資料３－⑤　PEG 化セルトリズマブ（certolizmab pegol）

Cimzia®
(certolizumab pegol)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CIMZIA® safely and effectively. See full prescribing information for CIMZIA.

CIMZIA (certolizumab pegol)
Lyophilized powder for solution for subcutaneous injection
Initial U.S. Approval: 2008

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

Tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred. Perform test for latent TB; if positive, start treatment for TB prior to starting CIMZIA. Monitor all patients for active TB during CIMZIA treatment, even if initial tuberculin skin test is negative (5.1, 5.2).

----------INDICATIONS AND USAGE----------
CIMZIA is a tumor necrosis factor (TNF) blocker indicated for:
- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy (1)

----------DOSAGE AND ADMINISTRATION----------
- 400 mg subcutaneously initially and at Weeks 2 and 4 (2.1)
- If response occurs, follow with 400 mg subcutaneously every four weeks (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- 200 mg lyophilized powder for reconstitution with 1 mL of sterile Water for Injection, USP (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious infections – do not start CIMZIA during an active infection. If an infection develops, monitor carefully, and stop CIMZIA if infection becomes serious (5.1)
- Hepatitis B virus reactivation – monitor HBV carriers during and several months after therapy. If reactivation occurs, stop CIMZIA and begin anti-viral therapy (5.3)
- Cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers (5.4)
- Anaphylaxis or serious allergic reactions may occur (5.5)
- Demyelinating disease, exacerbation or new onset, may occur (5.6)
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping CIMZIA (5.7)
- Heart failure, worsening or new onset may occur (5.9)
- Lupus-like syndrome – stop CIMZIA if syndrome develops (5.10)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥5% and higher than placebo): upper respiratory tract infection, urinary tract infection, and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-866-822-0068 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Anakinra – increased risk of serious infections (5.8, 7.1)
- Live vaccines – do not give with CIMZIA (5.11, 7.2)
- Laboratory tests – may interfere with aPTT tests (7.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 4/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Cimzia®
(certolizumab pegol)

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving CIMZIA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with TNF blockers such as CIMZIA. However, active tuberculosis has developed in patients receiving CIMZIA whose tuberculin test was negative.

Evaluate patients for tuberculosis risk factors and test for latent tuberculosis infection prior to initiating CIMZIA and during therapy. Initiate treatment of latent tuberculosis infection prior to therapy with CIMZIA. Monitor patients receiving CIMZIA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection *[see Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

CIMZIA is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended initial adult dose of CIMZIA is 400 mg (given as two subcutaneous injections of 200 mg) initially, and at Weeks 2 and 4. In patients who obtain a clinical response, the recommended maintenance regimen is 400 mg every four weeks.

2.2 Preparation Instructions

CIMZIA should be prepared by a health care professional.

CIMZIA is provided in a package that contains everything required to reconstitute and inject the drug as described below. CIMZIA should be brought to room temperature before reconstituting to facilitate dissolution.

Reconstitute two 200 mg vials of CIMZIA for each dose. Using appropriate aseptic technique, reconstitute each lyophilized vial of CIMZIA with 1 mL of sterile Water for Injection, USP, using a syringe with a 20 gauge needle. Gently swirl each vial of CIMZIA without shaking so that all of the lyophilized powder comes into contact with the sterile Water for Injection. Leave the vials undisturbed to fully reconstitute (this may take as long as 30 minutes). Reconstituted CIMZIA has a concentration of approximately 200 mg/mL.

Do not leave reconstituted CIMZIA at room temperature for more than 2 hours prior to administration. Once reconstituted, CIMZIA can be stored in the vials for up to 24 hours at 2 to 8 °C (36 to 46 °F) prior to injection. Do not freeze.

2.3 Administration Instructions

CIMZIA should be administered by a health care professional.

Once reconstituted, CIMZIA is a clear to opalescent, colorless to pale yellow liquid with no visible particulates or gels in solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted CIMZIA with obvious particulate matter or discoloration should be discarded.

Prior to injecting, reconstituted CIMZIA should be at room temperature. Using a new 20 gauge needle for each vial, withdraw the reconstituted solution into a separate syringe for each vial, resulting in two syringes each containing 1 mL of CIMZIA (200 mg). Switch each 20 gauge needle to a 23 gauge needle and inject the full contents of each syringe subcutaneously into separate sites on the abdomen or thigh.

3 DOSAGE FORMS AND STRENGTHS

CIMZIA is supplied as a sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. Each single-use vial provides approximately 200 mg certolizumab pegol.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious infections, sepsis, and cases of opportunistic infections, including fatalities, have been reported in patients receiving TNF blockers, including CIMZIA. Many of the serious infections reported have occurred in patients on concomitant immunosuppressive therapy that, in addition to their Crohn's disease, could predispose them to infections. In postmarketing experience with TNF blockers, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms, and infections have been noted in all organ systems. Infections have been reported in patients receiving CIMZIA alone or in conjunction with immunosuppressive agents.

Do not initiate treatment with CIMZIA in patients with active infections, including chronic or localized infections. Monitor patients for signs and symptoms of infection while on and after treatment with CIMZIA. Patients who develop a new infection while undergoing treatment with CIMZIA should be monitored closely. Discontinue administration of CIMZIA if a patient develops a serious infection. Exercise caution when considering the use of CIMZIA in patients with a history of recurrent infection, concomitant immunosuppressive therapy, or underlying conditions that may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. The benefits and risks of CIMZIA

treatment should be carefully considered before initiation of CIMZIA therapy *[see Adverse Reactions (6.1)]*.

5.2 Tuberculosis

As observed with other TNF blockers, tuberculosis associated with the administration of CIMZIA in clinical studies has been reported, including fatalities.

Before initiation of therapy with CIMZIA, evaluate patients for tuberculosis risk factors and test for latent tuberculosis infection. Initiate treatment of latent tuberculosis infections prior to therapy with CIMZIA. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG). If latent infection is diagnosed, institute appropriate prophylaxis in accordance with the current guidelines from the Centers for Disease Control and Prevention.

Consider the possibility of undetected latent tuberculosis, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with CIMZIA should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF blockers.

Consider anti-tuberculosis therapy prior to initiation of CIMZIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating CIMZIA should also be considered in patients who have several, or highly significant, risk factors for tuberculosis infection and have a negative test for latent tuberculosis, but the decision to initiate anti-tuberculosis therapy in the patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consult a physician with experience in the treatment of tuberculosis.

Monitor patients receiving CIMZIA for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. Instruct patients to seek medical advice if signs/symptoms (e.g., persistent cough, wasting, weight loss, low grade fever) suggestive of a tuberculosis infection occur.

5.3 Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating CIMZIA therapy. Exercise caution in prescribing CIMZIA for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

5.4 Malignancies

In the controlled portions of clinical studies of some TNF blockers, more cases of malignancies have been observed among patients receiving TNF blockers compared to control patients. During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other investigational uses, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.6 (0.4, 0.8) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.2, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients.

Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn's disease or other diseases that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy. The potential role of TNF blocker therapy in the development of malignancies is not known.

5.5 Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed *[see Adverse Reactions (6.1)]*.

5.6 Neurologic Reactions

Use of TNF blockers, including CIMZIA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA; the causal relationship to CIMZIA remains unclear *[see Adverse Reactions (6.1)]*.

5.7 Hematological Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia

(e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA *[see Adverse Reactions (6.1)]*. The causal relationship of these events to CIMZIA remains unclear.

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

5.8 Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blockers. Therefore, the combination of CIMZIA and anakinra is not recommended *[see Drug Interactions (7.1)]*.

5.9 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in CHF of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using CIMZIA in patients who have heart failure and monitor them carefully.

5.10 Autoimmunity

Treatment with CIMZIA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, discontinue treatment *[see Adverse Reactions (6.1)]*.

5.11 Immunizations

No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. Do not administer live vaccines or attenuated vaccines concurrently with CIMZIA.

5.12 Immunosuppression

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4) and Adverse Reactions (6.1)]*. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions were:

- Serious Infections *[see Warnings and Precautions (5.1, 5.2)]*
- Malignancies *[see Warnings and Precautions (5.4)]*

The data described below reflect exposure to CIMZIA at 400 mg subcutaneous dosing in studies of patients with Crohn's disease. In the safety population in controlled studies, a total of 620 subjects with Crohn's disease received CIMZIA at a dose of 400 mg, and 614 subjects received placebo (including subjects randomized to placebo in Study CD2 following open label dosing of CIMZIA at Week 0, 2, 4). In controlled and uncontrolled studies, 1,564 subjects received CIMZIA at some dose level, of whom 1,350 subjects received 400 mg CIMZIA. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18 and 64.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for CIMZIA and 9% for placebo. The most common adverse reactions (occurring in ≥ 5% of Cimzia-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with CIMZIA was upper respiratory infection (20% CIMZIA, 13% placebo), urinary tract infection (7% CIMZIA, 6% placebo), and arthralgia (6% CIMZIA, 4% placebo).

The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo. The most common adverse reactions leading to the discontinuation of CIMZIA (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% CIMZIA, 0.2% placebo), diarrhea (0.4% CIMZIA, 0% placebo), and intestinal obstruction (0.4% CIMZIA, 0% placebo).

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Infections

The incidence of infections in controlled clinical studies was 38% for CIMZIA-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infection (20% CIMZIA, 13% placebo). The incidence of serious infections during the controlled clinical studies was 3% for CIMZIA-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis *[see Warnings and Precautions (5.1, 5.2)]*.

Tuberculosis and Opportunistic Infections

In completed and ongoing clinical studies that include over 4,650 patients, the overall rate of tuberculosis is approximately 0.5 per 100 patient-years. The rate in Crohn's disease studies was 0.3 cases per 100 patient-years. The reports include cases of pulmonary and disseminated tuberculosis. Cases of opportunistic infection have also been reported in clinical trials. Some cases of opportunistic infections and tuberculosis have been fatal *[see Warnings and Precautions (5.2)]*.

Malignancies

In clinical studies of CIMZIA, the overall incidence rate of malignancies was similar for CIMZIA-treated and control patients. For some TNF blockers, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients *[see Warnings and Precautions (5.4)]*.

Autoantibodies

In clinical studies in Crohn's disease, 4% of patients treated with CIMZIA and 2% of patients treated with placebo that had negative baseline ANA titers developed positive titers during the studies. One of the 1,564 Crohn's disease patients treated with CIMZIA developed symptoms of a lupus-like syndrome. The impact of long-term treatment with CIMZIA on the development of autoimmune diseases is unknown *[see Warnings and Precautions (5.10)]*.

Immunogenicity

Patients were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. The overall percentage of antibody positive patients was 8% in patients continuously exposed to CIMZIA, of which approximately 80% were neutralizing *in vitro*. No apparent correlation of antibody development to adverse events or efficacy was observed. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively).

The following adverse events were reported in antibody-positive patients (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.

The data reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to certolizumab pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dermatitis allergic, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope *[see Warnings and Precautions (5.5)]*.

Other Adverse Reactions

The most commonly occurring adverse reactions in controlled trials of Crohn's disease were described above. Other serious or significant adverse reactions reported in controlled and uncontrolled studies in Crohn's disease and other diseases under investigation, occurring in patients receiving CIMZIA at doses of 400 mg or other doses include:

Blood and lymphatic system disorders: Anemia, leukopenia, lymphadenopathy, pancytopenia, and thrombophilia.

Cardiac disorders: Angina pectoris, arrhythmias, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, and pericarditis.

Eye disorders: Optic neuritis, retinal hemorrhage, and uveitis.

General disorders and administration site conditions: Bleeding and injection site reactions.

Hepatobiliary disorders: Elevated liver enzymes and hepatitis.

