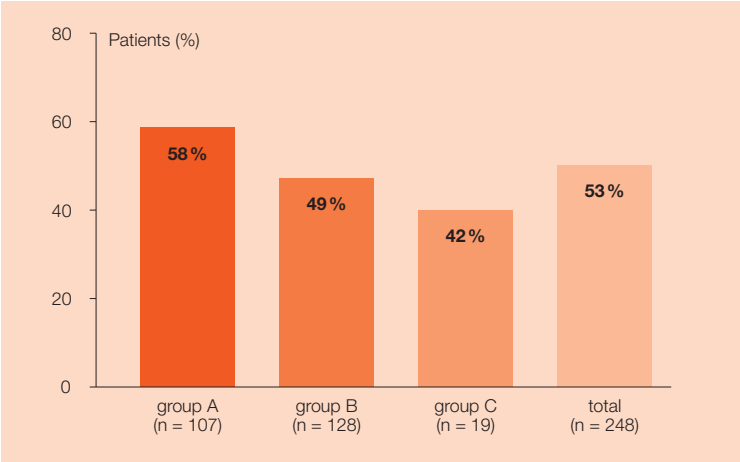

Figure 17: Response rates at treatment of active Crohn's disease with 3 × 1 Budenofalk® 3mg capsule per day with regard to disease localization. Group A: only terminal ileum and/or cecum and/or colon ascendens; group B: as group A and in addition colon transversum and/or colon descendens and/or sigma and/or rectum; group C: as group B and in addition upper gastrointestinal tract (duodenum, jejunum, upper and middle part of ileum).

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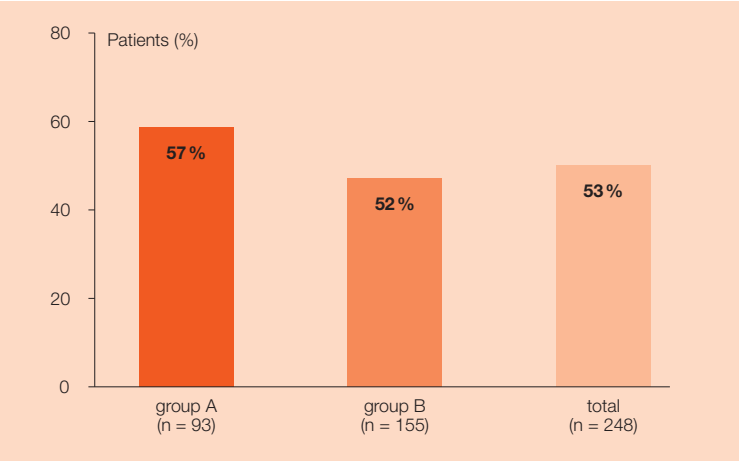

Figure 18: Response rates at treatment of active Crohn's disease with 3 × 1 Budenofalk® 3mg capsule per day with regard to the occurrence of extraintestinal manifestations. Group A: patients with at least one extraintestinal manifestation at the start of the study; group B: patients without extraintestinal manifestation at the start of the study.

If efficacy of different oral budesonide formulations is compared with classic glucocorticoids like prednisone and 6-methylprednisolone in active Crohn's disease, the results correspond to a large degree. Accordingly, response rates between 51% and 60% were achieved for budesonide and between 60% and 73% for prednisolone or 6-methylprednisolone, respectively. Although there was noted a trend towards higher response rates under the classic glucocorticoids in all studies, it was not seen any significant difference. However, comparing the rates of side effects, a statistically significant difference was shown in favour of budesonide in all studies as follows from Table 9 (CAMPIERI et al. 1997, GREENBERG et al. 1994, GROSS et al. 1996, RUTGEERTS et al. 1994).

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Remission rates (steroid-induced side effects) in %

Reference	Placebo	Budesonide 3 mg	Budesonide 9 mg	Budesonide 15 mg	Prednisone(P)/ Prednisolone (PN)/6-methyl-prednisolone (6-MP)
Rutgeerts et al. (1994)			53 (33)		PN 66 (55)
Greenberg et al. (1994)	20 (26)	33 (15)	51 (26)	43 (38)	
Campieri et al. (1997)			60 (50) 42 (44)		PN 60 (59)
Gross et al. (1996)*			56 (29)		6-MP 73 (70)
Bar-Meir et al. (1998)*			51 (44)		P 53 (66)

* including patients with involvement of distal colon and rectum

Table 9: Therapeutic effect and rates of side effects (in brackets) using budesonide preparations or classic glucocorticoids in patients with active Crohn's disease.

Main effects of the clinical efficacy due to oral budesonide preparations are achieved within the first two weeks after therapy start (see Figures 19, 20). Later on, a permanent but lower reduction of CDAI and a further small increase of the remission rate are observed. Therefore, a starting dosage of 3 × 3 mg/day pH-modified release budesonide is the optimal dose to treat patients with moderately active Crohn's disease activity. However, in patients with higher disease activity 3 × 6 mg budesonide per day might be more effective during the first 2–6 weeks of therapy.

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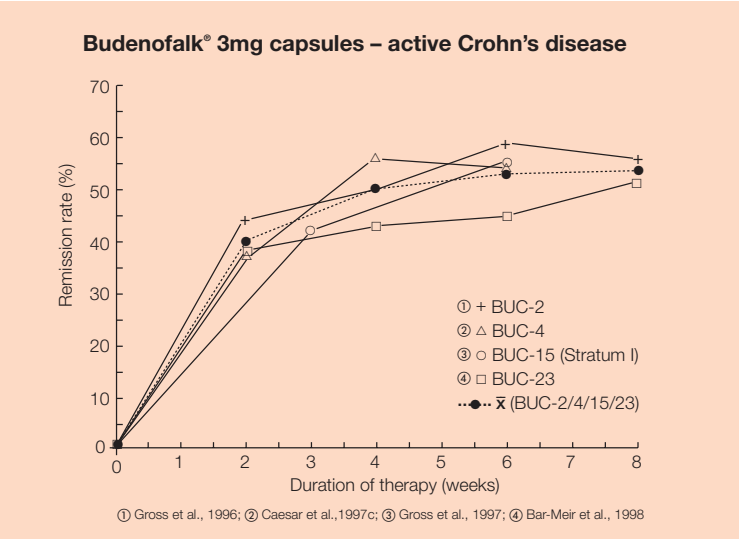

Figure 19: Remission rates (%) as parameter of the clinical efficacy of Budenofalk® 3mg capsules (daily dosage 3 × 3 mg = 9 mg/day) in patients with active Crohn's disease depending on therapy time.

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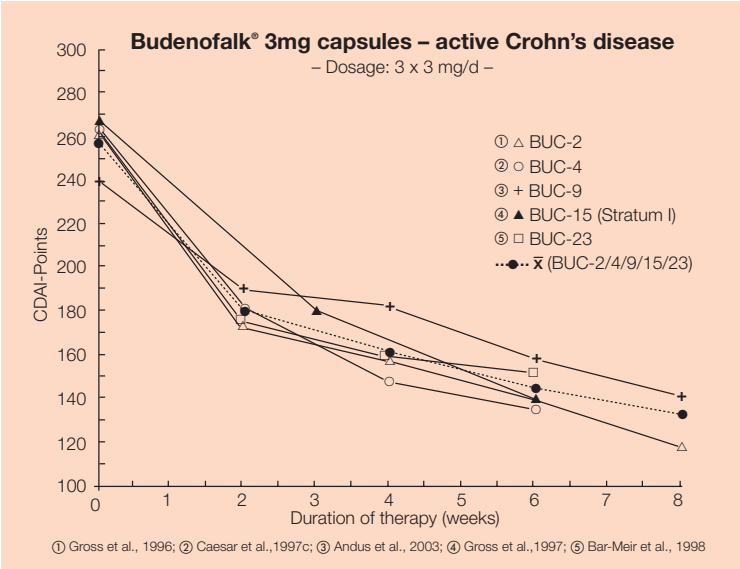

Figure 20: CDAI reduction as parameter of the clinical efficacy of Budenofalk® 3mg capsules (3 × 3 mg/day) in patients with active Crohn's disease depending on therapy time.

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6.5 Budenofalk® 3mg capsules in clinical practice – results of a postmarketing surveillance study

After the introduction of Budenofalk® 3mg capsules in Germany in the year 1998, a postmarketing surveillance study according to § 65 Abs. 6 AMG was performed from June 1999 to December 2000. The treatment of 419 outpatients with an acute episode of Crohn's disease was documented under medical routine conditions. The result of the treatment was judged after 12 weeks and optionally after 24 weeks. Most of the patients suffered from chronic Crohn's disease. Following results were obtained (HÜPPE 2003):

Dosage

At the beginning, 404 patients (96.4%) were treated with 3 × 1 Budenofalk® 3mg capsule. After 12 weeks, only 42.2% still took 3 × 1 Budenofalk® 3mg capsule, whereas the 2 × 1 application increased to 20.3% and the 1 × 1 application to 18.1%.

Improvement of clinical symptoms

Clinical symptoms improved remarkably. Within the first 4 weeks, stool frequency decreased from initially 6 stools per day to 3 per day (see Figure 21). After 8 weeks, a median stool frequency of 2 stools per day was reached. Abdominal pain decreased, too. Whereas at the beginning only 5.3% of the patients did not complain about abdominal pain, 76.9% after 12 weeks were free from pain. This success was maintained up to the optional documentation after 24 weeks with 73.6% of patients without pain at this time.

The therapeutic success, defined by being free of complaints or significant improvement of symptoms, was 72.8% for the whole group. It was dependent on the localization of the inflammatory processes, with 75.9% for afflictions of the ileum and/or colon ascendens and 59.7% for distal intestinal regions. The success of patients under monotherapy with Budenofalk® 3mg capsules were comparable (77.3%) with the whole group.

