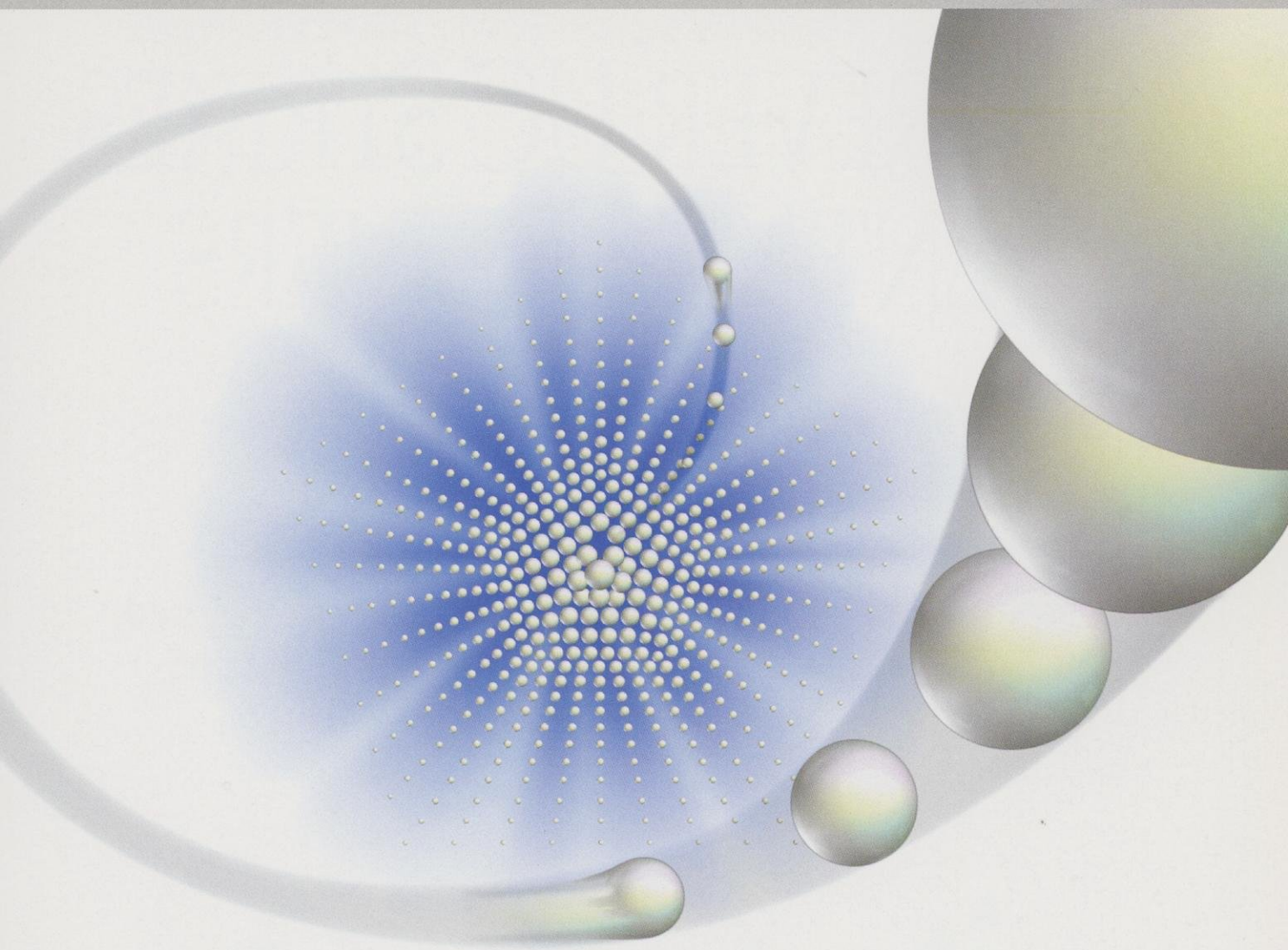
Pentasa advertisement.

[s.l.]: [s.n.], 1992

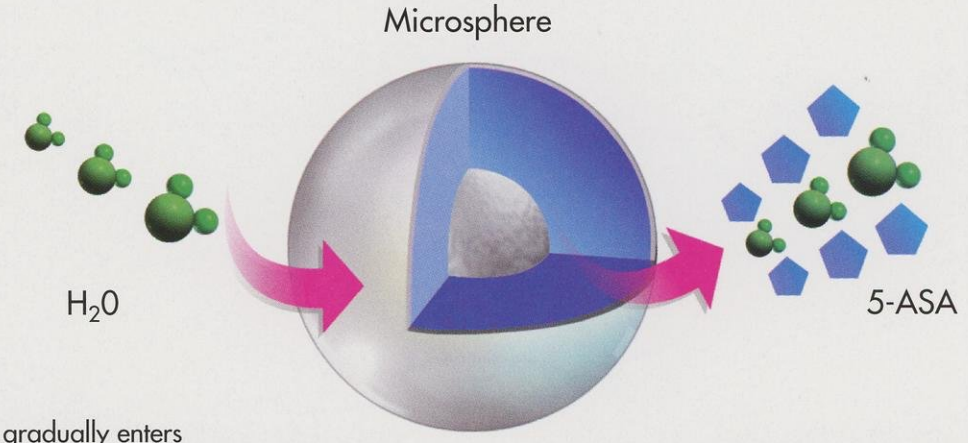


A New View of 5-ASA Delivery

WHEREVER UC STRIKES, PENTASA® DELIVERS

Only Pentasa has it–controlled, continuous 5-ASA delivery–for clinical efficacy at all UC disease locations[1]

Unique semipermeable microspheres are designed to continuously release therapeutic quantities of 5-ASA throughout the gastrointestinal tract[1]



