UCERIS- budesonide (11.beta.,16.alpha.(s)) tablet
Santarus, Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use UCERIS safely and effectively. See full prescribing information for UCERIS.
UCERIS (budesonide) extended release tablets, for oral use
Initial U.S. approval: 1997

INDICATIONS AND USAGE

UCERIS (budesonide) is a glucocorticosteroid indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is one 9 mg tablet to be taken once daily in the morning with or without food for up to 8 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

- extended release tablets: 9 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to budesonide or any of the ingredients in UCERIS tablets (4)

WARNINGS AND PRECAUTIONS

- Hypercorticism and adrenal suppression: Since UCERIS is a glucocorticosteroid, follow general warnings concerning glucocorticoids. (5.1)
- Transferring patients from systemic glucocorticoids: Risk of impaired adrenal function when transferring from glucocorticoid treatment with higher systemic effects to glucocorticoid treatment with lower systemic effects, such as UCERIS. Taper patients slowly from systemic corticosteroids if transferring to UCERIS. (5.2)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 2%) are headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Santarus, Inc at (1-888-778-0887) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Avoid Cytochrome P450 3A4 inhibitors (e.g., ketoconazole, grapefruit juice). May cause increased systemic corticosteroid effects. (2.2, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Monitor patients for signs and/or symptoms of hypercorticism. (5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

UCERIS (budesonide) extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Mild to Moderate Ulcerative Colitis

The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is 9 mg taken orally once daily in the morning with or without food for up to 8 weeks. UCERIS should be swallowed whole and not chewed, crushed or broken.

2.2 CYP3A4 Inhibitors

If concomitant administration with ketoconazole, or any other CYP3A4 inhibitor, is indicated, patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Avoid grapefruit juice, which is known to inhibit CYP3A4, when taking UCERIS. In these cases, discontinuation of UCERIS or the CYP3A4 inhibitor should be considered [See *Drug Interactions* (7) *and Clinical Pharmacology* (12.3)].

3 DOSAGE FORMS AND STRENGTHS

White, round, biconvex extended release tablets debossed with “MX9”. Each extended release tablet contains 9 mg budesonide.

4 CONTRAINDICATIONS

UCERIS is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. Anaphylactic reactions have occurred with other budesonide formulations [See *Adverse Reactions* (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression

When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since UCERIS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.

5.2 Transferring Patients from Systemic Glucocorticosteroid Therapy

Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as UCERIS, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously.

5.3 Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure.

How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered.

Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections.

Replacement of systemic glucocorticosteroids with UCERIS tablets may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic drug.

5.4 Increased Systemic Glucocorticoid Susceptibility

Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis [See *Use in Specific Populations* (8.6)].

5.5 Other Glucocorticosteroid Effects

Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

Systemic glucocorticosteroid use may result in the following:

- Hypercorticism and Adrenal Suppression [*See Warnings and Precautions* (5.1)]
- Symptoms of steroid withdrawal in those patients transferring from Systemic Glucocorticosteroid Therapy [*See Warnings and Precautions* (5.2)]
- Immunosuppression [*See Warnings and Precautions* (5.3)]
- Increased Systemic Glucocorticosteroid Susceptibility [*See Warnings and Precautions* (5.4)]
- Other Glucocorticosteroid Effects [*See Warnings and Precautions* (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of UCERIS has been evaluated in controlled and open-label clinical trials which enrolled a combined total of 1105 patients with ulcerative colitis.

In two 8-week, placebo-controlled studies in patients with active disease (Study 1 and Study 2), a total of 255 patients received UCERIS 9 mg, 254 patients received UCERIS 6 mg, and 258 patients received placebo. They ranged in age from 18-77 years (mean 43), 56% were male, and 75% were Caucasian. The most common adverse reactions were headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation. The adverse reactions occurring in 2% or more of patients on therapy with UCERIS 9 mg are summarized in Table 1.