Immune system disorders: Alopecia totalis.

Psychiatric disorders: Anxiety, bipolar disorder, and suicide attempt.

Renal and urinary disorders: Nephrotic syndrome and renal failure.

Reproductive system and breast disorders: Menstrual disorder.

Skin and subcutaneous tissue disorders: Dermatitis, erythema nodosum, and urticaria.

Vascular disorders: Vasculitis.

6.2 Adverse Reaction Information from Other Sources

Cases of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, have been identified during post-approval use of other TNF blockers. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF blocker has shown an increased risk of serious infections, an increased risk of neutropenia, and no added benefit compared to these medicinal products alone. Therefore, the combination of

anakinra with other TNF blockers, including CIMZIA, may also result in similar toxicities *[see Warnings and Precautions (5.8)]*.

7.2 Live Vaccines

Do not give live (including attenuated) vaccines concurrently with CIMZIA *[see Warnings and Precautions (5.11)]*.

7.3 Laboratory Tests

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-LA test from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays has not been observed. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Reproduction studies have been performed in rats at doses up to 100 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF. There are, however, no adequate and well-controlled studies of CIMZIA in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CIMZIA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of CIMZIA did not include sufficient numbers of patients 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. A population pharmacokinetic analysis of all patients enrolled in CIMZIA clinical studies concluded that there was no apparent difference in drug concentration regardless of age. Because there is a higher incidence of infections in the elderly population in general, use caution when treating the elderly *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

The maximum tolerated dose of certolizumab pegol has not been established. Doses of up to 800 mg subcutaneous and 20 mg/kg intravenous have been administered without serious adverse reactions. In cases of overdosage, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

CIMZIA (certolizumab pegol) is a TNF blocker. CIMZIA is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα), conjugated to an approximately 40kDa polyethylene glycol (PEG2MAL40K). The Fab' fragment is manufactured in E. coli and is subsequently subjected to purification and conjugation to PEG2MAL40K, to generate certolizumab pegol. The Fab' fragment is composed of a light chain with 214 amino acids and a heavy chain with 229 amino acids. The molecular weight of certolizumab pegol is approximately 91 kilodaltons.

CIMZIA is supplied as a sterile, white, lyophilized powder for solution for subcutaneous injection. Reconstituted CIMZIA is a clear to opalescent solution that is colorless to pale yellow without particulates or gels. After reconstitution with 1 mL sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial provides approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Certolizumab pegol binds to human TNFα with a KD of 90pM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα (IC_{90} of 4 ng/mL for inhibition of human TNFα in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin α (TNFβ). Certolizumab pegol cross-reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNFα was the physiologically active molecule.

Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNFα in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNFα and IL-1β production in human monocytes.

Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes, nor does certolizumab pegol induce neutrophil degranulation.

A tissue reactivity study was carried out *ex vivo* to evaluate potential cross-reactivity of certolizumab pegol with cryosections of normal human tissues. Certolizumab pegol showed no reactivity with a designated standard panel of normal human tissues.

12.2 Pharmacodynamics

Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of Crohn's disease. TNFα is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNFα in patients with Crohn's disease have been shown to reflect clinical severity of the disease. After treatment with certolizumab pegol, patients with Crohn's disease demonstrated a decrease in the levels of C-reactive protein (CRP).

12.3 Pharmacokinetics

A total of 78 healthy subjects received doses of up to 800 mg certolizumab pegol subcutaneously and up to 10 mg/kg intravenously in three pharmacokinetic studies. Data from these studies demonstrate that single intravenous and subcutaneous doses of certolizumab pegol have predictable dose-related plasma concentrations with a linear relationship between the dose administered and the maximum serum concentration (C_{max}), and the Area Under the certolizumab pegol plasma concentration versus time Curve (AUC). Patients with Crohn's disease were dosed subcutaneously every four weeks with certolizumab pegol at 100, 200, or 400 mg and at 400 mg every two weeks for three doses, followed by a maintenance dose of 400 mg every four weeks. Certolizumab pegol plasma concentrations were broadly dose-proportional and pharmacokinetics observed in patients with Crohn's disease were consistent with those seen in healthy subjects.

The pharmacokinetics of certolizumab pegol were evaluated in a cross-study population pharmacokinetic analysis of data from 1580 subjects, of whom 1268 were patients with Crohn's disease. The population pharmacokinetic analysis concluded that age, gender, creatinine clearance, and white blood cell count did not influence the pharmacokinetics of certolizumab pegol. The population pharmacokinetic analysis did not allow any conclusion to be drawn on the effect of hepatic impairment because of the small number of patients with significant liver dysfunction included in the analysis.

Anti-certolizumab pegol antibodies, repeated administration, weight, and immunosuppressant use were covariates that had a statistically significant effect on the pharmacokinetics of certolizumab pegol. Only the presence of antibodies had more than a 30% effect on C_{max} and/or AUC.

None of the subject-dependant covariates identified in the population pharmacokinetic analysis had an effect that would require dose adjustment.

Pharmacokinetic parameters in Japanese subjects were similar to those in Caucasian subjects following subcutaneous dosing at three dose levels in a biocomparability study.

- **Absorption**

Following subcutaneous administration, peak plasma concentrations of certolizumab pegol were attained between 54 and 171 hours post-injection. Certolizumab pegol has bioavailability (F) of approximately 80% (ranging from 76% to 88%) following subcutaneous administration

compared to intravenous administration. Steady-state concentrations range from 0.5 to 90 mcg/mL for a fixed dose of 400 mg of certolizumab pegol. For patients developing anti-certolizumab pegol antibodies, the steady state concentrations range from 0.5 to 75 mcg/mL.

- **Distribution**

The steady state volume of distribution (Vss) was estimated as 6.4 L in the population pharmacokinetic analysis.

- **Metabolism and Elimination**

Pegylation, the covalent attachment of PEG polymers to peptides, delays the elimination of these entities from the circulation by a variety of mechanisms, including decreased renal clearance, proteolysis, and immunogenicity. Accordingly, certolizumab pegol is an antibody Fab' fragment conjugated with PEG in order to extend the terminal plasma elimination half-life of the Fab' to a value comparable with a whole antibody product. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all doses tested. The clearance following subcutaneous dosing was estimated as 17 mL/h in the population pharmacokinetic analysis, with an inter-subject variability of 38% (CV) and an inter-occasion variability of 16%. The route of elimination of certolizumab pegol has not been studied in human subjects.

- **Drug Interaction Studies**

Formal drug-drug interaction studies have not been conducted with CIMZIA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of CIMZIA have not been conducted to assess its carcinogenic potential. Certolizumab pegol was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Since certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab fragment (cTNF PF), similar to certolizumab pegol. cTNF PF had no effects on the fertility and general reproductive performance of male and female rats at intravenous doses up 100 mg/kg, administered twice weekly.

14 CLINICAL STUDIES

14.1 Crohn's Disease

The efficacy and safety of CIMZIA were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI[1]) of 220 to 450 points, inclusive. CIMZIA was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1

Study CD1 was a randomized placebo-controlled study in 662 patients with active Crohn's disease. CIMZIA or placebo was administered at Weeks 0, 2, and 4 and then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower.

The results for Study CD1 are provided in Table 1. At Week 6, the proportion of clinical responders was statistically significantly greater for CIMZIA-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Table 1 Study CD1 – Clinical Response and Remission, Overall Study Population

Timepoint	% Response or Remission (95% CI)	
	Placebo (N = 328)	**CIMZIA 400 mg (N = 331)**
Week 6		
Clinical Response[#]	**27%** (22%, 32%)	**35%** (30%, 40%)*
Clinical Remission[#]	**17%** (13%, 22%)	**22%** (17%, 26%)
Week 26		
Clinical Response	**27%** (22%, 31%)	**37%** (32%, 42%)*
Clinical Remission	**18%** (14%, 22%)	**29%** (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	**16%** (12%, 20%)	**23%** (18%, 28%)*
Clinical Remission	**10%** (7%, 13%)	**14%** (11%, 18%)

* p-value < 0.05 logistic regression test
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Study CD2

Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn's disease. All patients who entered the study were dosed initially with CIMZIA 400 mg at Weeks 0, 2, and 4 and then assessed for clinical response at Week 6 (as defined by at least a 100-point reduction in CDAI score). At Week 6, a group of 428 clinical responders was randomized to receive either CIMZIA 400 mg or placebo, every four weeks starting at Week 8, as maintenance therapy through Week 24. Non-responders at Week 6 were withdrawn from the study. Final evaluation was based on the CDAI score at Week 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis.

The results for clinical response and remission are shown in Table 2. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the CIMZIA-treated group compared to the group treated with placebo.

Table 2 Study CD2 - Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	CIMZIA 400 mg x3 + Placebo N = 210	**CIMZIA 400 mg N = 215**
Week 26		
Clinical Response[#]	**36%** (30%, 43%)	**63%** (56%, 69%)*
Clinical Remission[#]	**29%** (22%, 35%)	**48%** (41%, 55%)*

* $p < 0.05$
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Baseline use of immunosuppressants or corticosteroids had no impact on the clinical response to CIMZIA.

15 REFERENCES

1. Best WR, Becktel JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70(3): 439-444

16 HOW SUPPLIED/STORAGE AND HANDLING

- **Pack Content**

Qty.	Item
2	Type I glass vials with rubber stopper and overseals each containing 200 mg of lyophilized CIMZIA for reconstitution.
2	2 mL Type I glass vials containing 1 mL sterile Water for Injection
2	3 mL plastic syringes
4	20 gauge luer-lock needles (1 inch)
2	23 gauge luer-lock needles (1 inch)
8	Alcohol swabs

NDC 50474-700-62

- **Storage and Stability**

Refrigerate intact carton at 2 to 8 °C (36 to 46 °F). Do not freeze. Do not separate contents of carton prior to use. Do not use beyond expiration date on container.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 Patient Counseling

Advise patients of the potential risks and benefits of CIMZIA therapy. Give patients the Medication Guide and allow them time to read it prior to starting CIMZIA therapy and to review it periodically. Any questions resulting from the patient's reading of the Medication Guide should be discussed. Because caution should be exercised in administering CIMZIA to patients with clinically important active infections, advise patients of the importance of informing their health care providers about all aspects of their health at each treatment visit.

- **Immunosuppression**

Inform patients that CIMZIA may lower the ability of the immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.

Counsel patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA.

- **Allergic Reactions**

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions.

- **Other Medical Conditions**

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report promptly any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

17.2 Medication Guide

MEDICATION GUIDE
CIMZIA® (CIM-zee-uh)
(certolizumab pegol)

Read the Medication Guide that comes with CIMZIA before you receive the first treatment, and before each time you get a treatment of CIMZIA. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about CIMZIA?

CIMZIA is a medicine that affects your immune system. CIMZIA can lower the ability of the immune system to fight infections. Serious infections, including tuberculosis (TB) have happened in patients taking CIMZIA. Some patients have died from these infections.

- Your doctor should test you for TB before starting CIMZIA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with CIMZIA.

Cimzia®
(certolizumab pegol)

Before starting CIMZIA, tell your doctor if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as a fever, cough, flu-like symptoms
- have any open cuts or sores on your body
- get a lot of infections or have infections that keep coming back
- have diabetes
- have HIV
- have tuberculosis (TB), or have been in close contact with someone with TB
- have or have had hepatitis B
- use the medicine Kineret® (anakinra)

After starting CIMZIA, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right away. CIMZIA can make you more likely to get infections or make any infection that you may have worse.

What is CIMZIA?
CIMZIA is a medicine called a Tumor Necrosis Factor (TNF) blocker. CIMZIA is used to reduce the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have not been helped enough by usual treatments.