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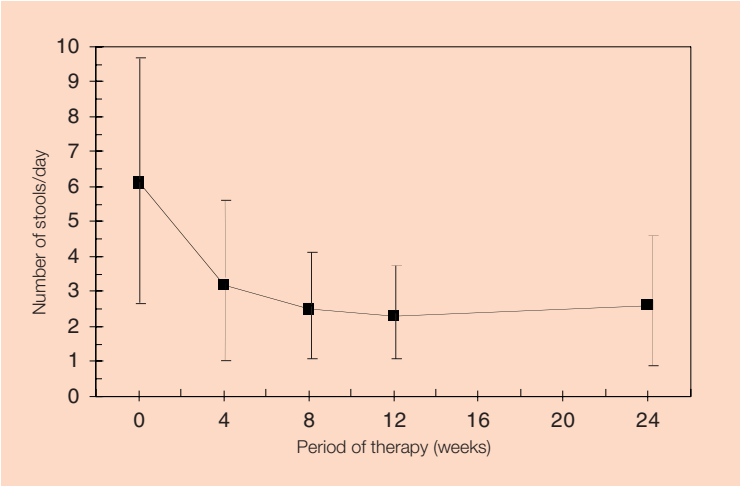

Figure 21: Budenofalk® 3mg capsules in acute Crohn's disease.

Tolerability

Most of the patients in this PMS study suffered from chronic Crohn's disease, having been treated for acute episodes before. The tolerability of pre-treatment systemically applied steroids had been good or very good only in 54.6% of all cases, whereas topically applied steroids had been tolerated good or very good in 92.7% and 5-ASA in 88.4% of all cases. In this study, the tolerability of 3 × 1 Budenofalk® 3mg capsule was ranked to be very good and good in 97.7% of all patients, confirming the remarkably better tolerability of topically applied budesonide compared to systemically applied steroids shown in controlled studies. Especially cosmetically irritating symp-

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toms decreased from more than 40% (increase in weight and moon face) or 25% (acne) under systemically steroid treatment to less than 6% under budesonide treatment (see Figure 22).

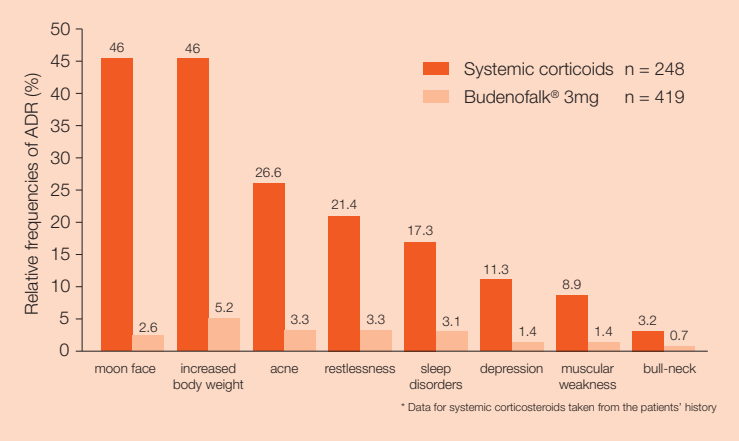

Figure 22: Budenofalk® 3mg capsules vs. systemic corticosteroids.

Long-term efficacy

At a post-study-examination of patients after 6 months, only 6.7% of patients receiving monotherapy with budesonide long-term, had a relapse. Under the combined therapy of budesonide + 5-ASA, the relapse rate was 9.4%. These results demonstrate a possible value of budesonide long-term treatment for relapse prophylaxis. In a study from STOCKBRÜGGER et al. (2003) 50% of patients were kept in remission over 2 years with budesonide or prednisolone doses adapted to disease activity.

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Quality of life

Quality of life was assessed in a subgroup of all patients (n = 79) included in the PMS study. The assessment was performed by telephone interviews with a duration of 45–60 minutes, 5–7 days after begin and after 12 weeks of treatment by a standardized questionnaire. The results show that the objectively documented decrease of symptoms is confirmed by the patient's perception. The good overall judgement led to a better processing of the psychological aspects of the disease. Furthermore, responders tolerated adverse events better than non-responders. These data confirm the improvement of well-being under budesonide and stress the aspect of psychological and clinical interactions to overcome the disabilities of a chronic disease.

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6.6 Replacement of systemically acting glucocorticoids by budesonide (Budenofalk® 3mg capsules) in steroid-dependent patients

Systemically acting corticosteroids often lead to severe steroid-specific side effects, especially during long-term use. Therefore, a change of steroid-dependent patients with inflammatory bowel diseases to a topically acting corticosteroid seems to be useful.

In a prospective, open, multicenter study (ANDUS et al. 2003), 178 patients with Crohn's disease with involvement of the ileum and/or ascending colon were changed from a conventional systemic glucocorticoid therapy to the locally acting glucocorticoid budesonide as Budenofalk® 3mg capsules. The primary objective of the study was the answer to the question if the replacement of a conventional, systemically acting glucocorticoid therapy (prednisolone) by the topically acting budesonide would markedly reduce the rate of steroid-specific side effects, but otherwise being equivalently effective.

At study start, 90 out of 178 patients were in remission (CDAI < 150), while the disease was still active (CDAI ≥ 150) in 88 patients. During the first 3 weeks, the systemic glucocorticoid therapy was gradually reduced, while the patients simultaneously received 3 × 3 mg budesonide per day (Budenofalk®

	Prednisolone (mg/day)	**Budenofalk® 3mg (mg/day)**
Week 0	30	0
Changing		
Week 1	20	9
Week 2	10	9
Week 3	0/10 (alternating)	9
1st Follow-up		
Week 4–9	0	9
4th Follow-up		

Table 10: Study design for the replacement of conventional systemic glucocorticoids (prednisolone) by 3 × 3 mg budesonide (Budenofalk® 3mg capsules) in Crohn's disease.

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3mg capsules). Subsequently, the patients exclusively received 3 × 3 mg budesonide per day (Budenofalk® 3mg capsules) for 6 weeks (Table 10).

After changing and subsequent treatment for 6 weeks with 3 × 3 mg budesonide, 77.8% of the 90 patients being in remission at the start of the study were still in remission. At the end of the 6-weeks treatment, 38.6% of patients with initially active disease had achieved remission. With regard to this remission rate, it has to be considered that this group of patients was treated with prednisolone up to the exclusive budesonide treatment without being able to achieve remission. Altogether, a therapeutic success was found in 58.4% of patients participating in the study (Figure 23).

The mean CDAI of the patients initially being in remission also remained stable under treatment with 3 × 3 mg budesonide. The mean CDAI of those patients, in whom the disease initially was still active under systemic glucocorticoid therapy, decreased from 219 points to 139 points during the course of the study. A lower dosage (3 × 1 mg) was not effective in comparison with placebo (GROSS et al. 1998; see also 8.1.2), whereas a difference between higher doses (3 × 2 mg, 3 × 3 mg and 3 × 6 mg daily for 6 weeks) could not be found (GROSS et al. 1997).

The number of patients complaining about steroid-specific side effects, as well as the number of those side effects reported during the study, was significantly reduced at termination of the study compared to the baseline value (see also section 9.5 and Table 16). Especially the reduction of patients with Cushing's syndrome after changing to budesonide was remarkable. In patients receiving 3 × 2 mg budesonide per day instead of prednisolone, the rate decreased from initially 32% to 17% at the end of the study, under 3 × 3 mg from 29% to 21% and under 3 × 6 mg from 23% to 21% (GROSS et al. 1997).

Altogether, the results of this study have shown that the replacement of systemic glucocorticoids by the topically acting budesonide allows a significant reduction of the rate of steroid-specific side effects in patients with active and postactive Crohn's disease, without reducing the desired therapeutical efficacy (ANDUS et al. 2003).

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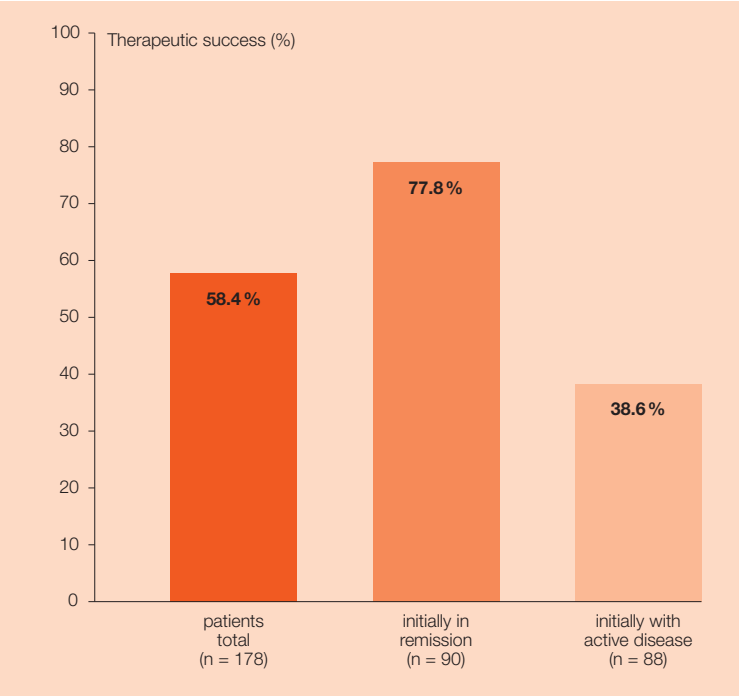

Figure 23: Therapeutic success in patients with Crohn's disease after changing from a systemic glucocorticoid to Budenofalk® 3mg capsules (3 × 3 mg budesonide).

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6.7 Current recommendations for therapy of Crohn's disease

Budesonide is nearly equally effective as systemically acting steroids. However, undoubtedly budesonide has an improved efficacy/safety ratio resulting in the statement, that the use of budesonide in the treatment of active Crohn's disease is good clinical practice at present (RUTGEERTS 2001).

According to the German guidelines for treatment of acute episodes of Crohn's disease and in agreement with newer review articles, budesonide at a dose of 9 mg/day could be used in mild or moderate cases and predominantly ileocecal afflictions (van DEVENTER 2001, SANDBORN & FEAGAN 2003, SCHÖLMERICH 2003). In severe cases, bridging the time until onset of action of azathioprine, budesonide may be considered (RUTGEERTS 2001).

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7 Clinical experience in collagenous colitis

Collagenous and lymphocytic colitis are similar in symptoms but different in origin, though the pathophysiology is unknown up to now. They are characterized by chronic watery diarrhea and abdominal pain. The diagnosis is to be confirmed only histologically because the macroscopy of the colon is usually normal. Informations on pathophysiology and treatment options are summarized in a review article (MÜHLHÖFER et al. 1999).