Water gradually enters through the protective semipermeable polymer membrane and dissolves the 5-ASA

Dissolved 5-ASA slowly diffuses out at a controlled rate, throughout the GI tract

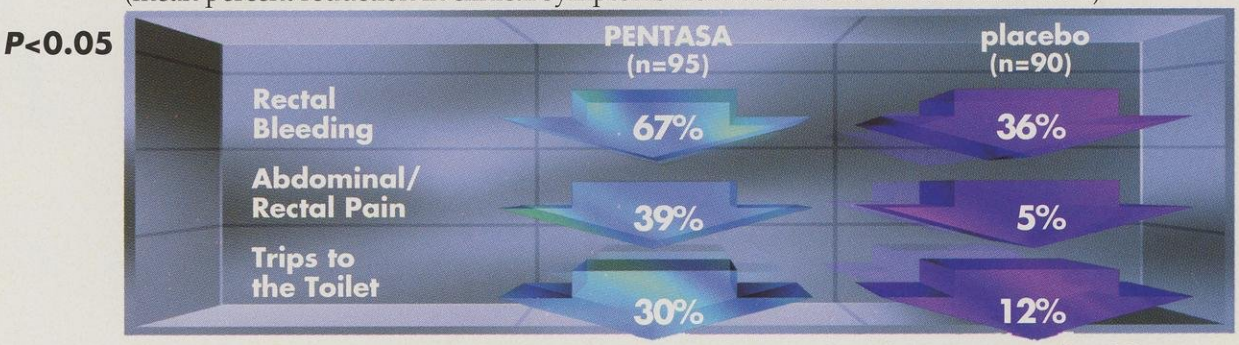
- Indicated for the induction of remission and for the treatment of mildly to moderately active UC[1]
- In an in vitro study, 5-ASA delivery was shown to be continuous at all the pH levels tested, from 1.5 to 7.5[2]

Please see brief summary of prescribing information on adjacent page.

PENTASA® DELIVERS REMISSION

- Proven to significantly reduce major clinical symptoms[2,3]

In an 8-week clinical study, Pentasa reduced patient-debilitating symptoms up to 67%
(mean percent reduction in clinical symptoms from baseline in Clinical Trial UC-1)



An 8-week placebo-controlled, double-blind, dose-ranging clinical trial involving patients with mildly to moderately active UC. Pentasa 4 g/day data presented above. Adapted from Hanauer et al.[3]

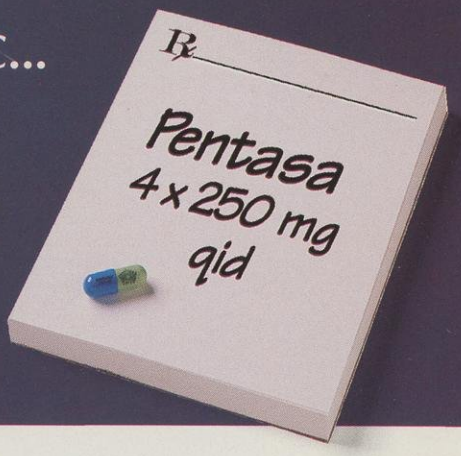
PENTASA® DELIVERS SAFELY

- Well tolerated at 4 g/day dosage[1]
- Low incidence of diarrhea (3.5% vs 7.5% with placebo)[1]
  In clinical trials, no single adverse event occurred in more than 4% of patients on Pentasa. Most common adverse events include diarrhea, nausea, headache, rash, abdominal pain, anorexia, nausea and vomiting (n=451)[1]
- Contains no sulfa–avoids sulfa-related semen abnormalities[1,4-6] and steroid-related osteoporosis[1,6,7] and hypokalemia[1,2,6]
- Exercise caution in patients with impaired hepatic or renal function; monitor patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria[1]

PENTASA®
(mesalamine) 250 mg
controlled-release capsules
PENTASA DELIVERS

FOR SAFELY INDUCING REMISSION OF MILDLY TO MODERATELY ACTIVE UC...

...PENTASA® DELIVERS



Prescribe Pentasa® — 4 x 250 mg, qid, #240 or #80

Brief Summary of Prescribing Information as of May 1993

PENTASA®
(mesalamine)
Controlled-Release Capsules 250 mg

INDICATIONS AND USAGE
PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS
PENTASA is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

PRECAUTIONS
General
Caution should be exercised if PENTASA is administered to patients with impaired hepatic function.
Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence cannot be ascertained, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

Renal
Caution should be exercised if PENTASA is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving PENTASA. In animal studies, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies of the carcinogenic potential of mesalamine in mice and rats are ongoing. No evidence of mutagenicity was observed in an in vitro Ames test and in an in vivo mouse micronucleus test. No effects on fertility or reproductive performance were observed in male or female rats at doses up to 400 mg/kg/day (2360 mg/M^2). For a 50-kg person (1.3 M^2 body surface area), this represents five times the recommended clinical dose (80 mg/kg/day) on a mg/kg basis and 0.8 times the clinical dose (2960 mg/M^2) on body surface area basis.
Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials.

Pregnancy
Category B. Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M^2) and rabbits at doses of 800 mg/kg/day (6856 mg/M^2) and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PENTASA should be used during pregnancy only if clearly needed.
Mesalamine is known to cross the placental barrier.

Nursing Mothers
Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02 μg/mL to 0.08 μg/mL and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively. N-acetylmesalamine, in quantities of 0.07 μg/mL to 0.77 μg/mL and 1.13 μg/mL to 3.44 μg/mL, was identified in the same fluids, respectively.
Caution should be exercised when PENTASA is administered to a nursing woman.

Pediatric Use
Safety and efficacy of PENTASA in children have not been established.