Table 1. Summary of Adverse Reactions in Two Placebo Controlled Trials Experienced by at Least 2% of the UCERIS 9 mg Group (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	**UCERIS 6 mg (N = 254) n (%)**	**Placebo (N = 258) n (%)**
Headache	29 (11.4)	37 (14.6)	27 (10.5)
Nausea	13 (5.1)	12 (4.7)	11 (4.3)
Decreased Blood Cortisol	11 (4.3)	6 (2.4)	1 (0.4)
Upper Abdominal Pain	10 (3.9)	8 (3.1)	5 (1.9)
Fatigue	8 (3.1)	5 (2.0)	5 (1.9)
Flatulence	6 (2.4)	8 (3.1)	5 (1.9)
Abdominal Distension	6 (2.4)	4 (1.6)	2 (0.8)
Acne	6 (2.4)	2 (0.8)	5 (1.9)

Urinary Tract Infection	5 (2.0)	1 (0.4)	1 (0.4)
Arthralgia	5 (2.0)	5 (2.0)	4 (1.6)
Constipation	5 (2.0)	1 (0.4)	2 (0.8)

Of UCERIS 9 mg patients, a total of 15% discontinued treatment due to any adverse event (including adverse reactions) compared with 17% in the placebo group.

Table 2 summarizes the percentages of patients reporting glucocorticoid related effects in the 2 placebo-controlled studies.

Table 2. Summary of Glucocorticoid Related Effects in Two Placebo-Controlled Trials (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	**UCERIS 6 mg (N = 254) n (%)**	**Placebo (N = 258) n (%)**
Overall	26 (10.2)	19 (7.5)	27 (10.5)
Mood changes	9 (3.5)	10 (3.9)	11 (4.3)
Sleep changes	7 (2.7)	10 (3.9)	12 (4.7)
Insomnia	6 (2.4)	6 (2.4)	8 (3.1)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Moon face	3 (1.2)	3 (1.2)	4 (1.6)
Fluid retention	2 (0.8)	3 (1.2)	3 (1.2)
Hirsutism	1 (0.4)	0	0
Striae rubrae	0	0	2 (0.8)
Flushing	0	1 (0.4)	3 (1.2)

No clinically significant differences were observed with respect to the overall percentages of patients with any glucocorticoid related effects between UCERIS and placebo after 8 weeks of induction therapy.

Study 3 was an open-label study evaluating UCERIS 9 mg once daily for 8 weeks in 60 patients who had previously completed an 8-week induction study (Study 1), but had not achieved remission. Among patients who took UCERIS 9 mg up to 16 weeks cumulatively across Study 1 and Study 3 combined, similar rates of adverse reactions and glucocorticoid-related effects were seen compared to those who took UCERIS 9 mg for 8 weeks in Study 1.

In Study 4, the safety of long-term treatment with UCERIS 6 mg was evaluated in a placebo-controlled 12-month maintenance study of 123 patients. Patients who had previously completed 8 weeks of therapy in any induction study (Study 1, 2, or 3) and were in remission were randomized to UCERIS 6 mg or placebo once daily for 12 months. In patients who took UCERIS 6 mg for up to 12 months, similar rates of adverse reactions were seen between placebo and UCERIS 6 mg. After up to 12 months of study treatment, 77% (27/35) of the patients in the UCERIS 6 mg and 74% (29/39) of the patients in the placebo treatment groups had normal bone density scans.

In Study 4, the glucocorticoid related effects were similar in patients with up to 12 months of therapy with UCERIS 6 mg and placebo. (Table 3)

Table 3. Summary of Glucocorticoid Related Effects Over 12-month Treatment (Study 4)

	UCERIS 6 mg (N = 62) n (%)	**Placebo (N = 61) n (%)**
Overall	9 (14.5)	7 (11.5)

Insomnia	4 (6.5)	4 (6.6)
Mood changes	4 (6.5)	2 (3.3)
Moon face	3 (4.8)	3 (4.9)
Sleep changes	3 (4.8)	3 (4.9)
Acne	3 (4.8)	0
Hirsutism	3 (4.8)	0
Flushing	1 (1.6)	1 (1.6)
Fluid retention	1 (1.6)	1 (1.6)

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of oral budesonide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: anaphylactic reactions

Nervous System Disorders: benign intracranial hypertension

Psychiatric Disorders: mood swings

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 inhibitors

Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, discontinuation of the UCERIS should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with UCERIS administration [See *Dosage and Administration* (2) *and Clinical Pharmacology* (12.3)].

7.2 Inhibitors of Gastric Acid Secretion

Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H_2-blockers and antacids)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving glucocorticosteroids during pregnancy. Such infants should be carefully observed.