Seven patients with collagenous colitis were initially treated with 3 × 1 Budenofalk® 3mg capsule daily (= 9 mg budesonide) for four weeks. Afterwards, the dose was reduced to 3 × 2 mg budesonide and was further reduced in 6 patients in absence of diarrhea to 3 × 1 mg budesonide per day given as pH-modified release capsules in week 9. The stool frequency significantly decreased from 10.43 ± 5.56/day to 1.86 ± 0.69/day ($p < 0.001$). Moreover, the stool consistency changed from watery (6 patients) or soft (1 patient) to soft (1 patient) or solid (6 patients). In all patients, a clinical improvement was achieved within the first 10 days which was maintained after dose reduction. In one case, no diarrhea recurred during 7 months after budesonide was stopped. In 3 out of 7 patients, biopsies were taken which showed a regression of both, the collagenous band and the lymphocytic infiltrate (TROMM et al. 1997, 1999).

In a further study, 3 female patients were treated for 7–9 weeks with 9 mg budesonide (Budenofalk® 3mg capsules) daily. Watery diarrhea disappeared in all of them after 7 weeks at the latest. The collagenous band reduced in one patient from 15 to 9 µm. Until the end of the observation period of 11 months, no patient had a relapse (JANETSCHEK & BÖCKMANN 1998).

After these pilot trials, a placebo-controlled study has been performed with Budenofalk® 3mg capsules, randomizing 28 patients (BAERT et al. 2002) to the different groups. 9 mg budesonide were applied once daily. Budesonide was significantly superior compared to placebo. The intention-to-treat analysis showed a clinical response under Budenofalk® 3mg capsules in 57.1% of the patients compared to placebo (21.4%). Stool consistency was improved by budesonide compared to placebo. In week 4, the difference between the treatment groups was significant (Figure 24). However, during this short treatment period, no histological change in the mean thickness of the collagen band but a significant decrease of the lamina propria infiltrate

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was observed in the budesonide group. These results of budesonide in the treatment of collagenous colitis are also confirmed by the findings of DELARIVE et al. (1998) and MIEHLKE et al. (2002).

Recently, studies on microscopic colitis – encompassing the two different diseases collagenous and lymphocytic colitis – were reviewed (ABDO et al. 2003, BAERT 2004, CHANDE et al. 2003, 2004). According to these reviews and the Cochrane meta-analysis, budesonide is the treatment of choice.

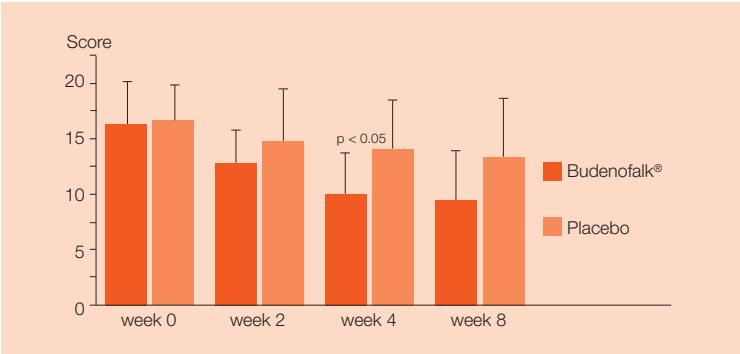

Figure 24: Evolution of the stool consistency score. The stool consistency score is a summation of scores 7 days before the visit on a 3-point-scale. 0 = formed, 1 = semi-liquid, 2 = liquid (BAERT et al. 2002).

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8 Efficacy of Budenofalk® 3mg capsules in other indications not licensed till now

8.1 Crohn's disease

8.1.1 Relapse prophylaxis/maintenance of remission

A clinical trial on relapse prophylaxis in Crohn's disease using 3 × 1 mg budesonide/day (budesonide capsules with pH-modified release) and a treatment period of one year resulted only in a delay of 27 days as compared to placebo until recurrence of a relapse (GROSS et al. 1998, Table 11). Similar results (16 days delay as compared to placebo) were obtained using another formulation of budesonide at a daily dose of 3 mg. However, the raise of the daily dose to 6 mg yielded in a substantial delay of 109 days until the recurrence of a relapse (FEAGAN et al. 1997). It is assumed, that an additional increase of the dose may result in even better outcomes. Therefore, clinical trials at a daily dose of 3 × 3 mg, i.e. 9 mg daily, budesonide (Budenofalk® 3mg capsules) are required to demonstrate a possible longer-term maintenance of remission in Crohn's disease.

Authors	Treatment groups	
	Budesonide	**Relapse rates at 1 year (budesonide/placebo in %)**
GREENBERG et al. (1996)	3 mg 6 mg	70/67 61/67 no difference
LÖFBERG et al. (1996)	3 mg 6 mg	74/63 59/63 no difference
FERGUSON et al. (1998)	3 mg 6 mg	46/60 48/60 no difference
GROSS et al. (1998)	3 × 1 mg	67/65 no difference

Table 11: Results of randomized placebo-controlled trials of budesonide for the maintenance of remission in Crohn's disease (according to PAPI et al. 2000, YANG & LICHTENSTEIN 2002).

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8.1.2 Postoperative maintenance of remission in Crohn's disease

Looking at the postoperative maintenance of remission with 3 × 1 mg/day budesonide (pH-modified budesonide release capsules) compared to placebo, only marginal effects concerning the endoscopic relapse rate were attained: 57% compared to 70% under placebo after 12 months (EWE et al. 1999). Similar results were reported by HELLERS et al. (1999) using another galenic preparation at a daily dose of 6 mg budesonide. However, the analysis of subgroups in this study revealed the possible importance of the indication for an operation. Within the subgroup of patients who underwent surgery due to stenosis, budesonide had no effects on the relapse rate. Within the budesonide subgroup of patients being operated due to enhanced inflammation activity ($n = 41$), the endoscopic relapse rate was remarkably lower after three months (21 vs. 47%, $p = 0.11$) as well as after 12 months (32 vs. 65%, $p = 0.047$).

In a further double-blind, placebo-controlled comparative study on the postoperative relapse prophylaxis using higher budesonide dosages (3 × 2 mg Budenofalk) per day, no significant differences between the treatment groups concerning the relapse rates were documented after 12 months (DEUSCH 1998). After one year, an endoscopically visible relapse (main criterion) was observed within 69% of the patients treated with budesonide and within 76% of patients who received placebo (intention-to-treat analysis). The per-protocol analysis resulted in 64% under budesonide treatment and 70% under placebo.

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8.2 Ulcerative colitis

While the therapeutic use of corticoids in Crohn's disease started relatively late, placebo-controlled studies of the 1950s proved the therapeutic benefit of local corticoid therapy in ulcerative colitis. This is mainly due to the possibility of topical glucocorticoid treatment in form of suppositories, enemas and foam if lower bowel parts are inflamed. However, the composition of the galenic formulas also plays an important role. While budesonide enemas have successfully been used for the treatment of distal ulcerative colitis, there are only few data available for the treatment of acute ulcerative colitis with oral budesonide formulations.

HÜPPE et al. (1993) reported a case of a 10 year old girl with acute left-sided ulcerative colitis, showing 8 relapses within 4 years with bloody diarrhea, weight loss and crampy abdominal pain, despite prednisolone treatment. In the following, the disease was chronically active, and prednisolone was withdrawn because of steroid-related side effects such as osteopenia, incipient cataract and moon face, and because of growth retardation and primary amenorrhea. Under a therapy with 3 × 3 mg budesonide capsules (Budenofalk® 3mg capsules) daily, the patient became clinically asymptomatic and the endoscopic findings showed complete remission of ulcerative colitis. The progression of osteopenia and growth retardation were stopped. The dosage could be reduced successfully to 3 × 1 mg budesonide (pH-modified release 1 mg capsules) per day.

In a further case report, CAESAR et al. (1997b) indicate the advantage of a change from oral systemic steroids to budesonide formulations. In a 25 year old patient, a left-sided ulcerative colitis, present since two and a half years, dose reduction below 12 mg prednisolone equivalent provoked exacerbation. Therapy therefore required a continuous, high-dose steroid treatment (3 months 40–100 mg prednisolone equivalent). As a consequence, the patient developed a severe, steroid-induced myopathia. Finally, he was unable to walk or to sit without help, and his general condition was severely reduced.

After reduction of the steroid dose and by simultaneous intensive physiotherapy, the myopathia improved, but with regard to the ulcerative colitis, severe complaints were observed with recurrence of blood in the stool. Therefore, a colectomy was indicated. However, after hospitalization, a

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conventional therapy attempt was made again using the topical steroid budesonide (1 budesonide enema at 2 mg/60 ml daily; Dr. Falk Pharma GmbH) which led to improvement of the myopathia, and practically abolished the symptoms of ulcerative colitis.

After 7 months, the patient suffered from a relapse following the discontinuation of the budesonide treatment by himself. A transient treatment with budesonide enemas was carried out again, overlapping by an oral administration of 3 × 3 mg budesonide (Budenofalk® 3mg capsules) per day, which was continued for one and a half year and was then reduced to 6 mg budesonide per day. In regard to the ulcerative colitis, the patient is in clinical and clinico-chemical remission under this therapy since two years. The steroid myopathia completely disappeared.

In 2 patients with severe, steroid-dependent chronically active pancolitis, DEUSCH et al. (1993) observed a marked improvement of the disease with a decrease of CAI by 2 or 4 points, associated with a decrease of the inflammatory parameters within 12–14 weeks under treatment with 3 × 3 mg budesonide (Budenofalk® 3mg capsules) daily. This beneficial effect persisted despite discontinuation of the prior prednisolone therapy.

The same study group (KÖHNE et al. 1994) could achieve similarly good results in steroid-dependent ulcerative colitis by a combination of 3 × 3 mg budesonide (Budenofalk® 3mg capsules) daily and budesonide 2 mg enemas. The administration of the systemic corticosteroids was continuously reduced, corresponding to the disease activity. In 5 of 7 patients with steroid-dependent ulcerative colitis, the use of this treatment schedule led to a marked clinical and endoscopic improvement which allowed a complete termination of the therapy with systemic steroids. Under the budesonide treatment, no steroid specific side effects were observed.