ADVERSE REACTIONS
In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received PENTASA therapy. Generally, PENTASA therapy was well tolerated. The most common events (ie, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).
In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in PENTASA-treated patients than in the placebo group (PENTASA 14% vs placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in the table below. Of these, only nausea and vomiting were more frequent in the PENTASA group. Withdrawal from therapy due to adverse events was more common on placebo than PENTASA (7% vs 4%).

Table 1. Adverse Events Occurring in More Than 1% of Either Placebo or PENTASA Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (PENTASA Comparison to Placebo)

Event	PENTASA n=451	Placebo n=173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	---
Abdominal Pain	5 (1.1%)	7 (4.0%)
Melena (Bloody Diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal Urgency	1 (0.2%)	4 (2.3%)
Nausea and Vomiting	5 (1.1%)	---
Worsening of Ulcerative Colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0.2%)	2 (1.2%)

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematologic, liver, and kidney function.
The following adverse events, presented by body system, were reported infrequently (ie, less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to PENTASA has not been established.

Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliases, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst

Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria

Nervous System: depression, dizziness, insomnia, somnolence, paresthesia

Cardiovascular: palpitations, pericarditis, vasodilation

Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.
Published case reports have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, or hepatitis while receiving mesalamine therapy.

Prescribing Information as of May 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

penb0593c

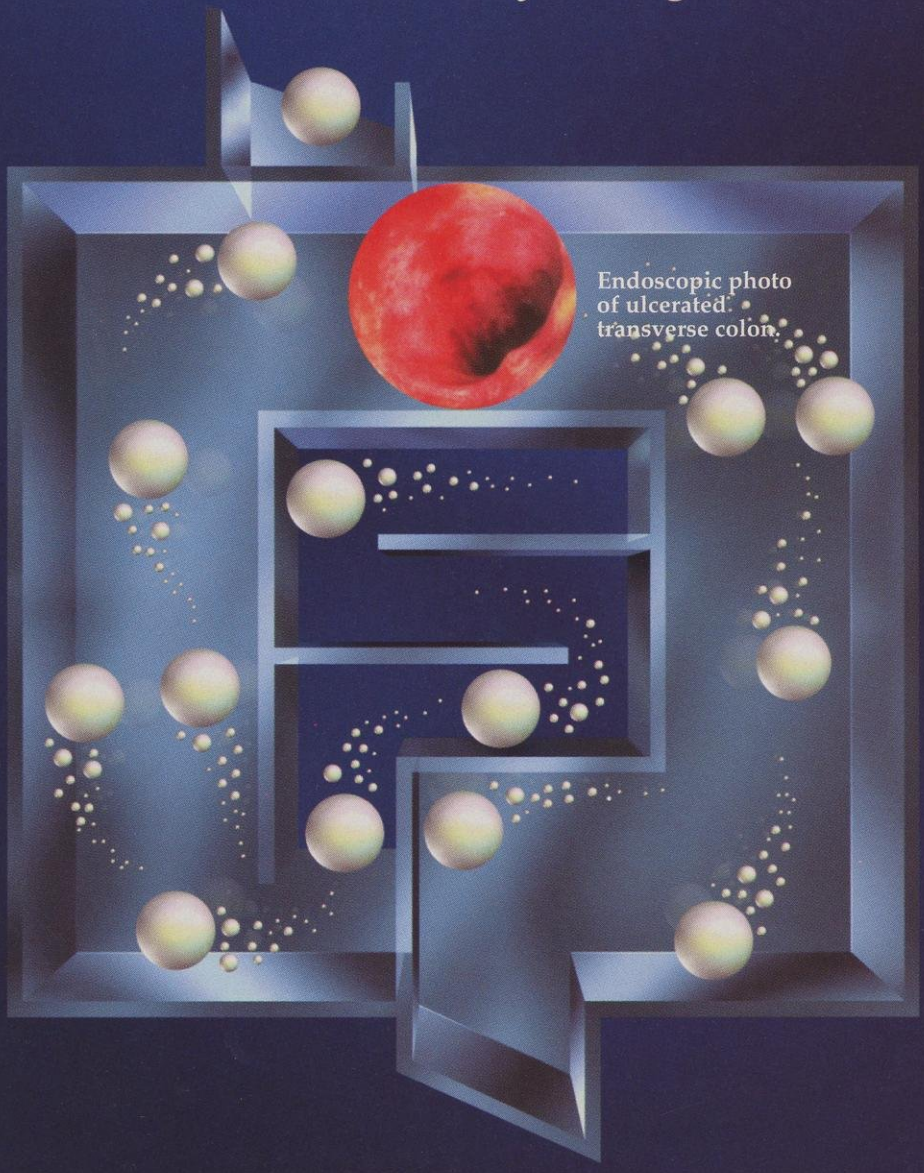
References:
1. Pentasa prescribing information.
2. Data on file, Marion Merrell Dow Inc.
3. Hanauer S, Schwartz J, Robinson M, et al. *Am J Gastroenterol.* 1993;88(8):1188-1197.
4. Peppercorn MA. *Ann Intern Med.* 1984; 3:377-386.
5. Birnie GG, McLeod TIF, Watkinson G. *Gut.* 1981;22:452-455.
6. *Drug Evaluations.* Annual 1992. Chicago Ill: American Medical Association; 1992:855-856, 1716-1717.
7. Lukert BP, Raisz LG. *Ann Intern Med.*1990;112:352-364.

