FERRING
PHARMACEUTICALS

ENJOY THE SIMPLE PLEASURES OF LIFE

CORTIMENT®MMX®
budesonide

COR/939/2014/CH3

FERRING PHARMACEUTICALS

ULCERATIVE COLITIS DISRUPTS THE SIMPLE PLEASURES IN LIFE

- Patients with ulcerative colitis may live with a considerable symptom burden despite medical treatment.[1, 2]

Symptoms experienced at least once a day[2] (n=4995)

	During a flare	Between flares
Bleeding	61%	28%
Abdominal cramping pain	87%	62%
Tired, weak or worn out	96%	83%
Urgent bowel movements	89%	66%
Diarrhoea	93%	61%

- Ulcerative colitis can have substantial psychosocial implications with consequent impact on quality of life.[3]
- The use of conventional corticosteroids for inflammatory diseases is associated with greater side effects than topical steroids.[4] A Survey in Europe on the impact of inflammatory bowel diseases on patients lives (N=4995) showed that[2]:
  - 42% of the patients experience side effects from taking corticosteroids.
  - 49% of the patients are worried about the impact of corticosteroids on their long-term health.

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THE THERAPEUTIC GOALS IN ULCERATIVE COLITIS ARE:[5]

- induction and maintenance of remission using well-tolerated drugs
- mucosal healing
- avoidance of surgical intervention
- decreasing the likelihood of cancer
- improved quality of life.

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CORTIMENT®MMX® IS DESIGNED FOR LOCAL DELIVERY OF A POTENT CORTICOSTEROID FOR PATIENTS WITH ULCERATIVE COLITIS[7]

ORAL ADMINISTRATION ONE DOSE DAILY

PATIENT CONVENIENCE
one small tablet once a day

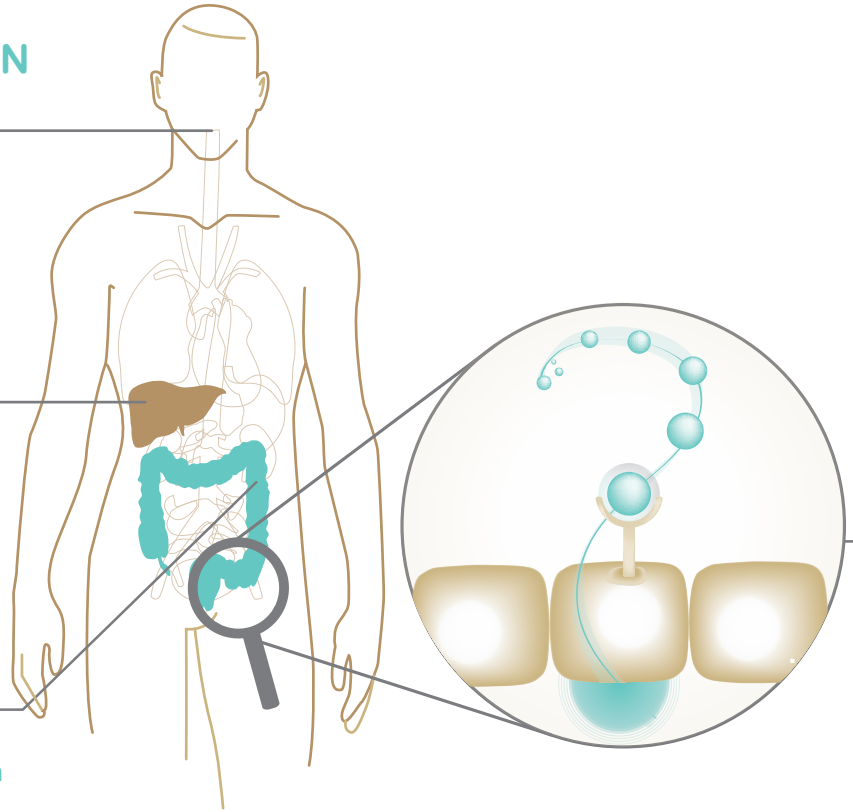
FIRST-PASS LIVER METABOLISM

- Metabolites with limited activity
- Low systemic exposure: about 10%[9]

= side effect profile similar to placebo[11,12]

COLONIC RELEASE SYSTEM

Targeted release for topical effect at the site of inflammation
= TOPICAL ACTIVITY[7]



POTENT ANTI-INFLAMMATORY ACTIVITY

>3 times RRA* versus prednisolone and hydrocortisone[10] (in vitro data)

*RRA = Relative Receptor Affinity, an indirect measure of corticosteroid activity.