What should I tell my doctor before starting treatment with CIMZIA?
CIMZIA may not be right for you. Before starting CIMZIA, tell your doctor about all of your medical conditions, including if you:

- **have an infection.** (See, 'What is the most important information I should know about CIMZIA?")
- **have or have had any type of cancer.**
- **have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis**
- **have heart failure**
- **are scheduled to receive a vaccine.** Do not receive a live vaccine while taking CIMZIA.

Tell your doctor if you are pregnant, planning to become pregnant, or breastfeeding. CIMZIA has not been studied in pregnant or nursing women.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Your doctor will tell you if it is okay to take your other medicines while taking CIMZIA. Especially, tell your doctor if you take:

- Kineret® (anakinra). You have a higher chance for serious infections when taking CIMZIA with Kineret®.

How should I receive CIMZIA?

- CIMZIA should be injected by a healthcare provider. Each dose of CIMZIA will be given as two separate injections under the skin in your stomach area (abdomen) or upper leg (thigh).
- Make sure to keep all of your injection and follow-up appointments with your doctor.

What are the possible side effects of CIMZIA?
Serious side effects have happened in patients taking CIMZIA including:

- **Serious infections including tuberculosis (TB).** See "What is the most important information I should know about CIMZIA?"
- **Cancer including lymphoma.**
- **Nervous System Problems** such as Multiple Sclerosis, seizures, or inflammation of the nerves of the eyes. Symptoms include dizziness, numbness or tingling, problems with your vision, and weakness in your arms or legs.
- **Allergic Reactions.** Signs of an allergic reaction include a skin rash, swollen face, or trouble breathing.
- **Blood Problems.** Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include a fever that doesn't go away, bruising or bleeding very easily, or looking very pale.
- **Heart Failure** including new heart failure or worsening of heart failure you already have. Symptoms include shortness of breath, or swelling of your ankles or feet.
- **Immune reactions including a lupus-like syndrome.** Symptoms include shortness of breath, joint pain, or a rash on the cheeks or arms that worsens with sun exposure.

Call your doctor right away if you develop any of the above side effects or symptoms.

The most common side effects of CIMZIA are:

- upper respiratory infections (flu, cold)
- urinary tract infections (bladder infections)
- joint pain

Injection site reactions happen in some people.

Tell your doctor about any side effect that bothers you or does not go away.

These are not all of the side effects with CIMZIA. Ask your doctor or pharmacist for more information.

General information about CIMZIA
Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides Do not use CIMZIA for a condition for which it was not prescribed. Do not give CIMZIA to other people, even if they have the same condition. It may harm them.

Cimzia®
(certolizumab pegol)

This Medication Guide summarizes the most important information about CIMZIA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CIMZIA that is written for health professionals.

For more information go to www.CIMZIA.com or call 1-866-822-0068.

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

What are the ingredients in CIMZIA?

The active ingredient is certolizumab pegol.
The inactive ingredients in CIMZIA include: sucrose, lactic acid, polysorbate. No preservatives are present.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Product developed and manufactured for:
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

US License No. 1736

Revised April 2008

資料３－⑥　メチルトレキソン（methylnaltrexone）

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-964

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection

Initial U.S. approval: 2008

INDICATIONS AND USAGE

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied. (*1*)

DOSAGE AND ADMINISTRATION

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period. (*2.2*)

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weights fall outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume. (*2.2*)

Patient Weight		**Injection Volume**	**Dose**
Pounds	Kilograms		
Less than 84	Less than 38	**See below***	0.15 mg/kg
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg
More than 251	More than 114	**See below***	0.15 mg/kg

*The injection volume for these patients should be calculated using one of the following (*2.2*):

- Multiply the patient weight in pounds by 0.0034 and round up the volume to the nearest 0.1 mL.
- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reduction of RELISTOR by one-half is recommended. (*8.6*)

DOSAGE FORMS AND STRENGTHS

12 mg/0.6 mL solution for subcutaneous injection in a single-use vial. (*3*)

CONTRAINDICATIONS

- RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (*4*)

---------- WARNINGS AND PRECAUTIONS ----------

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician. (*5.1*)

---------- ADVERSE REACTIONS ----------

The most common (> 5%) adverse reactions reported with RELISTOR are abdominal pain, flatulence, nausea, dizziness and diarrhea. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

In an *in vitro* study, methylnaltrexone bromide was a weak inhibitor of cytochrome P450 (CYP) isozyme CYP2D6 activity, but in an *in vivo* study it did not significantly affect the metabolism of the CYP2D6 substrate, dextromethorphan (*7.1*)

---------- USE IN SPECIFIC POPULATIONS ----------

Safety and efficacy of RELISTOR have not been established in pediatric patients. (*8.4*)

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

Revised: 4/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR SUBCUTANEOUS INJECTION ONLY

RELISTOR should be injected in the upper arm, abdomen or thigh.

2.2 Dosing

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period [*see Clinical Studies (14)*].

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume.

Patient Weight			
Pounds	Kilograms	**Injection Volume**	**Dose**
Less than 84	Less than 38	**See below***	0.15 mg/kg
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg
More than 251	More than 114	**See below***	0.15 mg/kg

*The injection volume for these patients should be calculated using one of the following:

- Multiply the patient weight in pounds by 0.0034 and round up the volume to the nearest 0.1 mL.
- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reduction of RELISTOR by one-half is recommended [*see Use in Specific Populations (8.6)*].

2.3 Preparation for Injection

RELISTOR is a sterile, clear, and colorless to pale yellow aqueous solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these are present, the vial should not be used.

Once drawn into the syringe, if immediate administration is not possible, store at ambient room temperature and administer within 24 hours [*see Patient Counseling Information (17)*].

3 DOSAGE FORMS AND STRENGTHS

12 mg/0.6 mL solution for subcutaneous injection in a single-use vial [*see Dosage and Administration (2.2)*].

4 CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Severe or Persistent Diarrhea

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.

5.2 Peritoneal Catheters

Use of RELISTOR has not been studied in patients with peritoneal catheters.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in patients with advanced illness receiving palliative care: Study 1 included a single-dose, double-blind, placebo-controlled period, whereas Study 2 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14)*]. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for 2 days). Both the methylnaltrexone bromide and placebo patients were on a stable laxative regimen for at least 3 days prior to study entry and continued on their regimen throughout the study.

The adverse reactions in patients receiving RELISTOR are shown in table below.

Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR*		
Adverse Reaction	**RELISTOR** N = 165	**Placebo** N = 123
Abdominal Pain	47 (28.5%)	12 (9.8%)
Flatulence	22 (13.3%)	7 (5.7%)
Nausea	19 (11.5%)	6 (4.9%)
Dizziness	12 (7.3%)	3 (2.4%)
Diarrhea	9 (5.5%)	3 (2.4%)

* Doses: 0.075, 0.15, and 0.30 mg/kg/dose

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450 Isozymes

In *in vitro* drug metabolism studies methylnaltrexone bromide did not significantly inhibit the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of CYP2D6. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

7.2 Drugs Renally Excreted

The potential for drug interactions between methylnaltrexone bromide and drugs that are actively secreted by the kidney has not been investigated in humans.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in pregnant rats at intravenous doses up to about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area and in pregnant rabbits at intravenous doses up to about 17 times the recommended maximum human subcutaneous dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, methylnaltrexone bromide should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Effects of RELISTOR on mother, fetus, duration of labor, and delivery are unknown. There were no effects on the mother, labor, delivery, or on offspring survival and growth in rats following subcutaneous injection of methylnaltrexone bromide at dosages up to 25 mg/kg/day.

8.3 Nursing Mothers

Results from an animal study using [^{3}H]-labeled methylnaltrexone bromide indicate that methylnaltrexone bromide is excreted via the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELISTOR is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of RELISTOR have not been established in pediatric patients.

8.5 Geriatric Use

In the phase 2 and 3 double-blind studies, a total of 77 (24%) patients aged 65-74 years (54 methylnaltrexone bromide, 23 placebo) and a total of 100 (31.2%) patients aged 75 years or older (61 methylnaltrexone bromide, 39 placebo) were enrolled. There was no difference in the efficacy or safety profile of these elderly patients when compared to younger patients. Therefore, no dose adjustment is recommended based on age.

8.6 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Dose-reduction by one-half is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min). In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold and resulted in a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

8.7 Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone bromide has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone bromide. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone bromide has not been studied.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylnaltrexone bromide is not a controlled substance.

9.2 Abuse

RELISTOR is a peripherally-acting mu-opioid receptor antagonist with no known risk of abuse.

9.3 Dependence

RELISTOR is a peripherally-acting mu-opioid receptor antagonist with no known risk of dependency.

10 OVERDOSAGE

10.1 Human Experience

During clinical trials of RELISTOR administered subcutaneously, no cases of methylnaltrexone bromide overdose were reported. In a study of healthy volunteers (n = 41), a single dose of 0.50 mg/kg administered as a subcutaneous injection was well-tolerated. A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an IV bolus.

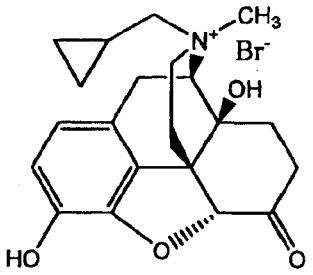
10.2 Management of Overdosage

No specific information is available on the treatment of overdose with RELISTOR. In the event of overdose, employ the usual supportive measures, e.g., clinical monitoring and supportive therapy as dictated by the patient's clinical status. Signs or symptoms of orthostatic hypotension should be monitored, and treatment should be initiated, as appropriate.

11 DESCRIPTION

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection, a peripherally-acting mu-opioid receptor antagonist, is a sterile, clear and colorless to pale yellow aqueous solution. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is $C_{21}H_{26}NO_4Br$, and the molecular weight is 436.36. Each 3 mL vial contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-opioid receptor. As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This allows methylnaltrexone bromide to function as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

12.2 Pharmacodynamics

Use of opioids induces slowing of gastrointestinal motility and transit. Antagonism of gastrointestinal mu-opioid receptors by methylnaltrexone bromide inhibits opioid-induced delay of gastrointestinal transit time in a dose-dependent manner in rats. The effects of methylnaltrexone bromide on central mu-opioid receptors were evaluated in a pharmacodynamic study in which subjects received a dose of remifentanil, sufficient to produce pupiliary constriction, followed by placebo, naloxone, or methylnaltrexone. Following remifentanil administration, the methylnaltrexone and placebo groups showed no change in pupiliary constriction while the naloxone group showed a marked change over the time interval tested.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration, methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours. Across the range of doses evaluated peak plasma concentration and area under the plasma concentration-time curve (AUC) increase in a dose-proportional manner, as shown in the table below.

PHARMACOKINETIC PARAMETERS OF METHYLNALTREXONE BROMIDE FOLLOWING SINGLE SUBCUTANEOUS DOSES

Parameter	0.15 mg/kg	0.30 mg/kg	0.50 mg/kg
C_{max} (ng/mL)[a]	117 (32.7)	239 (62.2)	392 (147.9)
t_{max} (hr)[b]	0.5 (0.25-0.75)	0.5 (0.25-0.75)	0.5 (0.25-0.75)
AUC_{24} (ng·hr/mL)[a]	175 (36.6)	362 (63.8)	582 (111.2)

[a] Expressed as mean (SD).

[b] Expressed as median (range).

Distribution

Methylnaltrexone bromide undergoes moderate tissue distribution. The steady-state volume of distribution (Vss) is approximately 1.1 L/kg. The fraction of methylnaltrexone bromide bound to human plasma proteins is 11.0% to 15.3%, as determined by equilibrium dialysis.