PENTASA®
(mesalamine) 250 mg
controlled-release capsules
PENTASA DELIVERS

MARION MERRELL DOW INC.
U S A
KANSAS CITY, MO 64114

WHEREVER UC STRIKES, PENTASA® DELIVERS

Only Pentasa has it—a unique controlled-release design—for continuous 5-ASA delivery throughout the GI tract[1]



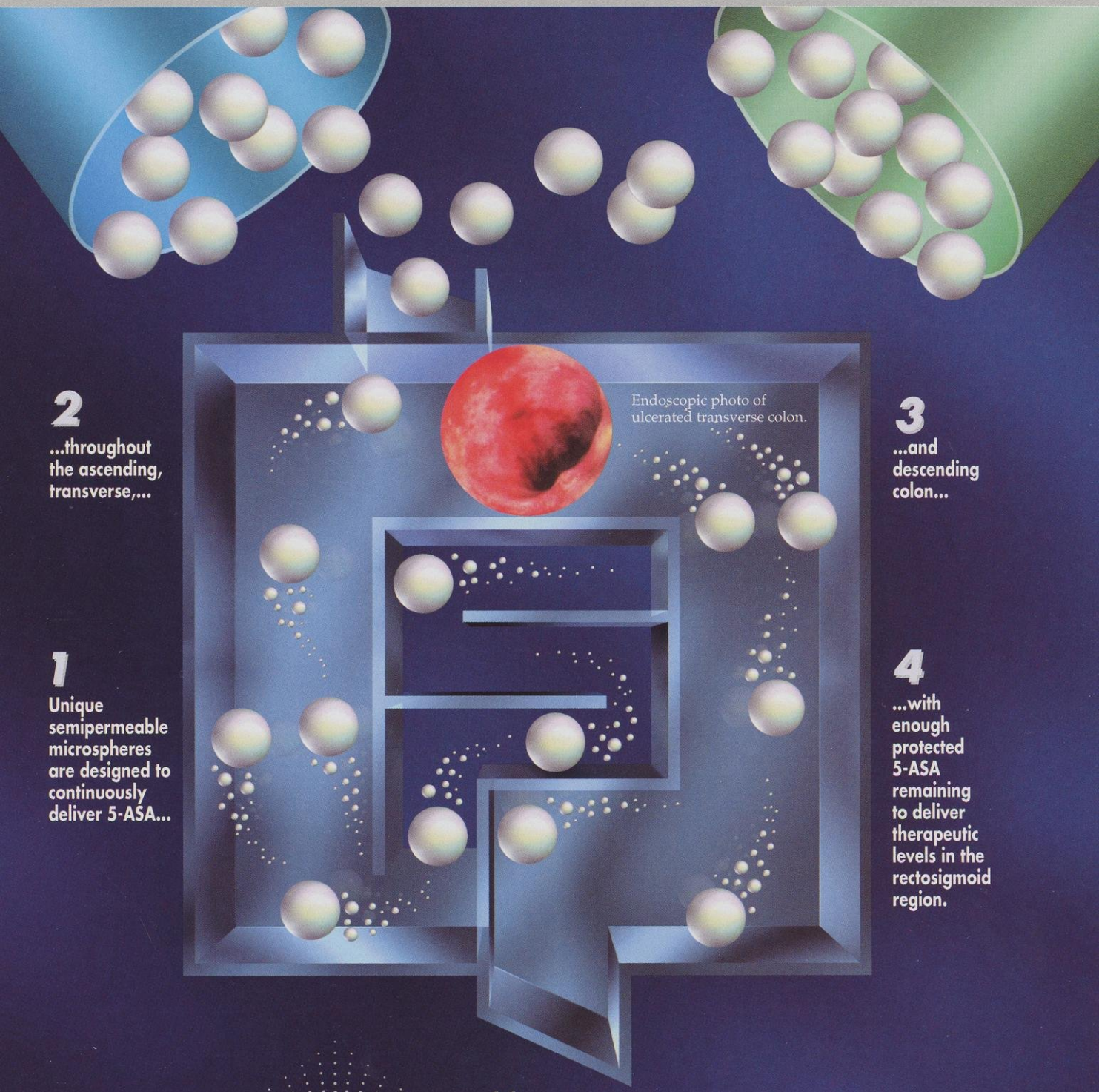
1 Unique semi-permeable microspheres are designed to continuously deliver 5-ASA...

2 ...throughout the ascending, transverse,...

3 ... and descending colon...

4 ...with enough protected 5-ASA remaining to ensure therapeutic levels in the rectosigmoid region.

- The only oral 5-ASA indicated for the induction of remission and treatment of mildly to moderately active UC[1]
- 5-ASA delivery was shown, in vitro, to be continuous at all pH levels tested, from 1.5 to 7.5[2]



1
Unique semipermeable microspheres are designed to continuously deliver 5-ASA...

2
...throughout the ascending, transverse,...

3
...and descending colon...

4
...with enough protected 5-ASA remaining to deliver therapeutic levels in the rectosigmoid region.

NEW

PENTASA®

(mesalamine) 250 mg

controlled-release capsules

PENTASA DELIVERS

PENTASA® DELIVERS EFFICACY

Proven to induce remission[1,3]

- In two clinical trials, significantly more UC patients on Pentasa 4 g/day achieved remission–strictly defined as complete resolution of symptoms plus improvement of endoscopic endpoints–than on placebo ($P<0.05$)[1,3]*†

Significantly reduces major clinical symptoms[2,3]

In an 8-week clinical study,
Pentasa reduced patient-debilitating symptoms up to 67%
(mean percent reduction in each symptom
from baseline in Clinical Trial UC-1)