8.3 Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum.[1] Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum budesonide concentration for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after inhalation. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide plasma concentrations obtained from five infants at about 90 minutes after breast feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant).

The recommended daily dose of UCERIS extended release tablets is higher (9 mg daily) compared with inhaled budesonide (up to 800 µg daily) given to mothers in the above study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5-10 nmol/L which is up to 10 times higher than the 1-2 nmol/L for a 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study.

Since there are no data from controlled trials on the use of UCERIS by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from UCERIS, a decision should be made whether to discontinue nursing or to discontinue UCERIS, taking into account the clinical importance of UCERIS to the mother.

Budesonide, is secreted in human milk. Data from budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of UCERIS, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation.

8.4 Pediatric Use

Safety and effectiveness of UCERIS in pediatric patients have not been established. Glucocorticosteroids, such as UCERIS may cause a reduction of growth velocity in pediatric patients.

8.5 Geriatric Use

Clinical studies of UCERIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, UCERIS should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Discontinuing the use of UCERIS tablets should be considered in these patients [See *Warnings and Precautions* (5.4)].

10 OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

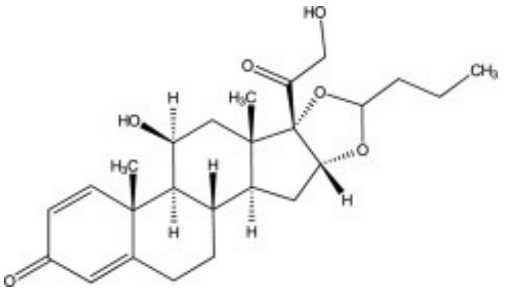
If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage may be reduced temporarily.

Single oral budesonide doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

11 DESCRIPTION

UCERIS (budesonide) extended release tablets, for oral administration, contain budesonide, a synthetic corticosteroid, as the active ingredient. Budesonide is designated chemically as (RS)-11β, 16α, 17,21 tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde.

Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water, sparingly soluble in alcohol, and freely soluble in chloroform.

UCERIS, a delayed and extended-release tablet, is coated with a polymer film, which breaks down at or above pH 7.0. The tablet core contains budesonide with polymers that provide for extended release of budesonide.

Each tablet contains the following inactive ingredients: stearic acid, lecithin, microcrystalline cellulose, hydroxypropylcellulose, lactose, silicon dioxide, magnesium stearate, methacrylic acid copolymer types A and B, talc, triethylcitrate, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Budesonide has a high topical glucocorticosteroid (GCS) activity and a substantial first-pass elimination. The formulation contains budesonide in an extended release tablet core. The tablet core is enteric coated to protect dissolution in gastric juice which delays budesonide release until exposure to a pH ≥ 7 in the small intestine. Upon disintegration of the coating, the core matrix provides extended release of budesonide in a time dependent manner.

12.2 Pharmacodynamics

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to GCS receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

Treatment with systemically active GCS, including UCERIS, is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. Markers, indirect and direct, of this are cortisol levels in plasma or urine and response to

ACTH stimulation.

In a study assessing the response to ACTH stimulation test in patients treated with Uceris 9 mg once daily, the proportion of patients with abnormal response was 47% at 4 weeks and 79% at 8 weeks.

12.3 Pharmacokinetics

Absorption

Following single oral administration of UCERIS 9 mg in healthy subjects, peak plasma concentration (C_{max}) was 1.35 ± 0.96 ng/mL, the time to peak concentration (T_{max}) on average was 13.3 ± 5.9 hours, although it varied across different individual patients, and the area under the plasma concentration time curve (AUC) was approximately 16.43 ± 10.52 ng·hr/mL. The pharmacokinetic parameters of UCERIS 9 mg have a high degree of variability among subjects. There was no accumulation of budesonide with respect to both AUC and C_{max} following 7 days of UCERIS 9 mg once daily dosing.

Food Effect

A food-effect study involving administration of UCERIS to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased by 27% while there was no significant decrease in AUC. Additionally, a mean delay in absorption lag time of 2.4 hours is observed under fed conditions.

Distribution

The mean volume of distribution (V_{SS}) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is about 0.8.