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CORTIMENT®MMX® HAS AN ADVERSE EVENT PROFILE COMPARABLE TO PLACEBO[11]

- CORTIMENT®MMX® combines local corticosteroid efficacy with low systemic exposure.[6,7]

Most adverse events were of mild-to-moderate intensity and of a non-serious character.

Potential corticosteroid effects occurred infrequently.

Treatment-emergent adverse events (TEAEs)[11]

Safety population (n=257)

	Placebo n=129	CORTIMENT®MMX® n=128
Related TEAEs	24.0%	25.8%
Serious TEAEs	3.9%	3.1%

Most common potential corticosteroid effects at final visit [11]

Safety population (n=257)

	Placebo n=129	CORTIMENT®MMX® n=128
Mood changes	5.4%	1.6%
Sleep changes	3.1%	2.3%
Insomnia	1.6%	0.8%
Acne	1.6%	0.8%
Moon face	3.1%	1.6%

Tables show safety data from study CORE II.[11] CORE I safety data are similar.[12]

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CORTIMENT®MMX® STUDIES USED A RIGOROUS DEFINITION OF REMISSION AND STRINGENT INCLUSION CRITERIA[7,11,12]

DEFINITION OF REMISSION, UCDAI ≤1 WITH:	INCLUSION CRITERIA
○ normal stool frequency	○ adult patients (18-75 years)
○ absence of bleeding	○ ulcerative colitis during at least six months
○ presence of normal mucosa without friability	○ mild or moderate active disease (UCDAI 4-10)
○ endoscopic improvement confirmed by full colonoscopy	○ abnormal histology in at least one of three biopsies from colonic lesions

UCDAI: Ulcerative colitis disease activity index

This rigorous definition of remission has an impact on the observed remission rates for active and placebo treatment arms.[7,11,12]

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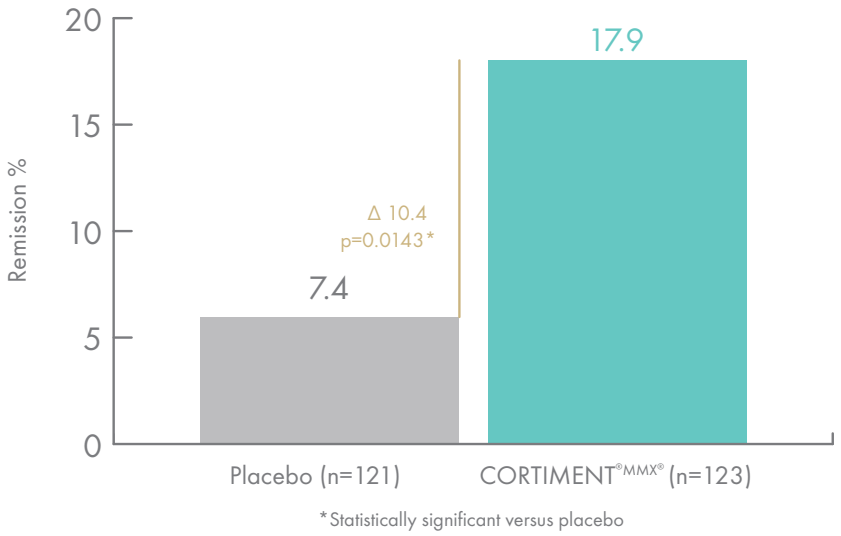
CORTIMENT®MMX® 9MG SHOWS 2,4 - 3,9 TIMES HIGHER REMISSION RATES COMPARED TO PLACEBO[11,12]

CORTIMENT®MMX® 9mg shows statistically significant results on the primary endpoint versus placebo.[11,12]