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Within the scope of compassionate use, 14 patients with steroid-dependent ulcerative colitis, being in the reduction phase of conventional glucocorticoids following a severe attack, were treated with Budenofalk® 3mg capsules (3 × 3 mg budesonide capsules per day) for 6 months. Primary parameters were changes in the clinical activity index (CAI) and changes in the daily dose of conventional steroids (KELLER et al. 1997, 2004).

During the 6-months' treatment period with Budenofalk® 3mg capsules, the CAI significantly improved ($p = 0.00016$) in 11 of 14 patients (78.6%) who went into remission. Termination of prednisolone therapy was possible within 3 months. Only 3 patients experienced a relapse (21.4%) which required the continuation of therapy with a conventional systemic steroid. No steroid-specific side effects were observed during the treatment with Budenofalk® 3mg capsules, and the drug was altogether well tolerated.

A comparison of different application regimes was performed by KOLKMAN et al. (2004) and PEÑA et al. (2004). They treated 15 patients with distal ulcerative colitis for 8 weeks either with 3 × 1 Budenofalk® 3mg capsule ($n = 8$) or 9 mg budesonide once daily ($n = 7$). The overall response rate after 8 weeks (CAI < 4 or decrease of CAI of at least 30%) was better with 9 mg once daily (71%) compared to 38% with 3 × 3 mg budesonide (38%, Figure 25). Therefore, the authors propose to apply 9 mg budesonide once daily instead of 3 × 3 mg budesonide in further studies (for pharmacokinetics in this trial see 4.2.2.4).

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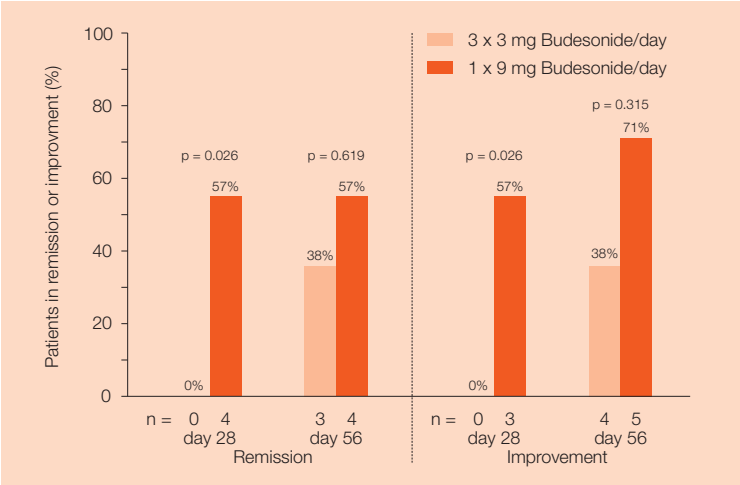

Figure 25: Ulcerative colitis: Clinical efficacy of Budenofalk® 3mg capsules.

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8.3 Inflammatory bowel diseases in children

In children with inflammatory bowel diseases, budesonide was applied as pH-modified release capsules (Budenofalk® 3mg capsules). LEVINE et al. (2001) compared retrospectively the outcome of budesonide with the treatment of prednisone in children with mild to moderate Crohn's disease (PCDAI 12.5–40). 48% of the 62 budesonide treated children achieved remission and 77% of the 58 children treated with prednisone. The difference of the cohorts were significant ($p = 0.001$). Among children who had not responded to mesalazine before corticoid treatment, the responder rates were higher with 59% for budesonide. 73% of children not responding to budesonide came into remission with prednisone.

In the controlled prospective study of BUJANOVER et al. (2001), a remission rate of 50% was observed under budesonide (Budenofalk® 3mg capsules) after 12 weeks in children with Crohn's disease.

In a recent prospective study (LEVINE et al. 2003), 33 pediatric Crohn's disease-patients were treated for 12 weeks with either 40 mg prednisone or 9 mg Budenofalk® 3mg capsules. The remission rate after 12 weeks was 47% (budesonide) and 50% (prednisone). Side effects occurred in 32% (budesonide) and 71% (prednisone), respectively ($p < 0.05$). Severity of cosmetic side effects was significantly lower in patients treated with budesonide ($p < 0.01$).

Budenofalk® 3mg capsules were administered in the frame of compassionate use in 188 children or adolescents at the age of 3–18 years with inflammatory bowel diseases. The duration of treatment was between 1 month and 31 months, and the daily dose was 9 mg budesonide in the majority of cases. Generally, the tolerability was stated to be very good to good, and drug-related adverse events were hardly observed. Only two cases of a steroid-specific side effect were reported from the group of the 10- to 18-year-old children (one case of a mild Cushing's syndrome, one case of a steroid acne).

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8.4 Increase of absorption or stool bulking due to Budenofalk® 3mg capsules in patients with bowel resection/ileostomy

In ileostomy and/or bowel resection, increased losses of liquid, minerals and electrolytes are observed due to the decreased absorption capacity associated with considerable and complex disturbances of health and impairment of quality of life for the patients.

In a double-blind, placebo-controlled, clinical study (ECKER et al. 2003), 40 ileostomy patients with Crohn's disease in remission or low disease activity with high intestinal output either received 3 × 1 Budenofalk® 3mg capsule or placebo daily for 9 days. Within this very short treatment period, 60% of patients out of the budesonide group showed a significant, clinically relevant reduction of the intestinal output (> 25%) which was associated with a stool bulking. This output reduction was classified as an original effect of budesonide (Budenofalk® 3mg capsules), independent of inflammation.

The stool bulking effect under Budenofalk® 3mg capsules is not only a short-term effect, but is also maintained during long-term therapy (the longest duration of therapy observed is about 3 years) without occurrence of visible side effects (ECKER 2004). An interruption of therapy led to an immediate increase of the ileostomy output. The renewed administration of Budenofalk® 3mg capsules again causes a rapid stool bulking (see Figure 26).

Treatment scheme:

Phase 1 (1 week, day 1 to 7 ± 1)	3 × 3 mg budesonide (Budenofalk® 3mg capsules) per day (in the morning, at noon, in the evening)
Phase 2 (4 weeks, day 8 to 35 ± 1)	no study medication
Phase 3 (1 week, day 36 to 42 ± 1)	reexposition with 3 × 1 Budenofalk® 3mg capsule per day (in the morning, at noon, in the evening)

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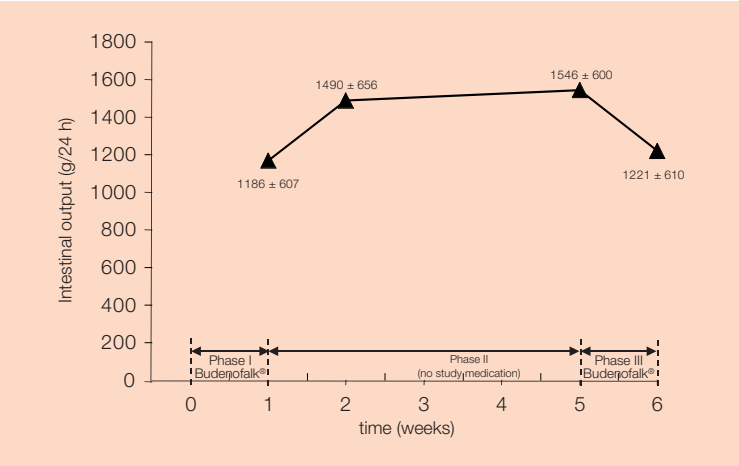

Figure 26: Effect of Budenofalk® 3mg capsules on the mean intestinal output in ileostomy patients (mean ± SD; ECKER 2004).

A double-blind, multicenter dose-finding study including 80 patients followed this first placebo-controlled study. These outpatients did not receive any limitation orders concerning their drinking habits in order to reflect normal conditions (ECKER 1998). Altogether, 7 centers participated in the study with 5 being located in Germany and 2 in Ukraine. The mean intestinal output was about 1000 g/24 h. Relating to sex, age, height, body weight and interval since ileostomy, the three dose groups (3 × 1 mg, 3 × 2 mg, 3 × 3 mg) were comparable.

In this study, response to a budesonide treatment was defined as a minimum of 25% reduction of the intestinal output compared to values of the prephase. The entire group had a response rate of 37.3% (per protocol) or 36.6%, respectively (intention-to-treat). Dose dependencies were noticed in the German patients: 3 × 1 mg budesonide lead to a response rate of 33.0%, 3 × 2 mg

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to 42.0% and 3 × 3 mg to 58.0%. On the other hand, response rates of patients from Ukraine decreased with increasing dosage: 3 × 1 mg budesonide lead to a response rate of 40.0%, 3 × 2 mg to 31.0% and 3 × 3 mg to 15.0% (Figure 27). At present the differences are difficult to explain, but might be due to ethnic differences and differences in the expression of IBD.

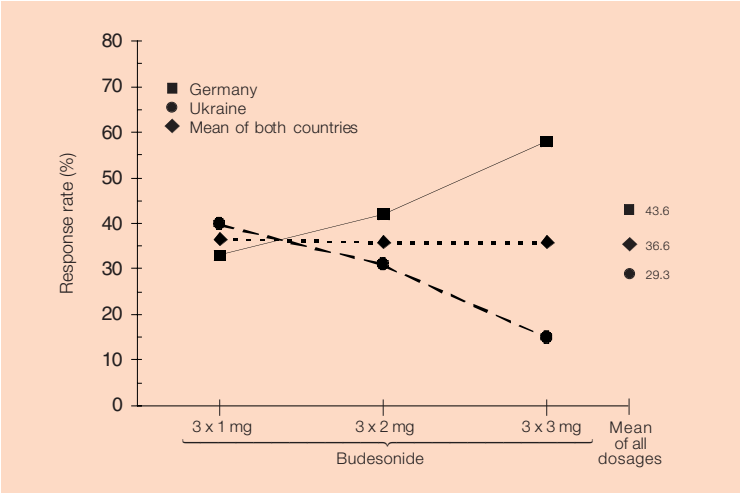

Figure 27: Response rates of ileostomy patients to Budenofalk® 3mg capsules treatment in respect to ileostomy output, separated by country.