Metabolism

Following absorption, budesonide is subject to high first-pass metabolism (80-90%). *In vitro* experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (<1/100) in relation to that of the parent compound.

In vivo investigations with intravenous doses in healthy subjects are in agreement with the *in vitro* findings and demonstrate that budesonide has a high plasma clearance, 0.9-1.8 L/min. These high plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

The plasma elimination half-life, $t_{1/2}$, after administration of intravenous doses ranges between 2.0 and 3.6 hours.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^{3}H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

Special Populations

Hepatic Impairment

In patients with liver cirrhosis, systemic availability of orally administered budesonide correlates with disease severity and is, on average, 2.5-fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the intravenous dose, no significant differences in CL or

V_{SS} are observed.

Renal Impairment

The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renally excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide (<1/100).

Drug-Drug Interactions

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide several-fold. Co-administration of ketoconazole results in an eight-fold increase in AUC of budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels [*See Dosage and Administration* (2) *and Drug Interactions* (7)].

Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (ie, ethinyl estradiol).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference glucocorticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis).

Mutagenesis

Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ($TK^{+/-}$) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocycte UDS test and the mouse micronucleus test.

Impairment of Fertility

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

14 CLINICAL STUDIES

Induction of Remission in Active Mild to Moderate Ulcerative Colitis

Two similarly-designed, randomized, double-blind, placebo-controlled studies were conducted in a total of 970 adult patients with active, mild to moderate ulcerative colitis (UC) which was defined as an Ulcerative Colitis Disease Activity Index (UCDAI of ≥ 4 and ≤ 10). Eight-hundred ninety-nine of these patients had histology consistent with active UC; this was considered the primary analysis population. UCDAI is a four-component scale (total score of 0 to 12) that encompasses the clinical assessments of stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity (score of 0 to 3 for each of the components).

The baseline median UCDAI score in both studies was 7.

In Study 1, 56% of patients were male, and the median age was 42 years. In Study 2, 57% of patients were male, and the median age was 44 years. In Study 1, 50% of patients were Caucasian, 7% were African American, and 34% were Asian. In Study 2, more than 99% were Caucasian.

Both studies compared UCERIS 9 mg and 6 mg with placebo and included an active reference arm (a mesalamine 2.4 g in Study 1; and a budesonide* 9 mg not approved for the treatment of UC in Study 2). The primary endpoint was induction of remission after 8 weeks of treatment. Remission was defined as a UCDAI score of ≤ 1, with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in an endoscopy-only score.[2] In both studies, UCERIS 9 mg extended release tablets demonstrated superiority to placebo in inducing remission (Table 4).

Table 4. Induction of Remission in Studies 1 and 2

Treatment Group	Study 1 n/N (%)	Study 2 n/N (%)
UCERIS 9 mg	22/123 (17.9)	19/109 (17.4)
UCERIS 6 mg	16/121 (13.2)	9/109 (8.3)
Reference Arm*	15/124 (12.1)	13/103 (12.6)
Placebo	9/121 (7.4)	4/89 (4.5)
Treatment Difference between UCERIS 9 mg and Placebo (95% CI)†	10.4% (2.2%, 18.7%)	12.9% (4.6%, 21.3%)

Remission is defined as a UCDAI score of ≤ 1, with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in an endoscopy-only score.[2]

The primary analysis population included only patients that had histology consistent with active UC.

CI=Confidence Interval

*The reference arm in Study 1 is a delayed release mesalamine 2.4 g; the reference arm in Study 2 is a budesonide 9 mg not approved for the treatment of UC.

†$p<0.025$ for UCERIS 9 mg vs. placebo in both Studies 1 and 2 based on the Chi-square test (alpha = 0.025)

15 REFERENCES

1. Falt A, Bengtsson T, Kennedy B, et al. Exposure of infants to budesonide through breast milk of asthmatic mothers. *J. Allergy Clin Immunol.* 2007;120(4):798-802.
2. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298: 82-6.

16 HOW SUPPLIED/STORAGE AND HANDLING

UCERIS (budesonide) extended release tablets 9 mg, are white, round, biconvex tablets and debossed

with “MX9”. They are supplied as follows:

NDC (68012-309-30): Bottles of 30 tablets.

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature].

Keep container tightly closed. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Patients being treated with UCERIS extended release tablets should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of UCERIS.