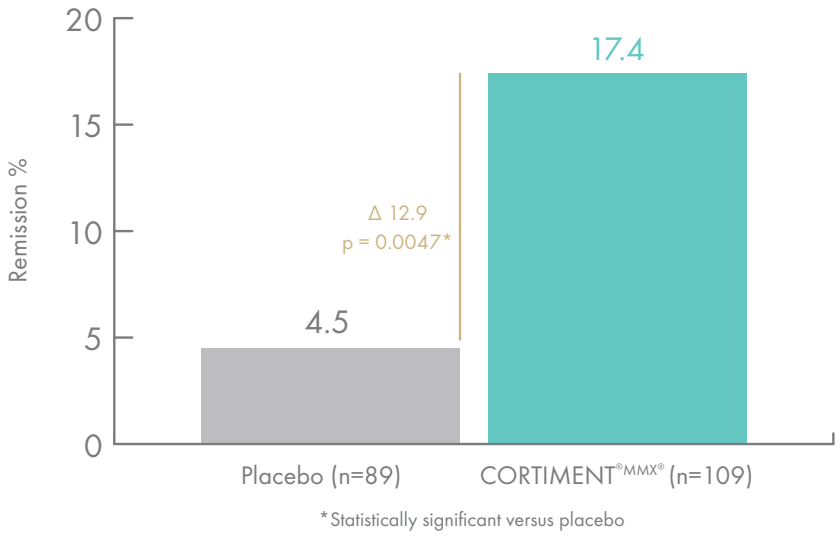
CLINICAL AND ENDOSCOPIC REMISSION at week 8

CORE I STUDY



*Statistically significant versus placebo

CORE II STUDY



*Statistically significant versus placebo

FERRING PHARMACEUTICALS

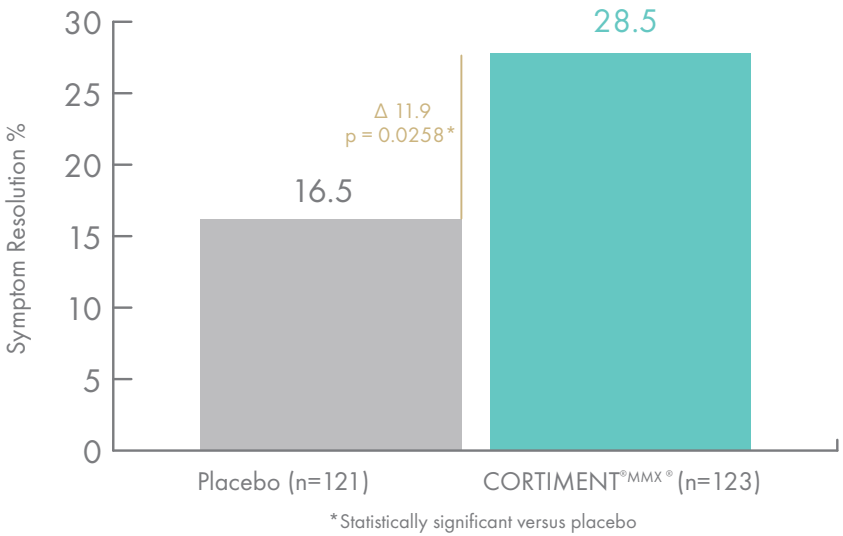
CORTIMENT®MMX® INDUCES SYMPTOM RESOLUTION AFTER 8 WEEKS[11,12]

- CORTIMENT®MMX® 9mg induces symptom resolution after 8 weeks.[11,12]