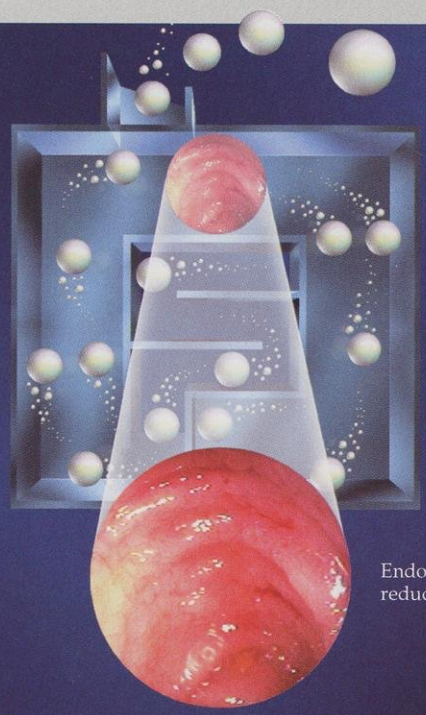
An 8-week placebo-controlled, double-blind, dose-ranging clinical trial involving patients with mildly to moderately active UC. Pentasa 4 g/day data presented above. Adapted from Hanauer et al.[3]

*Clinical trial UC-1: Pentasa 4 g/day, n=95; placebo, n=90.[1,3]

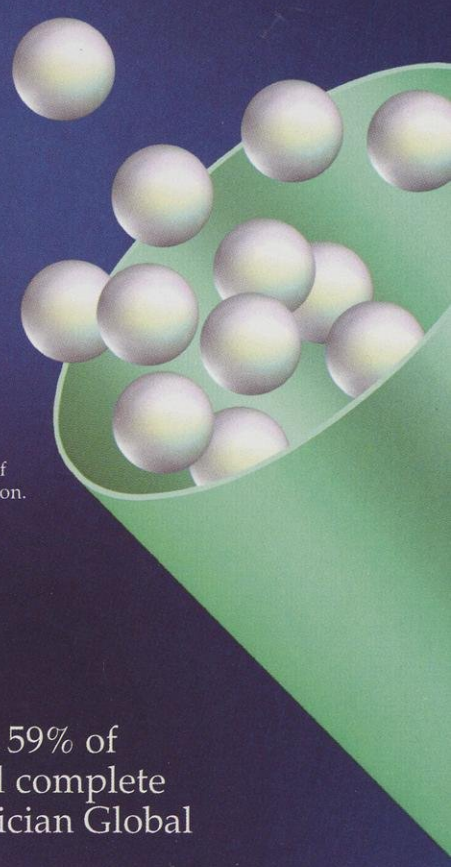
†Clinical trial UC-2: Pentasa 4 g/day, n=85; placebo, n=83.[1,2]

‡Physician Global Assessment consists of six categories that are (1) complete relief of symptoms, (2) marked improvement of symptoms, (3) moderate improvement of symptoms, (4) slight improvement of symptoms, (5) no change in symptoms, and (6) worsening of symptoms

Please see brief summary of prescribing information on adjacent page.



Endoscopic photo of reduced inflammation.



- In Clinical Trials UC-1 and UC-2, 55% to 59% of patients on Pentasa 4 g/day experienced complete or marked improvement, based on Physician Global Assessment (PGA)[1-3*†‡]
- In Clinical Trial UC-1, reductions in disease activity and symptom severity were seen in over 80% of patients on Pentasa 4 g/day, based on PGA[3*‡]

Treats both pancolitis and left-sided disease[2,3]

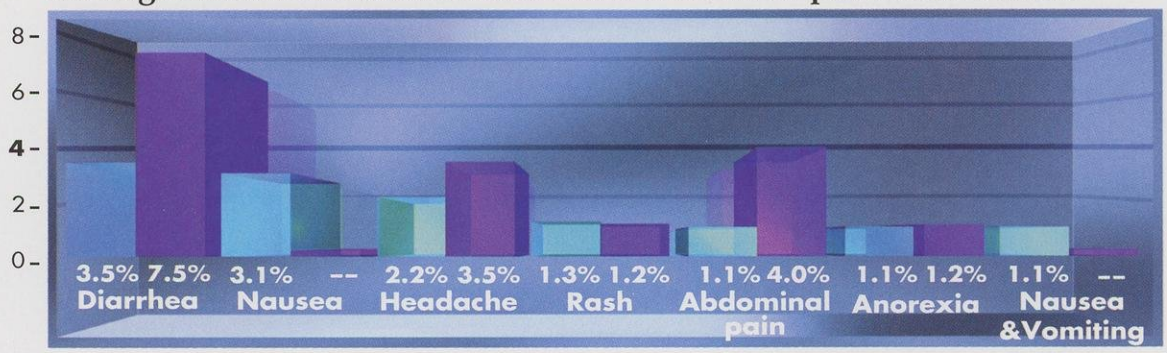
- In Clinical Trial UC-1, 52% of patients with pancolitis and 62% of patients with distal UC experienced complete relief or marked improvement on Pentasa 4 g/day, based on PGA (placebo: 32%-pancolitis, 37%-distal UC)[3*‡]

NEW
PENTASA®
(mesalamine) 250 mg
controlled-release capsules
PENTASA DELIVERS

PENTASA® DELIVERS SAFELY

Well tolerated[1]

In combined results from two clinical trials (n>600), no single adverse event occurred in more than 4% of patients on Pentasa[1]



Two 8-week, placebo-controlled, dose-ranging clinical trials involving patients with mildly to moderately active UC. Adapted from Pentasa prescribing information.[1]

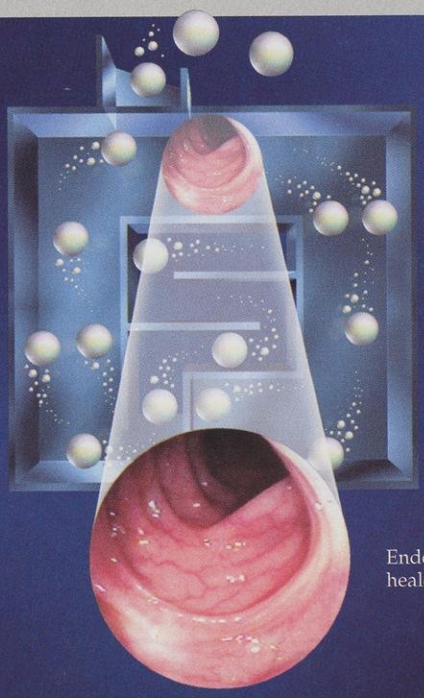
- **Overall rate of adverse events similar to placebo[1]**