17.1 Hypercorticism and Adrenal Suppression

Patients should be advised that UCERIS extended release tablets may cause systemic glucocorticosteroid effects of hypercorticism and adrenal suppression. Patients should taper slowly from systemic corticosteroids if transferring to UCERIS extended release tablets [*See Warnings and Precautions* (5.1) *and* (5.2)].

17.2 Immunosuppression

Patients who are on immunosuppressant doses of glucocorticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician immediately. If exposure to such a person occurs, and the patient has not had chicken pox or been properly vaccinated, a physician should be consulted immediately. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex [See *Warnings and Precautions* (5.3)].

17.3 How to Take UCERIS extended release tablets

UCERIS extended release tablets should be swallowed whole with water and NOT CHEWED, CRUSHED, OR BROKEN. Patients should be advised to avoid the consumption of grapefruit juice for the duration of their UCERIS therapy [See *Dosage and Administration* (2)].

Manufactured for Santarus, Inc., San Diego, CA 92130 • 1-888-778-0887

Manufactured by: Cosmo S.p.A., Milan, Italy.

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U.S. Patent Nos: 7,410,651; 7,431,943; RE43799; 8,293,273.
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S-0067A

FDA-approved Patient Labeling

UCERIS (u SAIR us)
(budesonide) (bew DEH so nide)
extended release tablets
What is UCERIS extended release tablets?

UCERIS is a prescription corticosteroid medicine used to help get mild to moderate ulcerative colitis (UC) under control (induce remission).

It is not known if UCERIS is safe and effective in children.

Who should not take UCERIS extended release tablets?

Do not take UCERIS extended release tablets if:

- you are allergic to budesonide or any of the ingredients in UCERIS extended release tablets. See the end of this leaflet for a complete list of ingredients in UCERIS extended release tablets.

What should I tell my healthcare provider before taking UCERIS extended release tablets?

Before you take UCERIS extended release tablets tell your healthcare provider if you:

- have liver problems
- are planning to have surgery
- have chicken pox or measles or have recently been near anyone with chicken pox or measles
- have an infection
- have or had a family history of diabetes, cataracts or glaucoma
- have or had tuberculosis
- have high blood pressure (hypertension)
- have decreased bone mineral density (osteoporosis)
- stomach ulcers
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if UCERIS extended release tablets will harm your unborn baby.
- are breastfeeding or plan to breastfeed. UCERIS extended release tablets can pass into your breast milk and may harm your baby. You and your healthcare provider should decide if you will take UCERIS extended release tablets or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter vitamins, and herbal supplements. UCERIS extended release tablets and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take UCERIS extended release tablets?

- Take UCERIS extended release tablets exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how many UCERIS extended release tablets to take.
- Take UCERIS extended release tablets in the morning.
- Take UCERIS extended release tablets capsules whole with water. Do not chew, crush, or break UCERIS extended release tablets before swallowing.
- If you take too much of UCERIS, call your healthcare provider right away or go to the nearest hospital emergency room.

What should I avoid while taking UCERIS extended release tablets?

- Do not eat grapefruit or drink grapefruit juice while taking UCERIS extended release tablets. Eating grapefruit or drinking grapefruit juice can increase the level of UCERIS extended release tablets in your blood.

What are the possible side effects of UCERIS extended release tablets?

UCERIS can cause some serious side effects, including:

- **Effects of having too much corticosteroid medicine in your blood (hypercorticism).** Long-time use of UCERIS extended release tablets can cause you to have too much glucocorticosteroid medicine in your blood. Tell your healthcare provider if you have any of the following signs and symptoms of hypercorticism:
  - acne
  - bruise easily
  - rounding of your face (moon face)

- ankle swelling
- thicker or more hair on your body and face
- a fatty pad or hump between your shoulders (buffalo hump)
- pink or purple stretch marks on the skin of your abdomen, thighs, breasts and arms

- **Adrenal suppression.** When UCERIS extended release tablets is taken for a long period of time (chronic use), the adrenal glands do not make enough steroid hormones (adrenal suppression). Tell your healthcare provider if you are under stress or have any symptoms of adrenal suppression during treatment with UCERIS extended release tablets including:

• tiredness	• vomiting
• weakness	• low blood pressure
• nausea	

- **Immune system effects and a higher chance of infections.**

UCERIS extended release tablets weaken your immune system. Taking medicines that weaken your immune system makes you more likely to get infections. Avoid contact with people who have contagious diseases such as chicken pox or measles, while taking UCERIS extended release tablets.