SYMPTOM RESOLUTION at week 8

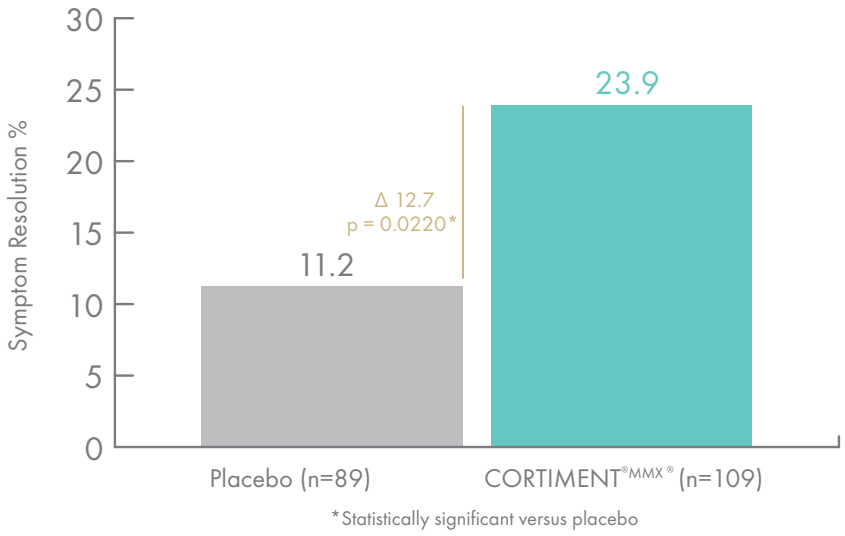
Combind rectal bleeding and stool frequency scores of 0

CORE I STUDY



*Statistically significant versus placebo

CORE II STUDY



*Statistically significant versus placebo

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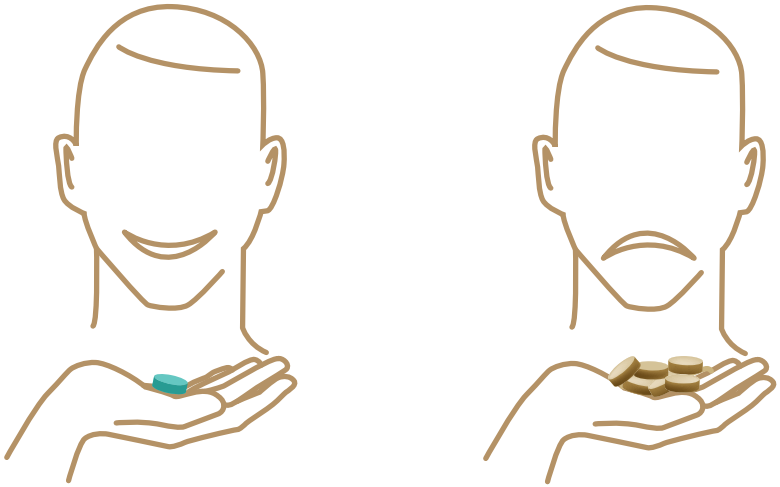
CORTIMENT®MMX® OFFERS SYMPTOM RESOLUTION WITH ONCE DAILY CONVENIENCE

- CORTIMENT®MMX® : one small 9mg tablet, once daily, for up to 8 weeks.[7]



CORTIMENT ®MMX®

- Patients generally prefer a low dose frequency and reduced pill burden.[5,8,13]
- Patients prefer oral intake over rectal use.[8]

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CORTIMENT®MMX®, ENJOY THE SIMPLE PLEASURES OF LIFE

- CORTIMENT®MMX® one small tablet, once daily, for up to 8 weeks
- CORTIMENT®MMX® is indicated for mild-to-moderate active ulcerative colitis where 5-ASA treatment is not sufficient
- CORTIMENT®MMX® is designed for local delivery of a potent corticosteroid
- CORTIMENT®MMX® has an adverse event profile comparable to placebo
- CORTIMENT®MMX® combines corticosteroid efficacy with low systemic exposure