Metabolism

In a mass balance study, approximately 60% of the administered radioactivity recovered with 5 distinct metabolites and none of the detected metabolites was in amounts over 6% of administered radioactivity. Conversion to methyl-6-naltrexol isomers (5% of total) and methylnaltrexone sulfate (1.3% of total) appear to be the primary pathways of metabolism. N-demethylation of methylnaltrexone to produce naltrexone is not significant.

Excretion

Methylnaltrexone bromide is eliminated primarily as the unchanged drug (85% of administered radioactivity). Approximately half of the dose is excreted in the urine and somewhat less in feces. The terminal half-life ($t_{1/2}$) is approximately 8 hours.

12.4 Effect on Cardiac Repolarization

In a randomized, double blind placebo- and (open-label) moxifloxacin-controlled 4-period crossover study, 56 healthy subjects were administered methylnaltrexone bromide 0.3 mg/kg and methylnaltrexone bromide 0.64 mg/kg by IV infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At both the 0.3 mg/kg and 0.64 mg/kg methylnaltrexone bromide doses, no significant effect on the QTc interval was detected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of methylnaltrexone bromide.

Mutagenesis

Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the *in vivo* mouse micronucleus test.

Impairment of Fertility

Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 81 times the recommended maximum human subcutaneous dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

A single subcutaneous dose of 500 mg/kg of methylnaltrexone bromide was not lethal to rats.

Reproduction studies have been performed in pregnant rats at intravenous doses up to 25 mg/kg/day (about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area) and in pregnant rabbits at intravenous doses up to 16 mg/kg/day (about 17 times the recommended maximum human subcutaneous dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide.

In an *in vitro* human cardiac potassium ion channel (hERG) assay, methylnaltrexone bromide caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 μM concentrations, respectively). Methylnaltrexone bromide had a hERG IC_{50} of > 1000 μM. In isolated dog Purkinje fibers, methylnaltrexone bromide caused prolongations in action potential duration (APD). The highest tested concentration (10 μM) in the dog Purkinje fiber study was about 18 and 37 times the C_{max} at human subcutaneous (SC) doses of 0.3 and 0.15 mg/kg, respectively. In isolated rabbit Purkinje fibers, methylnaltrexone bromide (up to 100 μM) did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone bromide concentration (100 μM) tested was about 186 and 373 times the human C_{max} at SC doses of 0.3 and 0.15 mg/kg, respectively. In anesthetized dogs, methylnaltrexone bromide caused decreases in blood pressure, heart rate, cardiac output, left ventricular pressure, left ventricular end diastolic pressure, and +dP/dt at ≥ 1 mg/kg. In conscious dogs, methylnaltrexone bromide caused a dose-related increase in QTc interval. After a single IV dosage of 20 mg/kg to beagle dogs, predicted C_{max} and AUC values were approximately 482 and 144 times, respectively, the exposure at human SC dose of 0.15 mg/kg and 241 times and 66 times, respectively, the exposure at a human SC dose of 0.3 mg/kg. In conscious guinea pigs,

methylnaltrexone caused mild prolongation of QTc (4% over baseline) at 20 mg/kg, IV. A thorough QTc assessment was conducted in humans [*see Pharmacokinetics (12.4)*].

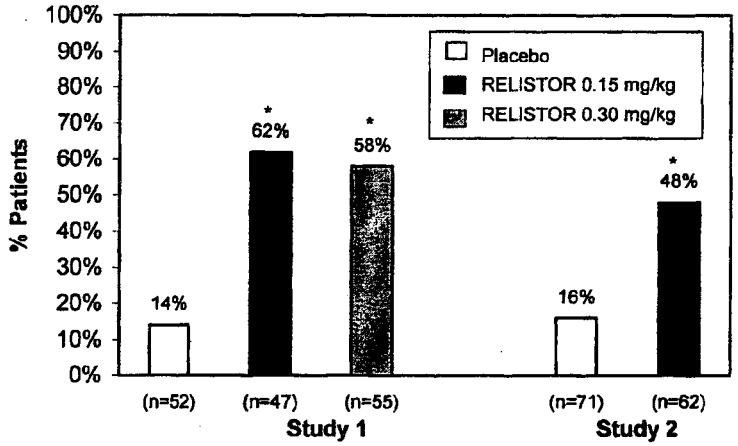
14 CLINICAL STUDIES

The efficacy and safety of RELISTOR in the treatment of opioid-induced constipation in advanced illness patients receiving palliative care was demonstrated in two randomized, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51% were females. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients had been receiving palliative opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for >2 days). Patients were on a stable opioid regimen ≥ 3 days prior to randomization (not including PRN or rescue pain medication) and received their opioid medication during the study as clinically needed. Patients maintained their regular laxative regimen for at least 3 days prior to study entry, and throughout the study. Rescue laxatives were prohibited from 4 hours before to 4 hours after taking an injection of study medication.

Study 1 compared a single, double-blind, subcutaneous dose of RELISTOR 0.15 mg/kg, or RELISTOR 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label 4-week dosing period, where RELISTOR could be used as needed, no more frequently than 1 dose in a 24 hour period. Throughout both study periods, patients maintained their regular laxative regimen. A total of 154 patients (47 RELISTOR 0.15 mg/kg, 55 RELISTOR 0.3 mg/kg, 52 placebo) were enrolled and treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medication. RELISTOR-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); $p < 0.0001$ for each dose versus placebo (Figure 1).

Study 2 compared double-blind, subcutaneous doses of RELISTOR given every other day for 2 weeks versus placebo. Patients received opioid medication ≥ 2 weeks prior to receiving study medication. During the first week (days 1, 3, 5, 7) patients received either 0.15 mg/kg RELISTOR or placebo. In the second week the patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 RELISTOR, 71 placebo) patients were analyzed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medication and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of study medication. RELISTOR-treated patients had a higher rate of laxation within 4 hours of the first dose (48%) than placebo-treated patients (16%); $p < 0.0001$ (Figure 1). RELISTOR-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52%) than did placebo-treated patients (9%); $p < 0.0001$. In both studies, in approximately 30% of patients, laxation was reported within 30 minutes of a dose of RELISTOR.

Figure 1. Laxation Response Within 4 Hours of the First Dose



* $p < 0.0001$ vs. Placebo

In both studies, there was no evidence of differential effects of age or gender on safety or efficacy. No meaningful subgroup analysis could be conducted on race because the study population was predominantly Caucasian (88%). The rates of discontinuation due to adverse events during the double blind placebo controlled clinical trials (Study 1 and Study 2) were comparable between RELISTOR (1.2%) and placebo (2.4%).

Durability of Response

Durability of response was demonstrated in Study 2, in which the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide was also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 1, and in two open-label extension studies (Study 1EXT and Study 2EXT) in which RELISTOR was given as needed for up to 4 months. During open-label treatment, patients maintained their regular laxative regimen. A total of 136, 21, and 82 patients received at least 1 open-label dose in studies 1, 1EXT, and 2EXT, respectively. Laxation response rates observed during double-blind treatment with RELISTOR were maintained over the course of 3 to 4 months of open-label treatment.

Opioid Use and Pain Scores

There was no relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either RELISTOR-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC NUMBER	PACK SIZE	CONTENTS
0008-1218-01	1 vial per carton	one 12 mg/0.6 mL single-use vial
0008-2513-02	7 trays per kit	Each tray contains: one 12 mg/0.6 mL single use vial, one 1 cc (mL) syringe with retractable (27-gauge x ½-inch) needle (VanishPoint®), two alcohol swabs

16.1 Storage

RELISTOR should be stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Do not freeze. **Protect from light.**

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Instruct patients that the usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

In approximately 30% of patients in clinical trials, laxation was reported within 30 minutes of a dose of RELISTOR; therefore, advise patients to be within close proximity to toilet facilities once the drug is administered.

Instruct patients not to continue taking RELISTOR if they experience severe or persistent diarrhea. Instruct patients that common side effects of RELISTOR include transient abdominal pain, nausea and vomiting. Advise patients to contact their healthcare provider if any of these symptoms persist or worsen.

Instruct patients to discontinue RELISTOR if they stop taking their opioid pain medication.

17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION

RELISTOR ***[rel' - i - store]***
(methylnaltrexone bromide)
Injection

Read the Patient Information that comes with RELISTOR before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is RELISTOR?

RELISTOR is a prescription medicine used to treat constipation that is caused by prescription pain medicines, called opioids, in patients receiving supportive care for their advanced illness, when other medicines for constipation, called laxatives, have not worked well enough.

What should I tell my healthcare provider before taking RELISTOR?

Tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if RELISTOR can harm your unborn baby. If you become pregnant while using RELISTOR, tell your healthcare provider right away.
- are breast-feeding or plan to breast-feed. It is not known if RELISTOR passes into your breast milk.

Tell your healthcare provider about all medicines you take. Continue taking your other medicines for constipation unless your healthcare provider tells you to stop taking them.

How should I take RELISTOR?

- Take RELISTOR exactly as your healthcare provider tells you.
- Take RELISTOR by an injection under the skin (subcutaneous injection) of the upper arm, abdomen, or thigh.
- Do not take more than one dose in a 24-hour period.
- Most patients have a bowel movement within a few minutes to a few hours after taking a dose of RELISTOR.
- If you stop taking your prescription pain medicine, check with your healthcare provider before continuing to take RELISTOR.
- If you take more RELISTOR than prescribed, talk to your healthcare provider right away.

See the detailed Patient Instructions for Use at the end of this Patient Information leaflet for information about how to prepare and inject RELISTOR.

What are the possible side effects of RELISTOR?

Common side effects of RELISTOR include:

- **abdominal (stomach) pain**
- **gas**
- **nausea**
- **dizziness**
- **diarrhea**
- If you get diarrhea that is severe or does not stop while taking RELISTOR, stop taking RELISTOR and call your healthcare provider.

- If you get abdominal pain that will not go away, or nausea or vomiting that is new or worse, call your healthcare provider.

These are not all of the possible side effects of RELISTOR. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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 RELISTOR?

- Store RELISTOR vials at 68 to 77°F (20 to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

General information about RELISTOR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use RELISTOR for a condition for which it was not prescribed. Do not give RELISTOR to other people, even if they have the same symptoms that you have. It may harm them.

THIS LEAFLET SUMMARIZES THE MOST IMPORTANT INFORMATION ABOUT RELISTOR. IF YOU WOULD LIKE MORE INFORMATION, TALK WITH YOUR DOCTOR. YOU CAN ASK YOUR PHARMACIST OR DOCTOR FOR INFORMATION ABOUT RELISTOR THAT IS WRITTEN FOR HEALTHCARE PROVIDERS. FOR MORE INFORMATION, GO TO WWW.RELISTOR.COM OR CALL 1-800-934-5556.

What are the ingredients in RELISTOR?

Active ingredient: methylnaltrexone bromide
Inactive ingredients: sodium chloride, edetate calcium disodium USP, glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Wyeth®

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Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

Progenics™
Pharmaceuticals

Under license from:
Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Patient Instructions for Use of RELISTOR VIAL AND STANDARD SYRINGE AND NEEDLE

Introduction

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a vial of RELSTOR, and a standard syringe.

The Patient Instructions for Use includes the following steps:

Step 1: Preparing the injection
Step 2: Preparing the syringe
Step 3: Choosing and preparing an injection site
Step 4: Injecting RELISTOR
Step 5: Disposing of supplies

Before starting, read and make sure that you understand the Patient Instructions for Use. If you have any questions, talk to your healthcare provider.