Tell your healthcare provider about any signs or symptoms of infection during treatment with UCERIS extended release tablets, including:

• fever	• chills
• pain	• feeling tired
• aches	• nausea and vomiting

- **Worsening of allergies.** If you take certain other corticosteroid medicines to treat allergies, switching to UCERIS extended release tablets may cause your allergies to come back. These allergies may include eczema (a skin disease) or rhinitis (inflammation inside your nose). Tell your healthcare provider if any of your allergies become worse while taking UCERIS extended release tablets.

The most common side effects of UCERIS extended release tablets include:

• headache	• bloating
• nausea	• acne
• decreased blood cortisol levels	• urinary tract infection
• stomach-area pain	• joint pain
• tiredness	• constipation
• stomach or intestinal gas	

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of UCERIS extended release tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store UCERIS extended release tablets?

- Store UCERIS extended release tablets at room temperature, between 68 °F to 77 °F (20 °C to 25 °C)
- Keep the bottle tightly closed to protect UCERIS from light and moisture.

Keep UCERIS extended release tablets and all medicines out of the reach of children.

General Information about UCERIS extended release tablets

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use UCERIS for a condition for which it was not prescribed. Do not give UCERIS to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about UCERIS that is written for health professionals.

For more information go to www.UCERIS.com or call (1-888-778-0887).

What are the ingredients in UCERIS extended release tablets?

Active Ingredients: budesonide

Inactive ingredients: stearic acid, lecithin, microcrystalline cellulose, hydroxypropylcellulose, lactose, silicon dioxide, magnesium stearate, methacrylic acid copolymer types A and B, talc, triethylcitrate, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

UCERIS (budesonide) Tablets are manufactured for Santarus, Inc., 3611 Valley Centre

Drive #400, San Diego, CA 92130, USA by: Cosmo S.p.A., Milan, Italy.

Revised 01/2013

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL 9 mg

NDC 68012-309-30

Uceris ™

(budesonide) extended release tablets

9 mg

Swallow tablet whole, do not chew or break.

30 Tablets|Rx Only

NDC 68012-309-30

UCERIS™

(budesonide) extended release tablets

9 mg

Swallow tablet whole, do not chew or break.

30 Tablets | Rx only

See package insert for statement of ingredients and dosage information.
Usual dose: one tablet daily, see Full Prescribing Information.
UCERIS should be swallowed whole and not chewed or broken.
Store and dispense: Keep container tightly closed.
Protect from light and moisture. Store at 25°C (77°F);
excursions permitted to 15-30°C (59-86°F).

Keep This And All Medications Out Of The Reach Of Children.

Manufactured for Santarus, Inc. 888-778-0887
San Diego, CA 92130 by Cosmo S.p.A., Milan, Italy.
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SANTARUS INC

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UCERIS

budesonide (11.beta.,16.alpha.(s)) tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68012-309
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BUDESONIDE (11.BETA.,16.ALPHA.(S)) (BUDESONIDE (11.BETA.,16.ALPHA.(S)))	BUDESONIDE (11.BETA.,16.ALPHA.(S))	9 mg

Inactive Ingredients

Ingredient Name	Strength
stearic acid	
lecithin, soybean	
cellulose, microcrystalline	
hydroxypropyl cellulose	
lactose	
silicon dioxide	
magnesium stearate	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1)	
talc	
triethyl citrate	
titanium dioxide	

Product Characteristics

Color	white (white)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	10mm
Flavor		**Imprint Code**	MX9
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68012-309-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA203634	01/14/2013	

Labeler - Santarus, Inc (104286369)

Establishment

Name	Address	ID/FEI	Business Operations
AndersonBrecon Inc		053217022	PACK(68012-309)

Establishment

Name	Address	ID/FEI	Business Operations
Cosmo SPA		630431955	MANUFACTURE(68012-309)

Establishment

Name	Address	ID/FEI	Business Operations
Sicor		338950678	API MANUFACTURE(68012-309)

Revised: 1/2013 Santarus, Inc