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8.5 Liver diseases/transplantation medicine

8.5.1 Autoimmune hepatitis

So far, only smaller studies are available concerning the use of budesonide for treatment of liver diseases and its use in transplantation medicine (MANNS & WIEGAND 2004). First positive results were reported by DANIELSSON & PRYTZ (1994) on 13 patients with chronic active autoimmune hepatitis, who were treated for 9 months with budesonide.

SCHÜLER et al. (1994) described one single case of budesonide treatment of a recurring, HCV negative autoimmune hepatitis type II after liver transplantation. Under the initial high-dosed prednisolone therapy, the female patient suffered from Cushing's syndrome. This led to a medication extension with 2 × 3 mg budesonide (gastric juice-soluble tablets, Dr. Falk Pharma GmbH), keeping a maintenance dose of daily 2.5 mg prednisone. Already after 5 months the biochemical liver values were within the standard range. Also the Cushing's syndrome regressed.

In a following pilot study, the authors (SCHÜLER et al. 1995a) treated 9 patients with 2 × 3 or 5 × 3 mg budesonide, respectively, for one year. 3 of these 9 patients received additional azathioprine (100 mg daily). In 4 patients, a complete remission, i.e. normal biochemical values for aminotransferase and γ-globulin, was attained, while 3 patients were in partial remission. One patient who suffered from an overlapping syndrome of autoimmune hepatitis and primary biliary cirrhosis as well as another patient with cirrhosis did not achieve a biochemical remission. Inflammatory infiltrations decreased in 2 patients, no change was observed in 1 patient, 4 patients showed a worse histological record, for 2 patients no histological record was available. In 5 of the 9 patients, side effects (Cushing's syndrome) occurred at study start. However, they disappeared as the budesonide dosage was reduced or as soon as the hepatic inflammations decreased. It has been concluded, that the metabolization of budesonide is reduced in patients with autoimmune hepatitis or severe hepatitis. The metabolization capacity normalizes, however, with reduction of inflammation and improvement of liver function (SCHÜLER et al. 1995b)

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Another research group also used budesonide (partly in combination with systemically acting corticoids and/or azathioprine) successfully in 6 patients with autoimmune hepatitis (OEHLER 1997).

In a prospective pilot study with 10 steroid dependent patients, therapeutical success, i.e. clinical/biochemical remission, occurred only in 3 patients, histological remission was obtained in 2 patients. In 4 patients, however, a decrease in bone density was described (CZAJA & LINDOR 2000). However, future studies are recommended to investigate safety, efficacy and tolerance of budesonide in the remission therapy of autoimmune hepatitis (MANNS & WIEGAND 2004).

8.5.2 Primary biliary cirrhosis

The therapy of primary biliary cirrhosis (PBC) at present is performed with ursodeoxycholic acid (UDCA). A combination of ursodeoxycholic acid and prednisolone improves the therapeutic result (LEUSCHNER et al. 1996). As patients with primary biliary cirrhosis need a life-time treatment, this therapy regime, however, represents a higher osteoporosis risk. Therefore, budesonide could be more advantageous due to its high first-pass effect in the liver.

In a controlled, 2-years double-blind study, 40 patients with primary biliary cirrhosis of early stages (stage I and II) were randomly distributed into 2 treatment groups: UDCA vs. UDCA + 3 × 1 Budenofalk® 3mg capsule (LEUSCHNER et al. 1998, 1999, LEUSCHNER 2004). Within the 2 years, cholestasis indicating enzymes (γ-GT, AP) as well as glutamate dehydrogenase, ALT and AST were significantly reduced in both treatment groups. This also appeared for the immunoglobulins IgM and IgG. Improvements in the budesonide group were significantly more pronounced ($p < 0.05$) compared to the UDCA alone group. Titers of antimitochondrial antibodies did not change. The point score of liver histology improved by 30.3% under combination and deteriorated by 3.5% in the UDCA group ($p < 0.001$). Differences in bone mineral density after 2 years were statistically not significant ($p = 0.43$). Budesonide had only little influence on the hypothalamic-pituitary-adrenal

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axis. One patient showed a budesonide related side effect (decrease of serum cortisol levels to zero with increase after end of the study), while in 3 only UDCA-treated patients complications of the liver disease occurred.

In a randomized study of 77 AMA-positive PBC patients (stages I-III), RAUTIAINEN et al. assessed the efficacy of UDCA (15 mg/kg body weight per day) with and without budesonide (6 mg per day) over 3 years. In this study, the combination of budesonide and UDCA resulted in a significant improvement in liver histology and in total bilirubin compared with the administration of UDCA alone. Only one patient in the budesonide group withdrew from therapy due to undesired side effects (RAUTIAINEN 2003).

In another study, 22 patients with more advanced PBC showing a suboptimal response to ursodeoxycholic acid, were additionally treated with 9 mg budesonide (Budenofalk® 3mg capsules) daily for one year (ANGULO et al. 2000). The results of this study could not confirm the first promising results of LEUSCHNER et al. (1999). In spite of a significant, but transitory or marginal improvement of total bilirubin serum levels and serum alkaline phosphatase, the Mayo risk score increased significantly and there was a significant loss of bone mass of the lumbar spine. However, in this study the efficacy of budesonide was not analyzed in context with the stage of the underlying disease. As was shown by GRÜNHAGE et al. (2002) and HEMPFLING et al. (2003), plasma clearance of budesonide may be decreased in late stage PBC with an increased risk of side effects, as it is also discussed by ANGULO et al. (2000) themselves.

8.5.3 Organ transplantations

8.5.3.1 Prevention of rejection reactions

The local application of budesonide in order to prevent rejection reactions was described by RUERS et al. (1988) in animal trials. Budesonide was applied to rats during heart transplantations directly into the left carotid artery of the transplanted aorta (120 µg/kg). A markedly improved survival time of the transplant was reached (20 days) compared to the control rats with only 7 days persistence. Also, the infusion of the same concentration of budesonide into the vena jugularis led to high budesonide concentrations within the transplant.

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8.5.3.2 Treatment of acute intestinal GvHD after bone marrow transplantation

After allogenic bone marrow transplantation for treatment of hematological malignancies, intestinal GvHD (graft-versus-host-disease) is an not to be underestimated cause of death. This disease occurs even under immunosuppressive therapy with systemically applied glucocorticoids. In a prospective, non-randomized study (BERTZ et al. 1999, BERTZ 2004), 22 patients with acute GvHD-dependent bowel disease (stage ≥ II) received increased doses of systemic immunosuppressives, mainly corticosteroids, and additionally 9 mg budesonide daily. In 17 of 22 patients (70%), the acute intestinal GvHD resolved and no relapse occurred after decreasing the systemic immunosuppressive therapy under maintenance of the budesonide medication. Intestinal infections were not observed.

Within the retrospectively analyzed control group, which did not receive a topical corticoid, only 8 of 19 cases with the intestinal GvHD improved. The step-by-step reduction of the systemic corticosteroid medication provoked relapses in 2 of 8 patients. Therefore, the total responder rate in this retrospectively analyzed group was only 31% and a lot smaller than under treatment with the topically acting corticosteroid preparation Budenofalk® 3mg capsules (70%).

8.5.3.3 Treatment of oral GvHD

A GvHD after stem cell transplantation may afflict not only the intestinal but also the oral mucosa. Clinical signs of the oral mucosa are erythema, leukoplakia, sclerodermous changes, xanthostomia, and pyogenic granuloma. The oral GvHD often does not respond to systemic treatment and needs topical effective agents. ELAD et al. (2003, 2004) treated 12 patients with chronic resistant oral GvHD with 3 mg budesonide (Budeson® = Budenofalk® 3mg) dissolved in 5 ml saline 2–3 × daily for up to 3 months. All patients responded to the mouthwash, and 7 of 12 patients showed a good or complete response, as judged by both the examiner and the patient. First signs of response were usually seen within the first 2–3 weeks of treatment.

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9 Systemic influence and tolerability of budesonide

As compared to the systemically acting glucocorticoids, the very low systemic bioavailability of the topically acting glucocorticoid budesonide (10–11%) is based on the intensive first-pass metabolism and has been demonstrated by a number of pharmacological studies in healthy volunteers and patients. Pharmacological as well as clinical studies in patients with inflammatory bowel diseases have shown that this low systemic bioavailability at therapeutic use of budesonide is associated with a reduction of the systemic side effects and therefore a significant improvement of the tolerability.

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9.1 Impact on inflammation cells and mediators

9.1.1 Leukocytes

In the budesonide dose-finding study by CAESAR et al. (1996, 1997a), the effect on the leukocyte count as parameter of systemic action of glucocorticoids was also investigated. This effect is demonstrated for the different budesonide dosages in Table 12, showing the number of patients for which a change of the leukocyte count was observed during the course of the study. Accordingly, there was no essential difference between the groups of 3 × 2 mg and 3 × 3 mg budesonide. However, the group at a dose of 3 × 6 mg showed an increase of about twice as much in the leukocyte counts.

Parameter	Direction of change	Change of the leukocyte count in %		
		Budesonide 6 mg/d (n = 104)	Budesonide 9 mg/d (n = 98)	Budesonide 18 mg/d (n = 102)
Number of leukocytes	↑	28.9 %	22.5 %	46.1 %
	↓	1.0 %	2.0 %	0.0 %

Table 12: Number of patients with newly arised or increasing changes of the leukocyte count during the course of the study using pH-modified release 1 mg capsules and Budenofalk® 3mg capsules.

9.1.2 Lymphocytes

Studies with healthy volunteers using Budenofalk® 3mg capsules revealed higher concentrations of peripheral lymphocytes compared to patients with ileostomy. On the other hand, the granulocyte level was much lower in the healthy volunteers. The pharmacodynamics of the blood cells of ileostomy patients treated with budesonide did not differ from those of the healthy volunteers (ECKER et al. 1993). The impact of the medication on the peripheral blood cells is small and lower as under 3 × 1 mg methylprednisolone (3 × 1 mg, TROMM et al. 1993a). When applying 3 × 1 Budenofalk® 3mg capsules, the effect on lymphocytes is nearly as great as an intravenous application of 0.5 mg methylprednisolone (TROMM et al. 1993a). Similar results were also documented when using budesonide enemas (MÖLLMANN et al. 1993b).