Gather the supplies you will need for your injection. These include:

1. RELISTOR vial
2. 1 mL syringe with a 27-gauge needle for subcutaneous use
3. 2 alcohol swabs
4. Cotton ball or gauze
5. Adhesive bandage

Important Notes:

- **Use the syringes and needles prescribed by your healthcare provider.**
- **Do not use a RELISTOR vial more than one time, even if there is medicine left in the vial.**
- **If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period. For more information about how to store RELISTOR, see the section called "How should I store RELISTOR?" in the FDA-Approved Patient Labeling.**
- **Safely throw away RELISTOR vials after use.**
- **Do not re-use syringes or needles.**
- **To avoid needle stick injuries, do not recap used needles.**

Step 1: Preparing the injection

1. Find a quiet place. Choose a flat, clean, well-lit working surface.

2. Wash your hands with soap and warm water before preparing for the injection.

3. Look at the vial of RELISTOR (Figure 1). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. If not, do not use the vial, and call your healthcare provider.

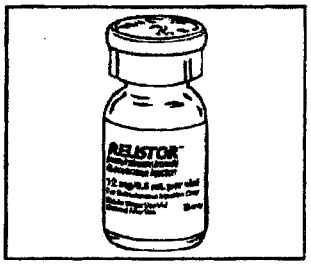

Figure 1

Step 2: Preparing the syringe

1. Remove the cap from the RELISTOR vial (Figure 2).

Figure 2

2. Wipe the rubber stopper with an alcohol swab (Figure 3).

Figure 3

3. Firmly hold the barrel of the syringe and pull the needle cap straight off (Figure 4). Do not touch the needle or allow it to touch any surface.

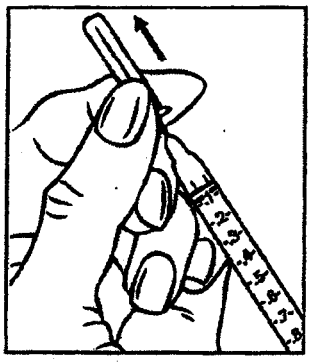

Figure 4

4. Carefully pull back the plunger to the line that matches the dose prescribed by your healthcare provider (Figure 5). For most patients, this will be the 0.4 ml mark which is an 8 mg dose or the 0.6 ml mark which is a 12 mg dose.

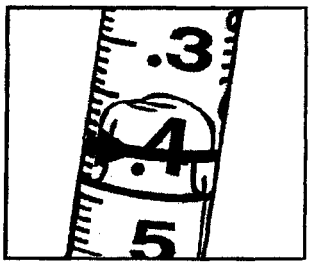

Figure 5

5. Insert the needle straight down into the rubber top of the vial (Figure 6). Do not insert it at an angle. This may cause the needle to bend or break. You will feel some resistance as the needle passes through the rubber top.

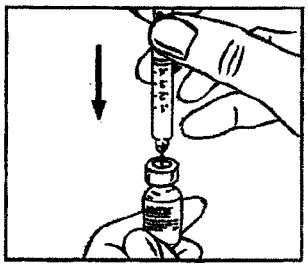

Figure 6

6. Gently push down the plunger until all of the air is out of the syringe and has gone into the vial (Figure 7).

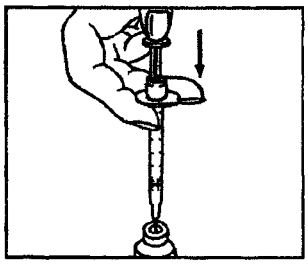

Figure 7

7. With the needle still in the vial, turn the vial and syringe upside down. Hold the syringe at eye level. Make sure the tip of the needle is in the fluid. Slowly pull back on the plunger (Figure 8) to the mark that matches your prescribed dose. For most patients, this will be the 0.4 ml mark which is an 8 mg dose or the 0.6 ml mark which is a 12 mg dose.

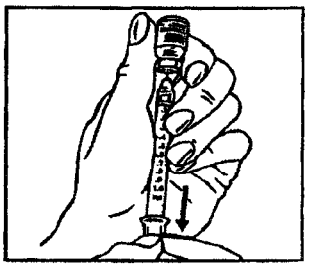

Figure 8

8. With the needle still in the vial, gently tap the side of the syringe to make any air bubbles rise to the top (Figure 9).

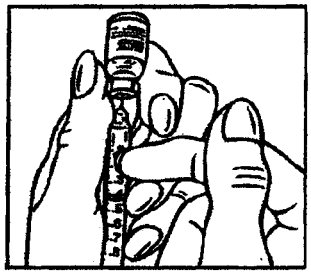

Figure 9

9. Slowly push the plunger up until all air bubbles are out of the syringe (Figure 10).

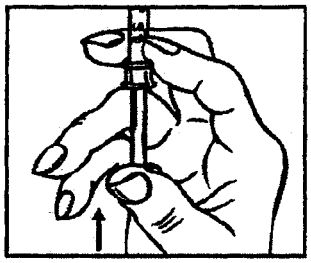

Figure 10

10. Make sure the tip of the needle is in the fluid. Slowly pull back the plunger to draw the right amount of liquid back into the syringe (Figure 11).

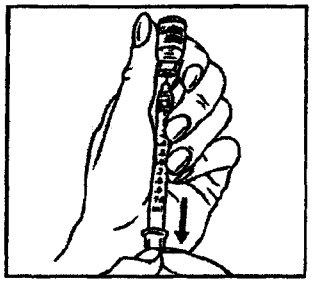

Figure 11

Check to be sure that you have the right dose of RELISTOR in the syringe.

11. Slowly withdraw the needle from the vial. Do not touch the needle or allow it to touch any surface. Safely throw away the unused medicine in the vial. See Step 5.

Step 3: Choosing and preparing an injection site

1. Choose an injection site — abdomen, thighs, or upper arms. See shaded areas in Figures 12 and 13 below. Do not inject at the exact same spot each time (rotate injection sites). Do not inject into areas where the skin is tender, bruised, red or hard. Avoid areas with scars or stretch marks.

   Figure 12. Abdomen or thigh – use these sites when injecting yourself or another person.

   Figure 13. Upper arm – use this site only when injecting another person.

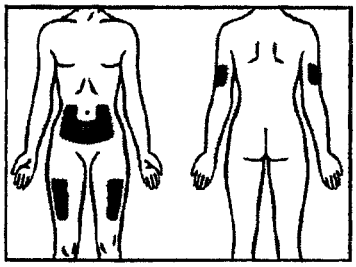

Figure12 Figure 13

2. Clean the injection site with an alcohol swab and let it air dry. Do not touch this area again before giving the injection (Figure 14).

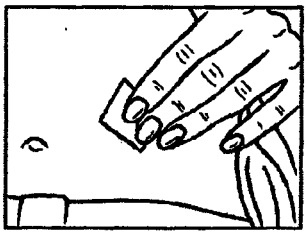

Figure 14

Step 4: Injecting RELISTOR

1. Pinch the skin around the injection site as you were instructed (Figure 15).

Figure 15

2. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (Figure 16).

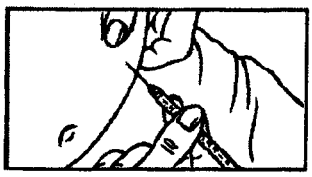

Figure 16

3. Let go of skin and slowly push down on the plunger until the syringe is empty (Figure 17).

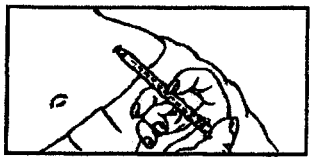

Figure 17

4. When the syringe is empty, quickly pull the needle out of the skin, being careful to keep it at the same angle as it was inserted. There may be a little bleeding at the injection site.

5. Hold a cotton ball or gauze over the injection site (Figure 18). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

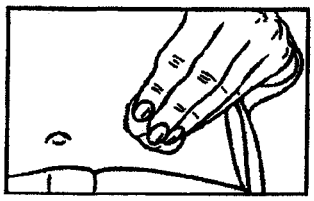

Figure 18

Step 5: Disposing of supplies

- **Do not re-use a syringe or needle.**
- **Do not recap a used needle.**
- Place used needle, syringes, and vials in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away (dispose of) the container. There may be state and local laws about how you should throw away used needles and syringes.

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W Number
ET
Revised Date

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection

Initial U.S. approval: 2008

INDICATIONS AND USAGE

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied. (*1*)

DOSAGE AND ADMINISTRATION

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period. (*2.2*)

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weights fall outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume. (*2.2*)

Patient Weight		**Injection Volume**	**Dose**
Pounds	Kilograms		
Less than 84	Less than 38	**See below***	0.15 mg/kg
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg
More than 251	More than 114	**See below***	0.15 mg/kg

*The injection volume for these patients should be calculated using one of the following (*2.2*):

- Multiply the patient weight in pounds by 0.0034 and round up the volume to the nearest 0.1 mL.
- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reduction of RELISTOR by one-half is recommended. (*8.6*)

DOSAGE FORMS AND STRENGTHS

12 mg/0.6 mL solution for subcutaneous injection in a single-use vial. (*3*)

CONTRAINDICATIONS

- RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (*4*)

WARNINGS AND PRECAUTIONS

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician. (*5.1*)

---------- **ADVERSE REACTIONS** ----------

The most common (> 5%) adverse reactions reported with RELISTOR are abdominal pain, flatulence, nausea, dizziness and diarrhea. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS** ----------

In an *in vitro* study, methylnaltrexone bromide was a weak inhibitor of cytochrome P450 (CYP) isozyme CYP2D6 activity, but in an *in vivo* study it did not significantly affect the metabolism of the CYP2D6 substrate, dextromethorphan (*7.1*)

---------- **USE IN SPECIFIC POPULATIONS** ----------

Safety and efficacy of RELISTOR have not been established in pediatric patients. (*8.4*)

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

Revised: 4/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR SUBCUTANEOUS INJECTION ONLY

RELISTOR should be injected in the upper arm, abdomen or thigh.

2.2 Dosing

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period [*see Clinical Studies (14)*].

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume.

Patient Weight		**Injection Volume**	**Dose**
Pounds	Kilograms		
Less than 84	Less than 38	**See below***	0.15 mg/kg
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg
More than 251	More than 114	**See below***	0.15 mg/kg

*The injection volume for these patients should be calculated using one of the following:

- Multiply the patient weight in pounds by 0.0034 and round up the volume to the nearest 0.1 mL.
- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reduction of RELISTOR by one-half is recommended [*see Use in Specific Populations (8.6)*].

2.3 Preparation for Injection

RELISTOR is a sterile, clear, and colorless to pale yellow aqueous solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these are present, the vial should not be used.

Once drawn into the syringe, if immediate administration is not possible, store at ambient room temperature and administer within 24 hours [*see Patient Counseling Information (17)*].

3 DOSAGE FORMS AND STRENGTHS

12 mg/0.6 mL solution for subcutaneous injection in a single-use vial [*see Dosage and Administration (2.2)*].

4 CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Severe or Persistent Diarrhea

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.

5.2 Peritoneal Catheters

Use of RELISTOR has not been studied in patients with peritoneal catheters.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in patients with advanced illness receiving palliative care: Study 1 included a single-dose, double-blind, placebo-controlled period, whereas Study 2 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14)*]. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for 2 days). Both the methylnaltrexone bromide and placebo patients were on a stable laxative regimen for at least 3 days prior to study entry and continued on their regimen throughout the study.

The adverse reactions in patients receiving RELISTOR are shown in table below.

Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR*		
Adverse Reaction	**RELISTOR** N = 165	**Placebo** N = 123
Abdominal Pain	47 (28.5%)	12 (9.8%)
Flatulence	22 (13.3%)	7 (5.7%)
Nausea	19 (11.5%)	6 (4.9%)
Dizziness	12 (7.3%)	3 (2.4%)
Diarrhea	9 (5.5%)	3 (2.4%)

* Doses: 0.075, 0.15, and 0.30 mg/kg/dose

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450 Isozymes

In *in vitro* drug metabolism studies methylnaltrexone bromide did not significantly inhibit the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of CYP2D6. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

7.2 Drugs Renally Excreted

The potential for drug interactions between methylnaltrexone bromide and drugs that are actively secreted by the kidney has not been investigated in humans.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in pregnant rats at intravenous doses up to about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area and in pregnant rabbits at intravenous doses up to about 17 times the recommended maximum human subcutaneous dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, methylnaltrexone bromide should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Effects of RELISTOR on mother, fetus, duration of labor, and delivery are unknown. There were no effects on the mother, labor, delivery, or on offspring survival and growth in rats following subcutaneous injection of methylnaltrexone bromide at dosages up to 25 mg/kg/day.

8.3 Nursing Mothers

Results from an animal study using [^{3}H]-labeled methylnaltrexone bromide indicate that methylnaltrexone bromide is excreted via the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELISTOR is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of RELISTOR have not been established in pediatric patients.

8.5 Geriatric Use

In the phase 2 and 3 double-blind studies, a total of 77 (24%) patients aged 65-74 years (54 methylnaltrexone bromide, 23 placebo) and a total of 100 (31.2%) patients aged 75 years or older (61 methylnaltrexone bromide, 39 placebo) were enrolled. There was no difference in the efficacy or safety profile of these elderly patients when compared to younger patients. Therefore, no dose adjustment is recommended based on age.

8.6 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Dose-reduction by one-half is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min). In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold and resulted in a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

8.7 Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone bromide has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone bromide. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone bromide has not been studied.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylnaltrexone bromide is not a controlled substance.

9.2 Abuse

RELISTOR is a peripherally-acting mu-opioid receptor antagonist with no known risk of abuse.

9.3 Dependence

RELISTOR is a peripherally-acting mu-opioid receptor antagonist with no known risk of dependency.

10 OVERDOSAGE

10.1 Human Experience

During clinical trials of RELISTOR administered subcutaneously, no cases of methylnaltrexone bromide overdose were reported. In a study of healthy volunteers (n = 41), a single dose of 0.50 mg/kg administered as a subcutaneous injection was well-tolerated. A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an IV bolus.

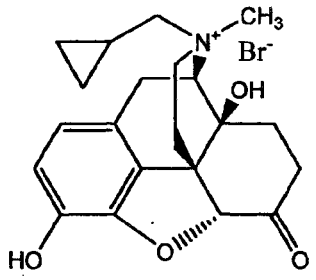
10.2 Management of Overdosage

No specific information is available on the treatment of overdose with RELISTOR. In the event of overdose, employ the usual supportive measures, e.g., clinical monitoring and supportive therapy as dictated by the patient's clinical status. Signs or symptoms of orthostatic hypotension should be monitored, and treatment should be initiated, as appropriate.

11 DESCRIPTION

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection, a peripherally-acting mu-opioid receptor antagonist, is a sterile, clear and colorless to pale yellow aqueous solution. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is $C_{21}H_{26}NO_4Br$, and the molecular weight is 436.36. Each 3 mL vial contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-opioid receptor. As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This allows methylnaltrexone bromide to function as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

12.2 Pharmacodynamics

Use of opioids induces slowing of gastrointestinal motility and transit. Antagonism of gastrointestinal mu-opioid receptors by methylnaltrexone bromide inhibits opioid-induced delay of gastrointestinal transit time in a dose-dependent manner in rats. The effects of methylnaltrexone bromide on central mu-opioid receptors were evaluated in a pharmacodynamic study in which subjects received a dose of remifentanil, sufficient to produce pupiliary constriction, followed by placebo, naloxone, or methylnaltrexone. Following remifentanil administration, the methylnaltrexone and placebo groups showed no change in pupiliary constriction while the naloxone group showed a marked change over the time interval tested.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration, methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours. Across the range of doses evaluated peak plasma concentration and area under the plasma concentration-time curve (AUC) increase in a dose-proportional manner, as shown in the table below.

PHARMACOKINETIC PARAMETERS OF METHYLNALTREXONE BROMIDE FOLLOWING SINGLE SUBCUTANEOUS DOSES

Parameter	0.15 mg/kg	0.30 mg/kg	0.50 mg/kg
C_{max} (ng/mL)[a]	117 (32.7)	239 (62.2)	392 (147.9)
t_{max} (hr)[b]	0.5 (0.25-0.75)	0.5 (0.25-0.75)	0.5 (0.25-0.75)
AUC_{24} (ng·hr/mL)[a]	175 (36.6)	362 (63.8)	582 (111.2)

[a] Expressed as mean (SD).

[b] Expressed as median (range).

Distribution

Methylnaltrexone bromide undergoes moderate tissue distribution. The steady-state volume of distribution (Vss) is approximately 1.1 L/kg. The fraction of methylnaltrexone bromide bound to human plasma proteins is 11.0% to 15.3%, as determined by equilibrium dialysis.

Metabolism

In a mass balance study, approximately 60% of the administered radioactivity recovered with 5 distinct metabolites and none of the detected metabolites was in amounts over 6% of administered radioactivity. Conversion to methyl-6-naltrexol isomers (5% of total) and methylnaltrexone sulfate (1.3% of total) appear to be the primary pathways of metabolism. N-demethylation of methylnaltrexone to produce naltrexone is not significant.

Excretion

Methylnaltrexone bromide is eliminated primarily as the unchanged drug (85% of administered radioactivity). Approximately half of the dose is excreted in the urine and somewhat less in feces. The terminal half-life ($t_{1/2}$) is approximately 8 hours.

12.4 Effect on Cardiac Repolarization

In a randomized, double blind placebo- and (open-label) moxifloxacin-controlled 4-period crossover study, 56 healthy subjects were administered methylnaltrexone bromide 0.3 mg/kg and methylnaltrexone bromide 0.64 mg/kg by IV infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At both the 0.3 mg/kg and 0.64 mg/kg methylnaltrexone bromide doses, no significant effect on the QTc interval was detected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of methylnaltrexone bromide.

Mutagenesis

Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the *in vivo* mouse micronucleus test.

Impairment of Fertility

Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 81 times the recommended maximum human subcutaneous dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

A single subcutaneous dose of 500 mg/kg of methylnaltrexone bromide was not lethal to rats.

Reproduction studies have been performed in pregnant rats at intravenous doses up to 25 mg/kg/day (about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area) and in pregnant rabbits at intravenous doses up to 16 mg/kg/day (about 17 times the recommended maximum human subcutaneous dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide.

In an *in vitro* human cardiac potassium ion channel (hERG) assay, methylnaltrexone bromide caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 μM concentrations, respectively). Methylnaltrexone bromide had a hERG IC_{50} of > 1000 μM. In isolated dog Purkinje fibers, methylnaltrexone bromide caused prolongations in action potential duration (APD). The highest tested concentration (10 μM) in the dog Purkinje fiber study was about 18 and 37 times the C_{max} at human subcutaneous (SC) doses of 0.3 and 0.15 mg/kg, respectively. In isolated rabbit Purkinje fibers, methylnaltrexone bromide (up to 100 μM) did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone bromide concentration (100 μM) tested was about 186 and 373 times the human C_{max} at SC doses of 0.3 and 0.15 mg/kg, respectively. In anesthetized dogs, methylnaltrexone bromide caused decreases in blood pressure, heart rate, cardiac output, left ventricular pressure, left ventricular end diastolic pressure, and +dP/dt at ≥ 1 mg/kg. In conscious dogs, methylnaltrexone bromide caused a dose-related increase in QTc interval. After a single IV dosage of 20 mg/kg to beagle dogs, predicted C_{max} and AUC values were approximately 482 and 144 times, respectively, the exposure at human SC dose of 0.15 mg/kg and 241 times and 66 times, respectively, the exposure at a human SC dose of 0.3 mg/kg. In conscious guinea pigs,

methylnaltrexone caused mild prolongation of QTc (4% over baseline) at 20 mg/kg, IV. A thorough QTc assessment was conducted in humans [*see Pharmacokinetics (12.4)*].

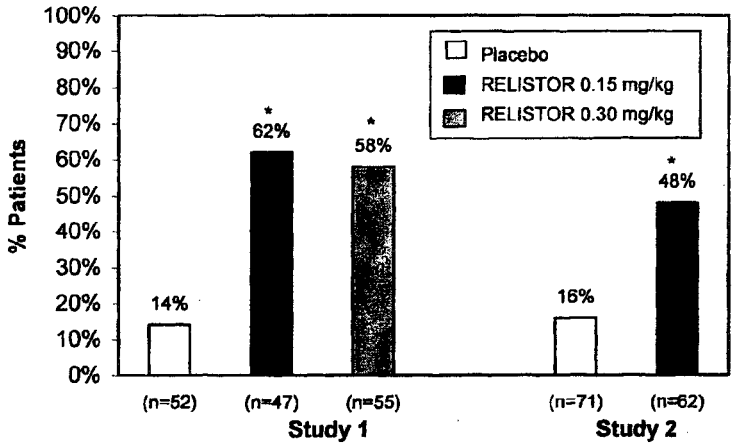
14 CLINICAL STUDIES

The efficacy and safety of RELISTOR in the treatment of opioid-induced constipation in advanced illness patients receiving palliative care was demonstrated in two randomized, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51% were females. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients had been receiving palliative opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for >2 days). Patients were on a stable opioid regimen ≥ 3 days prior to randomization (not including PRN or rescue pain medication) and received their opioid medication during the study as clinically needed. Patients maintained their regular laxative regimen for at least 3 days prior to study entry, and throughout the study. Rescue laxatives were prohibited from 4 hours before to 4 hours after taking an injection of study medication.

Study 1 compared a single, double-blind, subcutaneous dose of RELISTOR 0.15 mg/kg, or RELISTOR 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label 4-week dosing period, where RELISTOR could be used as needed, no more frequently than 1 dose in a 24 hour period. Throughout both study periods, patients maintained their regular laxative regimen. A total of 154 patients (47 RELISTOR 0.15 mg/kg, 55 RELISTOR 0.3 mg/kg, 52 placebo) were enrolled and treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medication. RELISTOR-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); $p < 0.0001$ for each dose versus placebo (Figure 1).

Study 2 compared double-blind, subcutaneous doses of RELISTOR given every other day for 2 weeks versus placebo. Patients received opioid medication ≥ 2 weeks prior to receiving study medication. During the first week (days 1, 3, 5, 7) patients received either 0.15 mg/kg RELISTOR or placebo. In the second week the patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 RELISTOR, 71 placebo) patients were analyzed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medication and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of study medication. RELISTOR-treated patients had a higher rate of laxation within 4 hours of the first dose (48%) than placebo-treated patients (16%); $p < 0.0001$ (Figure 1). RELISTOR-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52%) than did placebo-treated patients (9%); $p < 0.0001$. In both studies, in approximately 30% of patients, laxation was reported within 30 minutes of a dose of RELISTOR.

Figure 1. Laxation Response Within 4 Hours of the First Dose



* $p < 0.0001$ vs. Placebo

In both studies, there was no evidence of differential effects of age or gender on safety or efficacy. No meaningful subgroup analysis could be conducted on race because the study population was predominantly Caucasian (88%). The rates of discontinuation due to adverse events during the double blind placebo controlled clinical trials (Study 1 and Study 2) were comparable between RELISTOR (1.2%) and placebo (2.4%).

Durability of Response

Durability of response was demonstrated in Study 2, in which the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide was also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 1, and in two open-label extension studies (Study 1EXT and Study 2EXT) in which RELISTOR was given as needed for up to 4 months. During open-label treatment, patients maintained their regular laxative regimen. A total of 136, 21, and 82 patients received at least 1 open-label dose in studies 1, 1EXT, and 2EXT, respectively. Laxation response rates observed during double-blind treatment with RELISTOR were maintained over the course of 3 to 4 months of open-label treatment.