- **Low incidence of diarrhea**
  In combined results from worldwide clinical trials (n>2100), only 3.4% of patients on Pentasa experienced diarrhea[1]

- **Low systemic absorption**
  Based on urinary excretion data, 20% to 30% of the 5-ASA in Pentasa is absorbed[1]

- **Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematologic, liver, and kidney function**
  Exercise caution in patients with impaired hepatic or renal function; monitor patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria[1]

Please see brief summary of prescribing information on adjacent page.



Endoscopic photo of healed colonic mucosa.

Pentasa® contains no sulfa and avoids the following major sulfa- and steroid-related side effects:

- Avoids sulfa-related semen abnormalities[1,4-6]
- Avoids steroid-related osteoporosis[1,6,7] and hypokalemia[1,2,6]

Pentasa® is effective first-line therapy for the induction of remission and treatment of mildly to moderately active ulcerative colitis

NEW

PENTASA®

(mesalamine) 250 mg

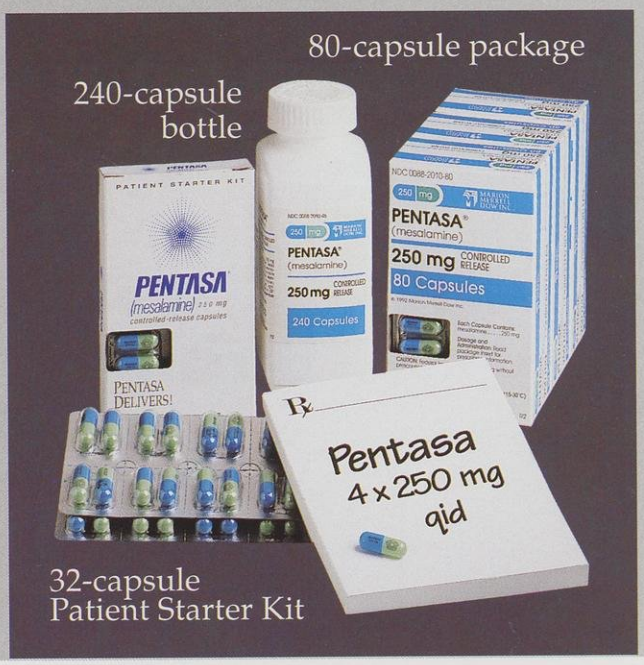
controlled-release capsules

PENTASA DELIVERS

NEW PENTASA® (mesalamine) controlled-release capsules

FOR SAFELY INDUCING REMISSION OF MILDLY TO MODERATELY ACTIVE UC... PENTASA® DELIVERS.

NEW
PENTASA®
(mesalamine) 250 mg
controlled-release capsules
PENTASA DELIVERS



Brief Summary of Prescribing Information as of May 1993

PENTASA®
(mesalamine)
Controlled-Release Capsules 250 mg

INDICATIONS AND USAGE
PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS
PENTASA is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

PRECAUTIONS
General
Caution should be exercised if PENTASA is administered to patients with impaired hepatic function.
Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence cannot be ascertained, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

Renal
Caution should be exercised if PENTASA is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving PENTASA. In animal studies, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies of the carcinogenic potential of mesalamine in mice and rats are ongoing. No evidence of mutagenicity was observed in an in vitro Ames test and in an in vivo mouse micronucleus test. No effects on fertility or reproductive performance were observed in male or female rats at doses up to 400 mg/kg/day (2360 mg/M²). For a 50-kg person (1.3 M² body surface area), this represents five times the recommended clinical dose (80 mg/kg/day) on a mg/kg basis and 0.8 times the clinical dose (2960 mg/M²) on body surface area basis.
Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials.

Pregnancy
Category B. Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M²) and rabbits at doses of 800 mg/kg/day (6856 mg/M²) and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PENTASA should be used during pregnancy only if clearly needed.
Mesalamine is known to cross the placental barrier.

Nursing Mothers
Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02 μg/mL to 0.08 μg/mL and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively. N-acetylmesalamine, in quantities of 0.07 μg/mL to 0.77 μg/mL and 1.13 μg/mL to 3.44 μg/mL, was identified in the same fluids, respectively.
Caution should be exercised when PENTASA is administered to a nursing woman.

Pediatric Use
Safety and efficacy of PENTASA in children have not been established.

ADVERSE REACTIONS
In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received PENTASA therapy. Generally, PENTASA therapy was well tolerated. The most common events (ie, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).
In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in PENTASA-treated patients than in the placebo group (PENTASA 14% vs placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in the table below. Of these, only nausea and vomiting were more frequent in the PENTASA group. Withdrawal from therapy due to adverse events was more common on placebo than PENTASA (7% vs 4%).

Table 1. Adverse Events Occurring in More Than 1% of Either Placebo or PENTASA Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (PENTASA Comparison to Placebo)

Event	PENTASA n=451	Placebo n=173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	---
Abdominal Pain	5 (1.1%)	7 (4.0%)
Melena (Bloody Diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal Urgency	1 (0.2%)	4 (2.3%)
Nausea and Vomiting	5 (1.1%)	---
Worsening of Ulcerative Colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0.2%)	2 (1.2%)

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematologic, liver, and kidney function.
The following adverse events, presented by body system, were reported infrequently (ie, less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to PENTASA has not been established.

Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliases, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst

Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria

Nervous System: depression, dizziness, insomnia, somnolence, paresthesia

Cardiovascular: palpitations, pericarditis, vasodilation

Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.
Published case reports have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, or hepatitis while receiving mesalamine therapy.

Prescribing Information as of May 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

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References:

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3. Hanauer S, Schwartz J, Robinson M, et al. *Am J Gastroenterol*. 1993;88(8):1188-1197.
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MARION MERRELL DOW INC.
U S A
KANSAS CITY, MO 64114

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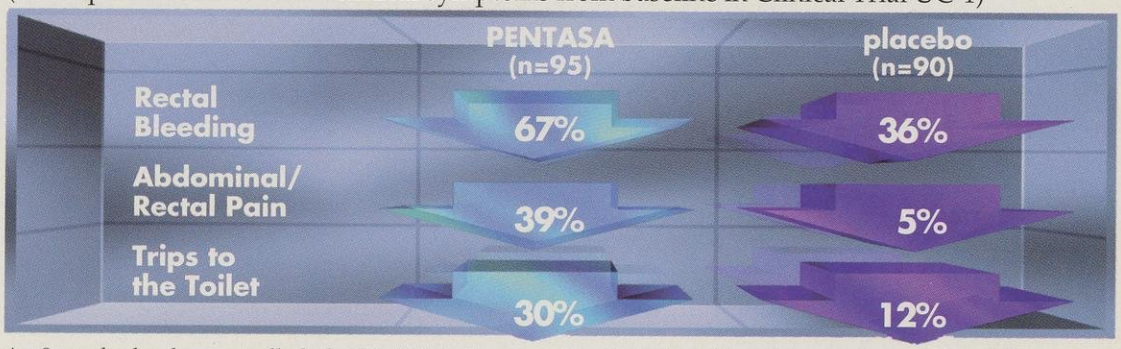
PENTASA® DELIVERS REMISSION

- Proven to significantly reduce major clinical symptoms[2,3]

In an 8-week clinical study, Pentasa reduced patient-debilitating symptoms up to 67%
(mean percent reduction in clinical symptoms from baseline in Clinical Trial UC-1)



An 8-week placebo-controlled, double-blind, dose-ranging clinical trial involving patients with mildly to moderately active UC. Pentasa 4 g/day data presented above. Adapted from Hanauer et al.[3]

PENTASA® DELIVERS SAFELY

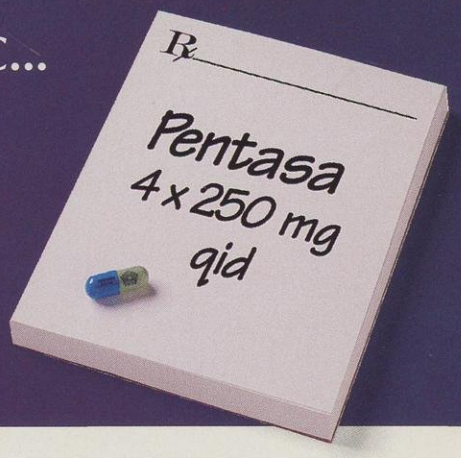
- Well tolerated at 4 g/day dosage[1]
- Low incidence of diarrhea (3.5% vs 7.5% with placebo)[1]
  In clinical trials, no single adverse event occurred in more than 4% of patients on Pentasa. Most common adverse events include diarrhea, nausea, headache, rash, abdominal pain, anorexia, nausea and vomiting (n=451)[1]
- Contains no sulfa–avoids sulfa-related semen abnormalities[1,4-6] and steroid-related osteoporosis[1,6,7] and hypokalemia[1,2,6]
- Exercise caution in patients with impaired hepatic or renal function; monitor patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria[1]

PENTASA®
(mesalamine) 250 mg
controlled-release capsules
PENTASA DELIVERS

FOR SAFELY INDUCING REMISSION OF MILDLY TO MODERATELY ACTIVE UC...

...PENTASA® DELIVERS

Prescribe Pentasa® — 4 x 250 mg, qid, #240 or #80



Brief Summary of Prescribing Information as of May 1993

PENTASA®
(mesalamine)
Controlled-Release Capsules 250 mg

INDICATIONS AND USAGE
PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS
PENTASA is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

PRECAUTIONS
General
Caution should be exercised if PENTASA is administered to patients with impaired hepatic function.
Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence cannot be ascertained, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

Renal
Caution should be exercised if PENTASA is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving PENTASA. In animal studies, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies of the carcinogenic potential of mesalamine in mice and rats are ongoing. No evidence of mutagenicity was observed in an in vitro Ames test and in an in vivo mouse micronucleus test. No effects on fertility or reproductive performance were observed in male or female rats at doses up to 400 mg/kg/day (2360 mg/M^2). For a 50-kg person (1.3 M^2 body surface area), this represents five times the recommended clinical dose (80 mg/kg/day) on a mg/kg basis and 0.8 times the clinical dose (2960 mg/M^2) on body surface area basis.
Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials.

Pregnancy
Category B. Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M^2) and rabbits at doses of 800 mg/kg/day (6856 mg/M^2) and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PENTASA should be used during pregnancy only if clearly needed.
Mesalamine is known to cross the placental barrier.

Nursing Mothers
Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02 μg/mL to 0.08 μg/mL and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively. N-acetylmesalamine, in quantities of 0.07 μg/mL to 0.77 μg/mL and 1.13 μg/mL to 3.44 μg/mL, was identified in the same fluids, respectively.
Caution should be exercised when PENTASA is administered to a nursing woman.

Pediatric Use
Safety and efficacy of PENTASA in children have not been established.