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BARTH et al. (1994) compared the effect on blood cells of 9 mg budesonide as Budenofalk® 3mg capsules, which was either applied as a single dose or divided into 8-h intervals (3 × 3 mg). The authors observed that in both cases the number of lymphocytes was reduced by approximately 30%, while the number of granulocytes increased by about 30%. However, it was shown that an application of 9 mg as one single dose only has a pharmacodynamic effect of 16–18 h. The authors conclude that the division of the dose to 3 × 3 mg is essential, if a continuous steroid concentration over the whole day is aimed.

TILLINGER et al. (1995a, 1998) investigated the effect of budesonide (Budenofalk® 3mg capsules) on the activation markers of peripheral leukocytes. Patients with active Crohn's disease (CDAI > 150) randomly received 3 × 3 mg budesonide daily or 48 mg 6-methylprednisolone, gradually tapering the dose. At study entry, both groups showed a marked up-regulation of CD71, CD25 and CD64 as the most prominent activation markers. In the 6-methylprednisolone group, CD71 and CD64 significantly decreased after 2 weeks of treatment ($p < 0.05$ or < 0.01, respectively). In contrast, budesonide had no effect on the expression of these activity markers. The clinical response to the treatment (decrease of CDAI and CRP) was some less pronounced in the budesonide group. However, the difference was statistically not significant.

As marker of systemic side effects of corticosteroids, lymphocytes, especially the CD4 subtype, may be used, as was shown in volunteers after oral application of different formulations of budesonide in comparison to placebo (WERNER et al. 1999).

9.1.3 Inflammation mediators

TILLINGER et al. (1995b, 1998) compared the effect of budesonide (Budenofalk® 3mg) and 6-methylprednisolone on the release of TNF-α and IL-1β from peripheral blood mononuclear cells (PBMC) in patients with active Crohn's disease. The patients randomly received either 3 × 3 mg budesonide daily or 6-methylprednisolone in a daily dose of 48 mg for two weeks which then was reduced to 32 mg in week 2. At the end of the study, the concentrations of

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TNF-α and IL-1β were assessed which were markedly increased at study entry. The clinical response to treatment was evaluated by the effect on CDAI and C-reactive protein (CRP).

At the end of the study, the release of TNF-α was significantly and that of IL-1β was markedly decreased in the 6-methylprednisolone group. Both parameters were not or only insignificantly reduced in the budesonide group. The clinical response with regard to CDAI, was significant in both groups, but was more pronounced in the 6-methylprednisolone group. CRP was significantly reduced in the 6-methylprednisolone group only (Table 13).

Substance	week	TNF-α (pg/ml) $\bar{x}$ ± SEM	IL-1β (pg/ml) $\bar{x}$ ± SEM	CDAI $\bar{x}$ ± SD	CRP $\bar{x}$ ± SD
6-methyl-prednisolone	0	1619 (578)	582 (249)	263 (56)	5.1 (4.7)
	2	516 (197)°	286 (155)**	157 (20)†	2.3 (1.9)*
Budesonide	0	3715 (1311)	1135 (325)	279 (45)	5.5 (7.1)
	2	3475 (1615)	1355 (537)	205 (79)*	3.9 (3.4)

week 0 vs. week 2: * $p \leq 0.05$; ** $p = 0.04$; o $p = 0.03$; † $p < 0.001$

Table 13: Effect on TNF-α, IL-1β, CDAI and CRP by a 2-weeks treatment of patients with active Crohn's disease with either 6-methylprednisolone or budesonide (Budenofalk® 3mg capsules) (TILLINGER et al. 1998).

These findings indicate that orally applied budesonide does not suppress the release of inflammatory cytokines from PBMC, and they give further evidence that there is no substantial systemic action of budesonide at a daily dose of 9 mg. However, this may also explain the delayed onset of clinical response to the budesonide treatment which became especially noticeable at a trial duration of only 2 weeks.

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9.2 Effects on plasma cortisol levels

Using oral budesonide formulations, suppression of the plasma cortisol level is expected but to a lower degree than with systemically acting corticosteroids.

In a pilot study of ROTH et al. (1993), the mean basal cortisol level decreased from 160 ng/ml to 33 ng/ml in 9 patients with active Crohn's disease after the 6-weeks treatment with budesonide (slow release Eudragit-coated form). A CRF (corticotropin releasing factor) stimulation test, conducted in altogether 5 patients at the beginning and at the end of therapy, showed that it remained possible to stimulate the pituitary gland and adrenal cortex in spite of the decreased basal cortisol levels (Figure 28).

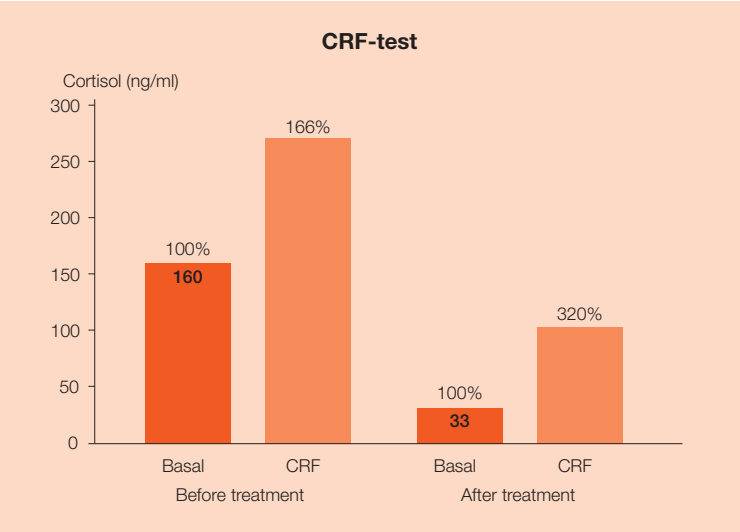

Figure 28: CRF-test before and after treatment with 3 × 3 mg budesonide (Budenofalk® 3mg capsules) daily for 6 weeks in patients with active Crohn's disease (ROTH et al. 1993).

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The changes of the plasma cortisol level during treatment with pH-modified release 1 mg budesonide capsules and Budenofalk® 3mg capsules were also investigated in the dose-finding study of CAESAR et al. (1996, 1997a) (see also chapter 6.2). The changes of the cortisol level under the different budesonide dosages are shown in Table 14.

Intention-to-treat-analysis	Plasma cortisol concentrations (µg/dl)		
	Budesonide 6 mg/d	Budesonide 9 mg/d	Budesonide 18 mg/d
Stratum 1 (without steroid pretreatment)			
at entry	14.3	18.9	13.8
after 6 weeks	10.2	8.2	4.6
at indiv. end of therapy	11.1	9.7	5.6
Stratum 2 (with steroid pretreatment)			
at entry	9.8	10.1	9.9
after 6 weeks	9.9	7.4	4.3
at indiv. end of therapy	8.9	7.4	4.6
Total			
at entry	11.6	13.1	11.1
after 6 weeks	10.1	8.5	4.3
at indiv. end of therapy	9.7	8.1	4.5

Table 14: Plasma cortisol concentrations (µg/dl) under pH-modified release 1 mg capsules and Budenofalk® 3mg capsules during the course of therapy.

Table 15 shows the number of patients for which the cortisol levels decreased below the value of 5.4 µg/dl, based on a normal range of reference of 5.4–19.6 µg/dl (see RUTGEERTS et al. 1994).

A decrease in the plasma cortisol level was observed in all three groups which was smallest in the group with 6 mg/day and was most distinct in the group with 18 mg/day. In stratum 1, the plasma cortisol level was below the

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Intention-to-treat-analysis	Budesonide 6 mg/d	Budesonide 9 mg/d	Budesonide 18 mg/d
Stratum 1			
at entry	7.7 %	3.1 %	3.1 %
after 6 weeks	20.0 %	34.5 %	76.7 %
at indiv. end of therapy	30.6 %	55.2 %	87.1 %
Stratum 2			
at entry	30.6 %	27.9 %	34.7 %
after 6 weeks	33.9 %	51.7 %	69.2 %
at indiv. end of therapy	60.3 %	69.2 %	88.6 %

Table 15: Number of patients with plasma cortisol concentration below 5.4 µg/dl under pH-modified release 1 mg capsules and Budenofalk® 3mg capsules during the course of therapy.

limit of 5.4 µg/dl in markedly less patients in the group with 9 mg/day than in the group with 18 mg/day (34.5 vs. 76.7%) which is comparable with the result of another 9 mg budesonide study (RUTGEERTS et al. 1994).

Pharmacokinetic studies in comparison to placebo did not show effects on the endogenous release of cortisol during a 24-hour profile at budesonide (Budenofalk® 3mg capsules) doses of 3 × 1 mg, 3 × 2 mg and 3 × 3 mg. Higher budesonide dosages of 1 × 9 mg or 1 × 18 mg per day, respectively, cause a significant cortisol suppression of about 40–50% in comparison with the placebo-daily profile. At steady-state conditions, a distributed daily dose of 3 × 3 mg showed similar effects on the cortisol suppression like a dose of 1 × 9 mg (MÖLLMANN & HOCHHAUS 1997).

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9.3 Effect on bone metabolism

Effects of oral application of budesonide compared to prednisolone on bone metabolism were shown in the study of BAR-MEIR et al. (1998). The serum osteocalcin level was used as marker of bone synthesis.

No significant changes of the osteocalcin level occurred neither under prednisone nor under budesonide. 100 patients with mild or moderate active Crohn's disease were given 9 mg budesonide (Budenofalk® 3mg capsules) daily over 8 weeks, while 101 patients received prednisone in decreasing dosages (40 mg daily for 2 weeks, then slowly reduction to 5 mg over 6 weeks). The osteocalcin level changed under budesonide from 9.2 ng/ml to 8.6 ng/ml, under prednisone treatment from 9.6 ng/ml to 10.0 ng/ml.

Measurements of bone mineral density under long-term treatment with Budenofalk® 3mg capsules was performed in two studies on patients with primary biliary cirrhosis (ANGULO et al. 2000, LEUSCHNER et al. 1998, 1999) and in one study with autoimmune hepatitis (CZAJA & LINDOR 2000). These results are – in comparison – contradictory.