Opioid Use and Pain Scores

There was no relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either RELISTOR-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC NUMBER	PACK SIZE	CONTENTS
0008-1218-01	1 vial per carton	one 12 mg/0.6 mL single-use vial
0008-2513-02	7 trays per kit	Each tray contains: one 12 mg/0.6 mL single use vial, one 1 cc (mL) syringe with retractable (27-gauge x ½-inch) needle (VanishPoint®), two alcohol swabs

16.1 Storage

RELISTOR should be stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Do not freeze. **Protect from light.**

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Instruct patients that the usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

In approximately 30% of patients in clinical trials, laxation was reported within 30 minutes of a dose of RELISTOR; therefore, advise patients to be within close proximity to toilet facilities once the drug is administered.

Instruct patients not to continue taking RELISTOR if they experience severe or persistent diarrhea. Instruct patients that common side effects of RELISTOR include transient abdominal pain, nausea and vomiting. Advise patients to contact their healthcare provider if any of these symptoms persist or worsen.

Instruct patients to discontinue RELISTOR if they stop taking their opioid pain medication.

17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION

RELISTOR ***[rel' - i - store]***
(methylnaltrexone bromide)
Injection

Read the Patient Information that comes with RELISTOR before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is RELISTOR?

RELISTOR is a prescription medicine used to treat constipation that is caused by prescription pain medicines, called opioids, in patients receiving supportive care for their advanced illness, when other medicines for constipation, called laxatives, have not worked well enough.

What should I tell my healthcare provider before taking RELISTOR?

Tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if RELISTOR can harm your unborn baby. If you become pregnant while using RELISTOR, tell your healthcare provider right away.
- are breast-feeding or plan to breast-feed. It is not known if RELISTOR passes into your breast milk.

Tell your healthcare provider about all medicines you take. Continue taking your other medicines for constipation unless your healthcare provider tells you to stop taking them.

How should I take RELISTOR?

- Take RELISTOR exactly as your healthcare provider tells you.
- Take RELISTOR by an injection under the skin (subcutaneous injection) of the upper arm, abdomen, or thigh.
- Do not take more than one dose in a 24-hour period.
- Most patients have a bowel movement within a few minutes to a few hours after taking a dose of RELISTOR.
- If you stop taking your prescription pain medicine, check with your healthcare provider before continuing to take RELISTOR.
- If you take more RELISTOR than prescribed, talk to your healthcare provider right away.

See the detailed Patient Instructions for Use at the end of this Patient Information leaflet for information about how to prepare and inject RELISTOR.

What are the possible side effects of RELISTOR?

Common side effects of RELISTOR include:

- **abdominal (stomach) pain**
- **gas**
- **nausea**
- **dizziness**
- **diarrhea**
- If you get diarrhea that is severe or does not stop while taking RELISTOR, stop taking RELISTOR and call your healthcare provider.

- If you get abdominal pain that will not go away, or nausea or vomiting that is new or worse, call your healthcare provider.

These are not all of the possible side effects of RELISTOR. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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 RELISTOR?

- Store RELISTOR vials at 68 to 77°F (20 to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

General information about RELISTOR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use RELISTOR for a condition for which it was not prescribed. Do not give RELISTOR to other people, even if they have the same symptoms that you have. It may harm them.

THIS LEAFLET SUMMARIZES THE MOST IMPORTANT INFORMATION ABOUT RELISTOR. IF YOU WOULD LIKE MORE INFORMATION, TALK WITH YOUR DOCTOR. YOU CAN ASK YOUR PHARMACIST OR DOCTOR FOR INFORMATION ABOUT RELISTOR THAT IS WRITTEN FOR HEALTHCARE PROVIDERS. FOR MORE INFORMATION, GO TO WWW.RELISTOR.COM OR CALL 1-800-934-5556.

What are the ingredients in RELISTOR?

Active ingredient: methylnaltrexone bromide
Inactive ingredients: sodium chloride, edetate calcium disodium USP, glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Wyeth®

Marketed by:
Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

Progenics™
Pharmaceuticals

Under license from:
Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Patient Instructions for Use of RELISTOR
VIAL AND SYRINGE WITH RETRACTABLE NEEDLE IN TRAY

Introduction:

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a RELISTOR tray containing a syringe with a retractable needle. A retractable needle is one that is pulled back so that it is covered after use, to prevent needle stick injury.

The Patient Instructions for Use includes the following steps:

Step 1: Preparing the injection
Step 2: Preparing the syringe
Step 3: Choosing and preparing an injection site
Step 4: Injecting RELISTOR
Step 5: Disposing of supplies

Before starting, read and make sure that you understand the Patient Instructions for Use. Familiarize yourself with the RELISTOR tray, which contains the supplies you need for an injection. If you have any questions, talk to your healthcare provider. Your tray should include the following:

1. RELISTOR vial
2. 1 mL syringe with retractable needle (VanishPoint®)
3. 2 alcohol swabs
4. Prescribing Information - information about RELISTOR that is written for healthcare professionals
5. Patient Instructions for Use of RELISTOR - instructions about RELISTOR that are written for patients

In addition, you will need a cotton ball or gauze, and you may need an adhesive bandage.

Important Notes:

- **Do not use a RELISTOR vial more than one time, even if there is medicine left in the vial.**
- **If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period. For more information about how to store RELISTOR, see the section called "How should I store RELISTOR?" in the FDA-Approved Patient Labeling.**
- **Safely throw away RELISTOR vials after use.**
- **Do not reuse syringes and needles.**
- **To avoid needle stick injuries, do not recap used needles.**

Step 1: Preparing the injection

1. Find a quiet place. Choose a flat, clean, well-lit working surface.

2. Wash your hands with soap and warm water before preparing for the injection.

3. Look at the vial of RELISTOR (Figure 1). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. If not, do not use the vial and call your healthcare provider.

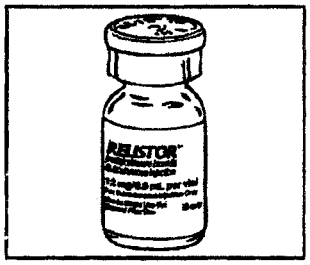


Figure 1

Step 2: Preparing the syringe

1. Remove the cap from the vial containing RELISTOR (Figure 2).

Figure 2

2. Wipe the rubber stopper with an alcohol swab (Figure 3).

Figure 3

3. Firmly hold the barrel of the syringe and remove the needle cap straight off (Figure 4). Do not touch the needle or allow it to touch any surface.

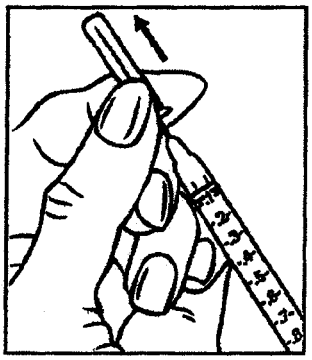


Figure 4

4. Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider (Figure 5). For most patients, this will be the 0.4 mL mark which is an 8 mg dose or the 0.6 mL mark which is a 12 mg dose.

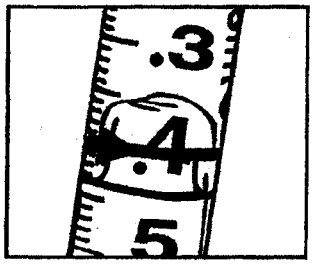


Figure 5

5. Insert the needle straight down into the rubber top of the RELISTOR vial (Figure 6). Do not insert it at an angle. This may cause the needle to bend or break. You will feel some resistance as the needle passes through the rubber top.

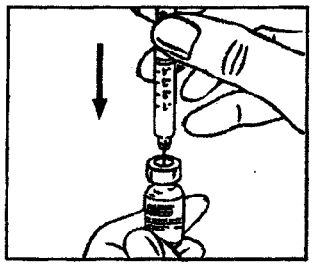


Figure 6

6. Gently push down the plunger until you feel resistance, and most of the air has gone out of the syringe and into the vial (Figure 7). **Do not push past the resistance point.** Doing this will make the needle retract (pull back) into the syringe barrel.

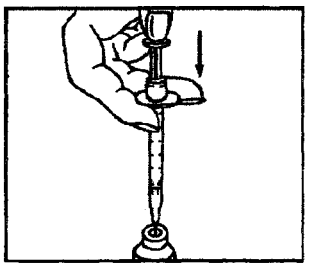


Figure 7

7. With the needle still in the vial, turn the vial and syringe upside down. Hold the syringe at eye level. Make sure the tip of the needle is in the fluid. Slowly pull back on the plunger (Figure 8) to the mark that matches your prescribed dose (usually the 0.4 mL mark which is an 8 mg dose or the 0.6 mL mark which is a 12 mg dose).

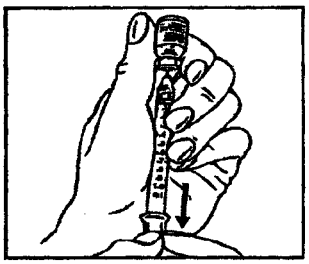


Figure 8

You may see some fluid or bubbles inside the vial when the syringe is filled. This is normal.

8. With the needle still in the vial, gently tap the syringe to make any air bubbles rise to the top (Figure 9).

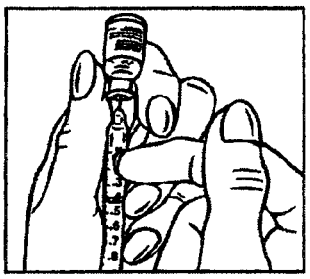


Figure 9

9. Slowly push the plunger up until all air bubbles are out of the syringe (Figure 10).

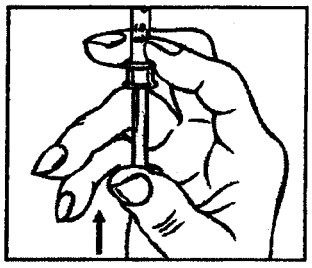


Figure 10

10. Make sure the tip of the needle is in the fluid. Slowly pull back the plunger to draw the right amount of liquid back into the syringe (Figure 11).

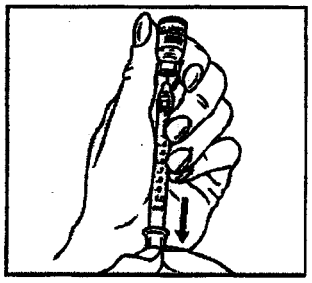


Figure 11

Check to be sure that you have the right dose of RELISTOR in the syringe.

Note: A small air bubble may stay in the syringe. This is okay and it will not affect the dose of medicine in the syringe.

11. Slowly withdraw the needle from the vial (do not touch the needle or allow the needle to touch any surface). Safely throw away the unused medicine in the vial. See Step 5.

Step 3: Choosing and preparing an injection site

1. Choose an injection site — abdomen, thighs, or upper arms. See shaded areas in Figures 12 and 13 below. Do not inject at the exact same spot each time (rotate injection sites). Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

   Figure 12. Abdomen or thigh – use these sites when injecting yourself or another person.

   Figure 13. Upper arm – use this site only when injecting another person.

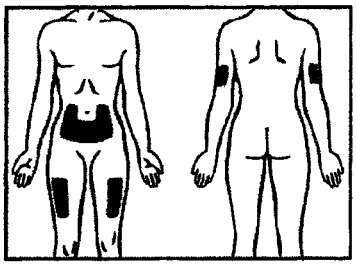


Figure 12 Figure 13

2. Clean the injection site with an alcohol swab and let it air dry. Do not touch this area again before giving the injection (Figure 14).