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PRESCRIBING INFORMATION

CORTIMENT®MMX® 9 mg, Budesonide Prolonged release tablets. **Indications:** CORTIMENT is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient. **Dosing:** The recommended daily dose for induction of remission is one 9 mg tablet in the morning, with or without food, for up to 8 weeks. **Contraindications:** Hypersensitivity to the active substance, soya oil, peanut oil or to any of the excipients. **Warnings and precautions:** CORTIMENT tablets should be used with caution in patients with infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts or with a family history of diabetes or glaucoma or with any other condition where the use of glucocorticoids may have unwanted effects. Reduced liver function may affect the elimination of glucocorticoids including budesonide, causing higher systemic exposure. Be aware of possible systemic side effects. When treatment is to be discontinued, it may be useful to gradually reduce the dose at the discretion of the treating physician. Treatment with CORTIMENT tablets results in lower systemic steroid levels than conventional oral glucocorticoid therapy. Transfer from other steroid therapy may result in symptoms relating to the change in systemic steroid levels. Some patients may feel unwell during the withdrawal phase. As corticosteroids are known to have immunological effects the co-administration of CORTIMENT tablets is likely to reduce the immune response to vaccines. CORTIMENT contains lecithin (derived from soya) and lactose. **Interactions:** No interaction studies have been performed Budesonide is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Inhibitors of this enzyme, e.g. ketoconazole, itraconazole, HIV protease inhibitors and grapefruit juice, can therefore increase systemic exposure to budesonide several times (see section 4.4). Since there is no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose could also be considered. Budesonide is unlikely to inhibit other drugs metabolized via CYP3A4, since budesonide has low affinity to the enzyme. Corticosteroid interactions that may present a significant hazard to selected patients are those with heart glycosides and diuretics. **Fertility, pregnancy and lactation:** Data on use of inhaled budesonide in a very large number of exposed pregnancies indicate no adverse effects. Although there are no data of outcomes of pregnancies after oral administration, the bioavailability after oral administration is low. In animal experiments, at high exposures, corticosteroids proved to be harmful. CORTIMENT should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. Budesonide is excreted in small amounts in breast milk. Due to the rapid budesonide clearance from the blood, on theoretical grounds, the exposure to the suckling child is expected to be low. However, there are no data. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from budesonide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Undesirable effects:** Occasionally, side effects typical of systemic glucocorticosteroids may occur. These side effects depend on the dosage, duration of treatment, concomitant or previous treatment with other glucocorticosteroids and individual sensitivity. Steroids class side effects include following disorders: Skin and subcutaneous tissue, Musculoskeletal, connective tissue and bone, Eye, Psychiatric, Gastrointestinal, Metabolism and Nutrition, Vascular, Immune system. **Overdose:** In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy. **Pharmacodynamic properties:** Budesonide is released into the intestinal tract at a controlled rate throughout the colon. – Clinical efficacy: 5-ASA is the Standard of Care for treatment of mild to moderate disease. Results of a head to head comparison with CORTIMENT and 5-ASA are not available. Therefore, the place in the therapeutic work-up remains to be established. Some patients may benefit from treatment initially with CORTIMENT. Please check with your local Ferring representative for local prescribing information and SmPC. **CORTIMENT®MMX® 9 mg: Ferring Pharmaceuticals, Switzerland**.

1. Dignass A, Eliakim R, Magro F et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012;6:965-990. 2. IMPACT 2010-2011 Crohn's and Ulcerative Colitis Patient Life Impact Survey. Presentation available at: http://efcca-solutions.net/european.php. Last accessed: February 2014. 3. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohns Colitis. 2007;1:10-20. 4. Dignass A, Lindsay JO, Sturm A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012;6:991-1030. 5. Siew N, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. Inflamm Bowel Dis. 2009;15:935-950. 6. Farkas K, Molnar T. Novel extended release budesonide formulation for treatment of ulcerative colitis. Expert Opin Pharmacother. 2014;15:131-137. 7. Ferring Pharmaceuticals. Cortiment®MMX® 9 mg SmPC. Date of Revision Text: October 2014. 8. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2006;23:577-585. 9. Ryrfeldt A, Andersson P, Edsbacker S et al. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. Eur J Respir Dis Suppl. 1982;122:86-95. 10. Mager DE, Moledina N, Jusko WJ. Relative immunosuppressive potency of therapeutic corticosteroids measured by whole blood lymphocyte proliferation. J Pharm Sci. 2003;92:1521-1525. 11. Travis SP, Danese S, Kupcinskas L et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut. 2014;63:433-441. 12. Sandborn WJ, Travis S, Moro L et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology. 2012;143:1218-26.e1. 13. Dignass AU, Bokemeyer B, Adamek H et al. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. Clin Gastroenterol Hepatol. 2009;7:762-769.