In the study of LEUSCHNER et al. (1998, 1999) on patients with primary biliary cirrhosis, 1 of 19 patients receiving 9 mg budesonide (Budenofalk tablets) daily additionally to 10–15 mg/kg BW ursodeoxycholic acid, showed a decreased bone density after two years. Analyzing 21 patients with PBC under 9 mg budesonide (Budenofalk® 3mg capsules) for one year, ANGULO et al. (2000) found a marked loss of average bone mass of the femoral neck and lumbar spine.

In 10 patients with autoimmune hepatitis, 2 patients showed decreased lumbar spine density after 3 × 3 mg budesonide daily (duration of therapy 2–12 months), and 2 patients a decrease in femur density, in 1 patient accompanied by lumbar spine changes (CZAJA & LINDOR 2000).

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Nevertheless, these results have to be interpreted in context with the severity of the liver disease. The main advantage of budesonide concerning tolerability is based on the fast first-pass mechanism after becoming systemically available. As was shown by GRÜNHAGE et al. (2002) and HEMPFLING et al. (2003), plasma clearance may be markedly decreased in late stage PBC leading to higher systemic side effects.

Summarizing current results on the influence of orally applied budesonide on bone mass and other possible side effects, VALENTINE (2002) stresses the necessity of prophylactic bone mass measurements under budesonide long-term treatment, because pre-treatment with steroids, impaired metabolism by liver diseases or interactions with other drugs influencing the metabolism of budesonide, should be taken into account.

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9.4 Influence of budesonide on other metabolic processes

Other metabolic processes possibly influenced by glucocorticoid treatment are the protein metabolism and the fat metabolism. One well known side effect of glucocorticoid treatment is an increase in weight. As was shown by AL-JAOUNI et al. (2002), prednisone decreases lipid oxidation and increases protein oxidation. These effects were not observed with budesonide. Similar results were presented by WOLTHERS et al. (2000) who described increased levels of amino acids in blood under prednisolone. In contrast, under budesonide amino acid levels remained unchanged, no loss of nitrogen in form of urea occurred, and the kinetics for urea synthesis in the liver were unaltered, too.

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9.5 Steroid-related side effects under short-term therapy of inflammatory bowel disease

In the controlled clinical studies performed on Crohn's disease till now, the systemically acting glucocorticoids were compared to the topically acting budesonide, or the patients were changed from systemic glucocorticoids to budesonide. The results showed a mainly statistically significant difference in favour of budesonide with regard to steroid-type adverse events, especially moon face and steroid acne.

Regarding exclusively the glucocorticoid-related side effects, the clinical comparative study of GROSS et al. (1996) showed a statistically significant difference (28.6% in the Budenofalk® 3mg capsules group vs. 69.7% in the 6-methylprednisolone group; see also chapter 6.3 and Figure 14).

In the comparative study of BAR-MEIR et al. (1998), the rate of R1-responders, i.e. patients with complete remission without occurrence of steroid-related adverse events, was significantly higher in the budesonide (Budenofalk® 3mg capsules) group (30.0%) than in the prednisone group (13.9%) ($p < 0.002$). A significant advantage in favour of budesonide in comparison with prednisone, with the same clinical efficacy, was also shown for the total rate of steroid-type side effects (especially moon face and steroid acne) (see also chapter 6.3 and Figure 16).

Spectrum and frequencies of steroid-related adverse events observed in this study are listed in Table 16 (BAR-MEIR et al. 1998).

While in the multicenter study by ANDUS et al. (2003) 116 of 178 patients (65.2%) complained about altogether 269 steroid-related side effects at start of study, at study end of a 6-weeks treatment with exclusively 3 × 3 mg budesonide (Budenofalk® 3mg capsules) only 52 of 120 patients (43.3%) reported on side effects, altogether 90. The reduction of the side effect rate was statistically significant, firstly with regard to the number of affected patients and secondly with regard to the number of reported side effects (Table 17; Figure 29).

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Symptom	Budesonide (n)	Prednisone (n)
Moon face	16	33
Acne	19	29
Moodiness	10	16
Headaches	9	12
Muscle's weakness	10	10
Dyspepsia	10	8
Vertigo	8	5
Swollen ankles	6	6
Hirsutism	2	10
Striae distensae	2	8
Hump	3	2
Fast development of hematomas	–	2

Table 16: Adverse events under treatment with budesonide (Budenofalk® 3mg capsules) or prednisone respectively observed during the 5th visit after 8 weeks (number of patients with according symptoms) (BAR-MEIR et al. 1998).

Steroid-related side effects	Start (n = 178)	1st Follow-up (stop of systemic glucocorticoids) (n = 172)	4th Follow-up (after 6 weeks Budenofalk®) (n = 120)
Number of Patients	116 (65.2 %)	95 (55.2 %)	52 (43.3 %)*
Number of reported side effects	269	191	90
Examples Cushing's syndrome steroid acne	 34 % 27 %	 27 % 20 %	 25 % 14 %

* $p < 0.0001$ vs start

Table 17: Development of the side effect rate after replacement of a systemic glucocorticoid therapy by the treatment with Budenofalk® 3mg capsules (3 × 3 mg budesonide/day) in patients with postactive and active Crohn's disease.

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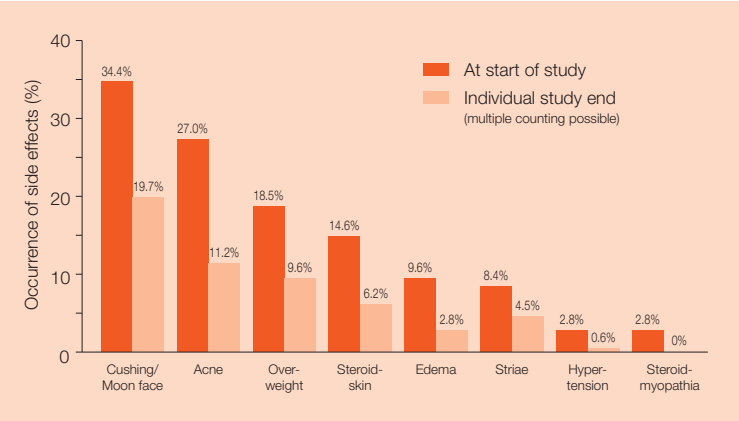

Figure 29: Decrease of corticosteroid-specific side effects after change from systemic glucocorticosteroids to Budenofalk® 3mg capsules (3 × 3 mg budesonide/day). Crohn's disease patients: n = 178.

In the dose-finding study by CAESAR et al. (1996, 1997a), the occurrence of typically or probably steroid-induced adverse events was analyzed in patients without steroid pre-treatment (stratum 1) as well as in patients included altogether in the tolerability analysis (Table 18).

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	Adverse events in %		
Group	Budesonide 6 mg/d (n = 40)	Budesonide 9 mg/d (n = 33)	Budesonide 18 mg/d (n = 32)
Stratum 1	20 %	21 %	31 %
Total	21 %	16 %	25 %

Table 18: Typically or probably steroid-induced adverse events during the course of the study under the treatment with pH-modified release 1 mg budesonide capsules and Budenofalk® 3mg capsules.

According to the results of this study, the number of steroid-induced side effects occurring under budesonide therapy is comparable with the incidence observed in previous studies, and is markedly lower than under standard therapy with systemically acting glucocorticoids. With regard to the tolerability analysis, it was striking that a Cushing's syndrome almost exclusively recurred or increased when already existing at study entry at 18 mg/day (7 at 18 mg/day, 1 at 6 mg/day, 0 at 9 mg/day). In all dosage groups, the number of patients with at least one steroid-type side effect only insignificantly decreased. In order to explain this lacking reduction, the possible continuation of these side effects from the pre-treatment with systemically acting steroids has to be considered. This is supported by the findings that only a minor reduction of the steroid-induced side effects could be observed even at the lowest dose of 6 mg/day, which hardly influenced the plasma cortisol level (see also chapter 9.2, Table 14). Furthermore, the number of patients with a plasma cortisol concentration of below 5.4 µg/dl at the beginning of the budesonide therapy was significantly higher in stratum 2 with steroid pre-treatment than in stratum 1 without steroid pre-treatment (see also Table 15).

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9.6 Impaired metabolization of budesonide and interaction potential

Budesonide is mainly metabolized in the liver. After oral administration, approximately 90% of the absorbed drug is eliminated by an extensive first-pass effect (MÖLLMANN et al. 1996a) involving the cytochrome P450 enzyme system. As was shown by JÖNSSON et al. (1995), the metabolism is mainly performed by isoenzymes within the CYP3A family. Therefore, severe liver diseases and other substrates metabolized by the same enzymes are risk factors for changed bioavailability of budesonide, increasing the risk of undesired effects. This may be a reason for the loss of bone mass in patients with primary biliary cirrhosis (ANGULO et al. 2000) leading to the recommendation not to use budesonide in late stage cirrhotic patients (HEMPFLING et al. 2003). In a patient with chronic autoimmune hepatitis and Child A cirrhosis, a daily dose of 9 mg budesonide led to facial swelling, leg edemas and weight gain explained by marked suppression of serum cortisol and no significant stimulation by CRH (GEIER et al. 2003).

In one double-blind 2-phase-crossover study with 10 healthy volunteers, the interaction of inhaled budesonide (1000 µg) with itraconazole, a potent cytochrome P4503A4-inhibitor, was described (RAASKA et al. 2002). They found an enhanced systemic effect of budesonide demonstrated by suppression of cortisol production. They conclude that long-term coadministration of budesonide with a potent CYP3A4-inhibitor like itraconazole may lead to an increased risk of adverse events of budesonide. This assumption was confirmed by a case report on a cystic fibrosis patient treated with itraconazole because of allergic bronchopulmonary aspergillosis and anti-inflammatory therapy with budesonide inhalation (MAIN et al. 2002). The patient developed a Cushing's syndrome which disappeared after cessation of itraconazole and budesonide treatment.

A patient treated with amiodarone for paroxysmal atrial fibrillation and chronic renal insufficiency developed a Cushing's syndrome after treatment with 9 mg/day budesonide for chronic diarrhea. The authors explain this report on Cushing's syndrome under budesonide by the impaired metabolization by the CYP3A system of the liver (AHLE et al. 2000).