ADVERSE REACTIONS
In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received PENTASA therapy. Generally, PENTASA therapy was well tolerated. The most common events (ie, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).
In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in PENTASA-treated patients than in the placebo group (PENTASA 14% vs placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in the table below. Of these, only nausea and vomiting were more frequent in the PENTASA group. Withdrawal from therapy due to adverse events was more common on placebo than PENTASA (7% vs 4%).

Table 1. Adverse Events Occurring in More Than 1% of Either Placebo or PENTASA Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (PENTASA Comparison to Placebo)

Event	PENTASA n=451	Placebo n=173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	---
Abdominal Pain	5 (1.1%)	7 (4.0%)
Melena (Bloody Diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal Urgency	1 (0.2%)	4 (2.3%)
Nausea and Vomiting	5 (1.1%)	---
Worsening of Ulcerative Colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0.2%)	2 (1.2%)

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematologic, liver, and kidney function.
The following adverse events, presented by body system, were reported infrequently (ie, less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to PENTASA has not been established.

Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliases, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst

Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria

Nervous System: depression, dizziness, insomnia, somnolence, paresthesia

Cardiovascular: palpitations, pericarditis, vasodilation

Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.
Published case reports have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, or hepatitis while receiving mesalamine therapy.

Prescribing Information as of May 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

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LICENSED FROM FERRING A/S, DENMARK
LICENSED US PATENT NOS. B1 4,496,533 AND 4,980,173

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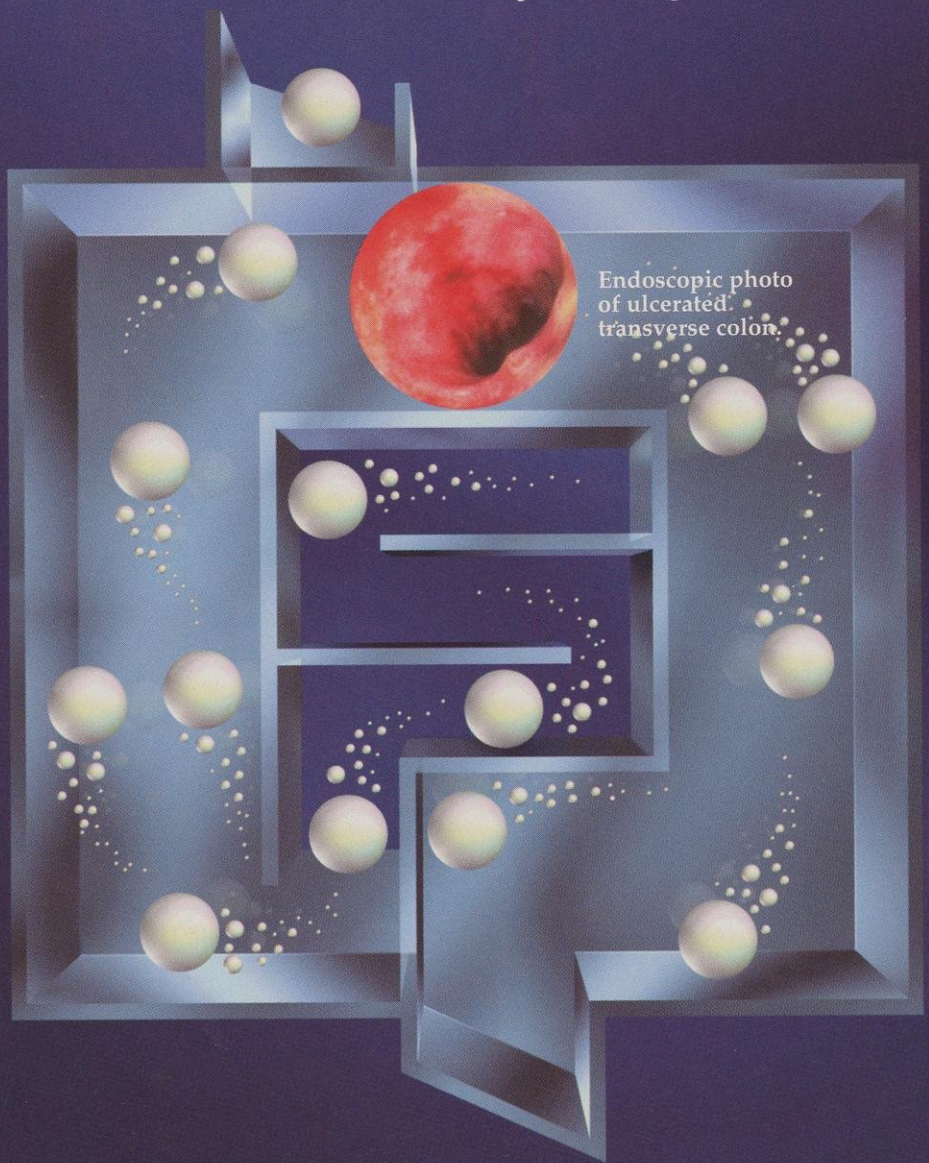
PENTASA®
(mesalamine) 250 mg
controlled-release capsules
PENTASA DELIVERS

MARION MERRELL DOW INC.
U S A
KANSAS CITY, MO 64114

WHEREVER UC STRIKES, PENTASA® DELIVERS

Only Pentasa has it—a unique controlled-release design—for continuous 5-ASA delivery throughout the GI tract[1]



1 Unique semi-permeable microspheres are designed to continuously deliver 5-ASA...

2 ...throughout the ascending, transverse,...

3 ... and descending colon...

4 ...with enough protected 5-ASA remaining to ensure therapeutic levels in the rectosigmoid region.

- The only oral 5-ASA indicated for the induction of remission and treatment of mildly to moderately active UC[1]
- 5-ASA delivery was shown, in vitro, to be continuous at all pH levels tested, from 1.5 to 7.5[2]