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In combination with oral contraceptives, an increase of the budesonide plasma level of 22% at a dose of 4.5 mg oral budesonide was found, which was not significant, in contrast to a significant 131% increase of plasma prednisolone at an oral dose of 20 mg prednisolone. The authors conclude that controlled ileal release capsules can be used safely in women using an oral contraceptive (EDSBÄCKER et al. 1999).

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9.7 Use in children

In an open labeled study, 8 children and 6 adults with active Crohn's disease received 9 mg budesonide daily (ileal controlled release formulation) for 7 days. The systemic exposure, systemic availability and cortisol suppression were similar in children and adults (LUNDIN et al. 2003). In another study, the systemic exposure to orally applied budesonide (CIR) in children with Crohn's disease seemed to be lower than in adult patients, but resulted in similar plasma cortisol suppression (LINDQUIST et al. 1999).

KUNDHAL et al. (2000) described in children with Crohn's disease of the distal ileum +/– right colon a subnormal growth under CIR capsules during the observation time of 6–13 months which might be explained by either inadequately controlled intestinal inflammation or direct suppression of the growth regulating system.

In a prospective evaluation, pH modified release budesonide 9 mg (Budenofalk® 3mg capsules) was studied in comparison to 40 mg prednisone for a treatment of 12 weeks (BUJANOVER et al. 2001). Cosmetic related side effects occurred in 8/19 budesonide and in 12/13 prednisone treated children, the difference being significant ($p < 0.01$). The same study group reported on 120 children in a retrospective study in which only 1/62 children under budesonide developed a severe adverse event and 8/58 under prednisone (LEVINE 2002, LEVINE et al. 2003). The author concludes that "budesonide appears to cause fewer overall side effects, fewer cosmetic side effects, less significant side effects, and less severe cosmetic disconfiguration". But they also put the attention on the risk of liver diseases and poor nutritional status which may increase the potential for side effects with oral budesonide.

From 188 children or young people at the age of 3–18 years with inflammatory bowel disease compassionately using Budenofalk® 3mg capsules, only two cases of a steroid-specific side effects were reported (one case of a mild Cushing's syndrome, one case of a steroid acne).

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On the basis of the data and evaluations regarding the treatment with Budenofalk® 3mg capsules in children, there is, according to the present knowledge, no concern for the treatment of children from the age of 3 years on because a good tolerability has been observed even over prolonged treatment periods (see also HÜPPE et al. 1993, chapter 8.2). However, Budenofalk® 3mg capsules should not be used outside clinical studies because of only poor experience until now.

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9.8 Use of budesonide during pregnancy

In women with inflammatory bowel disease, an active inflammation is thought to be more harmful than an adequate medication to control the disease. The available treatment options are discussed in a recent review (CONNELL & MILLER 1999).

Salicylates seem to be safe even during pregnancy. For glucocorticoids, only experiences on prednisolone, dexamethasone and betamethasone are available. Because of dexamethasone and betamethasone crossing the placenta more freely than prednisolone, most data have been obtained for prednisolone. Generally, one has to consider possible aggravation of pregnancy related complications like glucose intolerance, hypertension, sodium retention and peripheral edema. Furthermore, neonatal adrenal insufficiency may occur because of the substance crossing the placenta. Other complications to be taken into account are growth retardation, stillbirth, placenta insufficiency, fetal distress and reduced neonatal birth weight. However, if adverse events like these occurred under treatment with prednisolone during pregnancy, the correlation to the current medical therapy or the effects of the underlying disease were not clear. The teratogenic risk of glucocorticoids during pregnancy seems not to be enhanced, either, though some reports on malformations have been published.

Up to now, no published data on the use of oral budesonide during pregnancy are available.

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Budenofalk® 3mg capsules

1. NAME OF THE MEDICINAL PRODUCT

Budenofalk® 3mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gastro-resistant capsule containing 3 mg budesonide.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.
The color of the capsule is pink.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon.
- Symptomatic relief of chronic diarrhea due to collagenous colitis.

Please note:
Treatment with Budenofalk® 3mg does not appear useful in patients with Crohn's disease affecting the upper gastrointestinal tract. Extraintestinal symptoms, e.g. involving the skin, eyes or joints, are unlikely to respond to Budenofalk® 3mg because of its local action.

4.2. Posology and method of administration

Posology:

Adults aged > 18 years:
The recommended daily dose is one capsule (containing 3 mg budesonide) three times daily (morning, midday and evening) about a half hour before meals.

Children:
Budenofalk® 3mg should not be taken by children due to insufficient experience in this age group.

Method of administration:

The capsules containing the gastro-resistant pellets should be taken before meals, swallowed whole with plenty of fluid (e.g. a glass of water).

The duration of treatment in active Crohn's disease and in collagenous colitis should be limited to 8 weeks.

The treatment with Budenofalk® 3mg should not be stopped abruptly, but withdrawn gradually (tapering doses). In the first week, the dosage should be reduced to two capsules daily, one in the morning, one in the evening. In the second week, only one capsule should be taken in the morning. Afterwards treatment can be stopped.

4.3. Contraindications:

Budenofalk® 3mg must not be used in:
- hypersensitivity to budesonide or any of the ingredients
- hepatic cirrhosis with signs of portal hypertension, e.g. late-stage primary biliary cirrhosis

4.4. Special warnings and special precautions for use

Treatment with Budenofalk® 3mg results in lower systemic steroid levels than conventional oral steroid therapy. Transfer from other steroid 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.

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 septicemia and tuberculosis may be masked and may reach an advanced stage before being recognized.

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 immunization with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids 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. Corticosteroids 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 impaired immune responsiveness. The antibody response to other vaccines may be diminished.

In patients with severe liver function disorders, the elimination of glucocorticosteroids including Budenofalk® will be reduced, and their systemic bioavailability will be increased.

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

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

4.5. Interaction with other medicinal products and other forms of interaction

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:
  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, and clarithromycin are also likely to give a marked increase of the plasma concentrations of budesonide. In addition, concomitant intake of grapefruit juice 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 corticosteroids have been reported in women also receiving estrogens 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 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® 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.

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Budenofalk® 3mg capsules

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4.6. Use during pregnancy and lactation

Administration during pregnancy should be avoided unless there are compelling reasons for Budenofalk® 3mg therapy. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development. The relevance of this to man has not been established.
Since it is not known if budesonide passes into breast milk, the infant should not be breast-fed during treatment with Budenofalk® 3mg.

4.7. Effects on ability to drive and use machines

No effects are known.

4.8. Undesirable effects

The following undesirable effects and frequencies of Budenofalk® 3mg have been spontaneously reported:

Very rare (< 1/10,000), including isolated reports:

- *Metabolism and nutritional disorders:* edema of legs, Cushing's syndrome.
- *Nervous system disorders:* Pseudotumor cerebri (including papilloedema) in adolescents.
- *Gastrointestinal disorders:* Constipation.
- *Musculoskeletal, connective tissue and bone disorders:* diffuse muscle pain and weakness, osteoporosis.
- *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 glucocorticosteroids. 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® 3mg (approx. by half) than with oral treatment of equivalent dosages of prednisolone.

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 the 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 edema formation, increased excretion of potassium, inactivity or atrophy of the adrenal cortex, growth retardation in children, disturbance of sex hormone secretion (e.g. amenorrhea, hirsutism, impotence)

Nervous system disorders:
depression, irritability, euphoria

Eyes disorders:
glaucoma, cataract

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

Gastrointestinal disorders:
stomach complaints, duodenal 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)

4.9. Overdose

To date, no cases of overdosage with budesonide are known. In view of the properties of budesonide contained in Budenofalk® 3mg, an overdose resulting in toxic damage is extremely unlikely.

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 3 × 3 mg budesonide/day significantly smaller than that of clinically equivalent effective doses of systemic glucocorticosteroids.

5.2. Pharmacokinetic properties

Absorption:
Budenofalk® 3mg capsules, which contain gastric juice resistant pellets, have – due to the specific coating of the pellets – 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 cecum, 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 Budenofalk® 3mg will be transferred normally into the colon.

Concomitant intake of food may delay release of pellets 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 liver (approximately 90%) to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-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):
Dependent on the type and severity of liver diseases and due to the fact that budesonide is metabolized by CYP3A4, the metabolization of budesonide might be decreased. Therefore, the systemic exposure of budesonide might be increased in patients with impaired hepatic functions, as has been shown for patients with autoimmune hepatitis (AIH). With improving the liver function and disease, metabolization of budesonide will normalize.

The bioavailability of budesonide has been found to be significantly higher in patients in the late stage of primary biliary cirrhosis (PBC Stage IV) than in patients in the early stages of primary biliary cirrhosis (PBC Stage I/II); on average, the areas under the plasma concentration-time curves were threefold greater in patients with late-stage PBC, following repeated administration of budesonide 3 × 3 mg daily, than in patients with early-stage PBC.

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 on the dose and duration and in dependence on the diseases these steroid effects might also be of relevance in man.

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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 tumors (female rats) was observed. These tumors 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 foetal development. But the relevance to man has not been established (see also section 4.6)

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Povidone K25, Lactose monohydrate, Sucrose, Talc, Maize starch, Methacrylic acid, methylmethacrylate copolymer (1:1) (Eudragit L 100), Methacrylic acid, methylmethacrylate copolymer (1:2) (Eudragit S 100), Poly(ethylacrylic acid, methylmethacrylate, trimethylammonium ethylmethacrylate chloride) (1:2:0.1) (Eudragit RS12.5), Poly(ethylacrylate, methylmethacrylate, trimethylammonium ethylmethacrylate chloride) (1:2:0.2) (Eudragit RL12.5), Dibutyl phthalate, Titanium dioxide (E 171), Water, Gelatin, Erythrosine (E127), Red iron oxide (E 172), Black iron oxide (E172), sodium laurilsulphate.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years.
This medicinal product must not be used after the expiry date.

6.4. Special precautions for storage

Do not store above 25 °C.

6.5. Nature and contents of container

Al/PVC/PVDC blister strips in cartons with 10, 50 and 90, 100, 120 capsules. Not all pack sizes may be marketed.

6.6. Instructions for use/handling

None

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

08637/0002

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF AUTHORIZATION

January 4, 1999

10. DATE OF (PARTIAL) REVISION OF THE TEXT

April 2004

Budenofalk 3mg
Budenofalk 3mg
Budenofalk 3mg

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