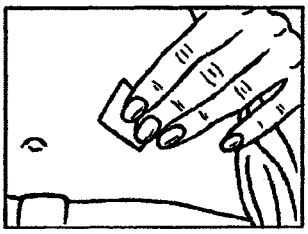


Figure 14

Step 4: Injecting RELISTOR

1. Pinch the skin around the injection site as you were instructed (Figure 15).

Figure 15

2. Insert the full length of the needle into the skin at 45-degree angle with a "quick dart-like" motion (Figure 16).

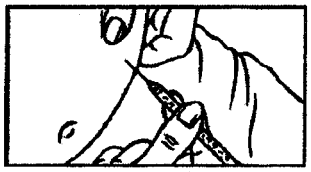


Figure 16

3. Let go of the skin and slowly push down on the plunger past the resistance point, until the syringe is empty and you hear a click (Figure 17).

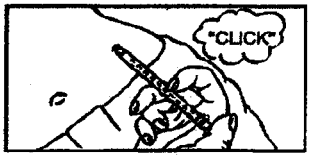


Figure 17

4. The click sound means that the needle (Figure 18) has been retracted (pulled back) into the syringe barrel (Figure 19).

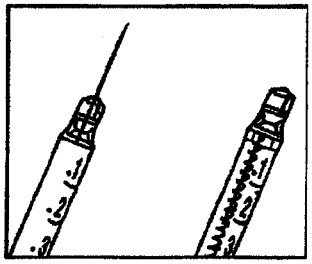


Figure 18 Figure 19

5. Hold a cotton ball or gauze over the injection site (Figure 20). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

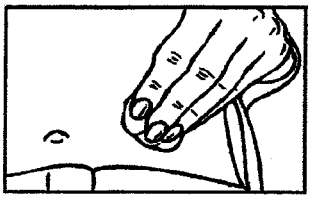


Figure 20

Step 5: Disposing of supplies

- **Do not** re-use a syringe or needle.
- **Do not** recap a used needle.
- Place used needles, syringes and vials in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as a detergent bottle), or a metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away (dispose of) the container. There may be state and local laws about how you should throw away used needles and syringes.
- **If you have any questions, talk to your healthcare provider or pharmacist.**

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資料３－⑦　フェブキソスタット（febuxostat）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of febuxostat.

Excipients: Each tablet contains 76.50 mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "80" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

4.2 Posology and method of administration

The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dl (357 μmol/l) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.

ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dl (357μmol/l).

Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

Special populations

Renal insufficiency
No dosage adjustment is necessary in patients with mild or moderate renal impairment. The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 ml/min, see section 5.2).

Hepatic impairment
The recommended dosage in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment. The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

Elderly

No dose adjustment is required in the elderly (see section 5.2).

Children and adolescents
As there has been no experience in children and adolescents, the use of febuxostat in such patients is not recommended.

Organ transplant recipients
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.8).

4.4 Special warnings and precautions for use

Cardio-vascular disorders
Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended (see section 4.8).

Acute gouty attacks (gout flare)
Febuxostat treatment should not be started until an acute attack of gout has completely subsided. As with other urate lowering medicinal products, gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended.
If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Xanthine deposition
As with other urate lowering medicinal products, in patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine (see section 4.5).

Theophylline
Febuxostat should be used with caution in patients concomitantly treated with theophylline and theophylline levels should be monitored in patients starting febuxostat therapy (see section 4.5).

Liver disorders
During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement (see section 5.1).

Thyroid disorders
Increased TSH values (>5.5 μIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

Lactose
Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactase malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine
Although interaction studies with febuxostat have not been performed, inhibition of xanthine oxidase (XO) is known to result in an increase in mercaptopurine or azathioprine levels. On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

Theophylline
Although interaction studies have not been performed with febuxostat, inhibition of XO may cause an increase in the theophylline level (inhibition of the metabolism of theophylline has been reported with other XO inhibitors). Hence caution is advised if these active substances are given concomitantly, and theophylline levels should be monitored in patients starting febuxostat therapy.

Naproxen and other inhibitors of glucuronidation
Febuxostat metabolism depends on UGT enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250mg BID was associated with an increase in febuxostat exposure (C_{max} 28%, AUC 41% and $t_{1/2}$ 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

Inducers of glucuronidation
Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/indometacin/hydrochlorothiazide/warfarin
Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.

No dose adjustment is necessary for warfarin when administered with febuxostat. After initiation of febuxostat therapy, monitoring of anticoagulant activity should be considered in patients receiving warfarin or similar agents.

Desipramine/CYP2D6 substrates.
Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro.* In a study in healthy subjects, 120 mg ADENURIC QD resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo.* Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

Antacids
Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in C_{max}, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

4.6 Pregnancy and lactation

Pregnancy
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breast feeding
It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As with other xanthine oxidase inhibitors adverse reactions such as somnolence, dizziness and paraesthesia have been reported. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADENURIC does not adversely affect performance.

4.8 Undesirable effects

A total of 2531 subjects received at least one dose of ADENURIC (10 mg – 300 mg) in clinical studies.

Phase 3 randomised controlled studies
In randomised controlled phase 3 clinical studies, >,1000 patients have been treated with the recommended doses of 80 mg or 120 mg (536 subjects enrolled in a 28 week study and 507 subjects enrolled in a 52 weeks study). The treatment-related events (ADRs) were mostly mild or moderate in severity.

The most commonly reported ADRs (investigator assessment) are liver function abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%), rash (1.5 %).

A numerically greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the pivotal Phase III (1.3 vs 0.3 events per 100 PYs) and long-term extension studies (1.4 vs 0.7 events per 100 PYs), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1000) adverse reactions suspected (investigator assessment) to be drug related occurring in the 80 mg/120 mg treatment groups and reported more than once in the total febuxostat treatment group are listed below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Treatment related adverse reactions in phase 3 randomized controlled studies

Investigations	Uncommon Blood amylase increase, platelet count decrease, blood creatinine increase, haemoglobin decrease, blood urea increase , LDH increase, triglycerides increase
Cardiac disorders	Rare Palpitations
Nervous system disorders	Common Headache Uncommon Dizziness, paraesthesia, somnolence, altered taste
Gastrointestinal disorders	Common Diarrhoea*, nausea* Uncommon: Abdominal pain, gastro-oesophageal reflux disease, vomiting*, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort,
Renal and urinary disorders	Uncommon Nephrolithiasis, haematuria, pollakiuria Rare Renal insufficiency
Skin and subcutaneous tissue disorders	Common Rash** Uncommon Dermatitis, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Uncommon Arthralgia, arthritis, myalgia, muscle cramp, musculoskeletal pain
Metabolism and nutrition disorders	Uncommon Weight increase, increased appetite
Vascular disorders	Uncommon Hypertension, flushing, hot flush,
General disorders and administration site conditions	Uncommon Fatigue, oedema, influenza like symptoms Rare Asthenia, thirst
Hepato-biliary disorders	Common LFT abnormalities
Psychiatric disorders	Uncommon Libido decreased Rare Nervousness, Insomnia

* Diarrhoea, nausea and vomiting are more frequent in patients concomitantly treated with colchicine

** No serious rashes or severe hypersensitivity reactions were noted in the clinical studies.

Long-term open label extension studies

In the long-term open label extension studies, the number of patients treated with febuxostat 80 mg/120 mg up to 1 year was 906, up to 2 years was 322, up to 3 years was 57, and up 4 years was 53. The treatment-related events reported during the long-term extension studies were similar to those reported in the Phase 3 studies (see Table 1). The most commonly reported treatment-related events (investigator assessment) are: liver function abnormalities, diarrhoea, headache, rash, hypertension.

The following treatment-related events were reported more than once in the total febuxostat treatment group and were reported as uncommon in subjects taking febuxostat 80 mg/120 mg in long-term extension studies (up to 4 years, >1,900 Patient-years of exposure). These treatment-related events were either not reported or reported at a lower frequency for these doses, in the pivotal Phase 3 studies: Diabetes, hyperlipidaemia, insomnia, hypoaesthesia, ECG abnormal, cough, dyspnoea, skin discolouration, skin lesion, bursitis, proteinuria, renal insufficiency, erectile dysfunction, blood potassium increase, blood TSH increase, lymphocyte count decreased, WBC decrease.

4.9 Overdose

No case of overdose has been reported. Patients with an overdose should be managed by symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations inhibiting uric acid production, ATC code: M04AA03

Mechanism of action

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition K_i value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Clinical studies results

The efficacy of ADENURIC was demonstrated in two Phase 3 pivotal studies (APEX study and FACT study described below) that were conducted in 1832 patients with hyperuricemia and gout. In each phase 3 pivotal study, ADENURIC demonstrated superior ability to lower

and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in each study was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). No patients with organ transplant have been included in these studies (see section 4.2).

APEX Study: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: placebo (n=134), ADENURIC 80 mg QD (n=267), ADENURIC 120 mg QD (n=269), ADENURIC 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dl or 100 mg QD [n=10] for patients with a baseline serum creatinine >1.5 mg/dl and ≤2.0 mg/dl). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.

The APEX study showed statistically significant superiority of both the ADENURIC 80 mg QD and the ADENURIC 120 mg QD treatment arms *versus* the conventionnally used doses of allopurinol 300mg (n = 258) /100mg (n = 10) treatment arm in reducing the sUA below 6 mg/dl (357 µmol/l) (see Table 2 and Figure 1).

FACT Study: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred sixty (760) patients were randomized: ADENURIC 80 mg QD (n=256), ADENURIC 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both ADENURIC 80 mg and ADENURIC 120 mg QD treatment arms *versus* the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dl (357 µmol/l).

Table 2 summarises the primary efficacy endpoint results:

Table 2
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)
Last Three Monthly Visits

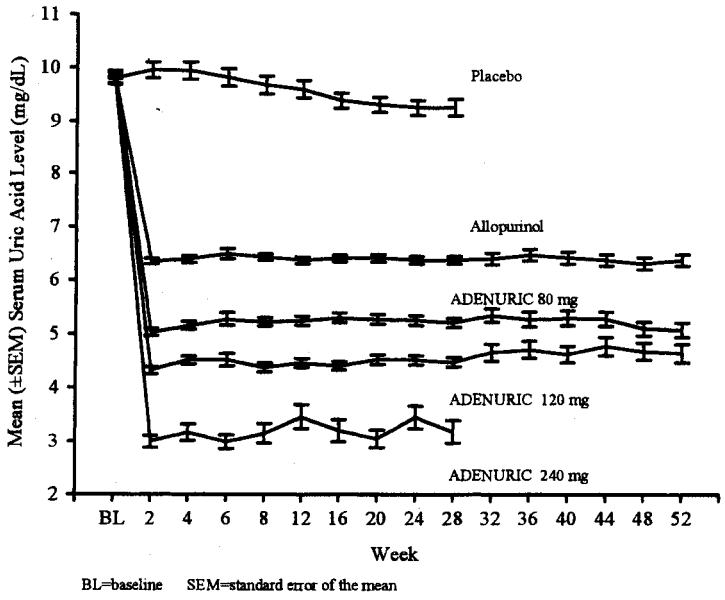
Study	ADENURIC 80 mg QD	ADENURIC 120 mg QD	Allopurinol 300 / 100 mg QD[1]
APEX (28 weeks)	48%* (n=262)	65%*,# (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*,# (n=519)	22% (n=519)

[1] results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤2.0 mg/dl) or 300 mg QD (n=509) were pooled for analyses.
* $p < 0.001$ vs allopurinol, # $p < 0.001$ vs 80 mg

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to <6.0 mg/dl (357 µmol/l) was noted by the Week 2 visit

and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the Phase 3 pivotal studies are shown in Figure 1.

Figure 1 Mean Serum Uric Acid Levels Combined Phase 3 Studies



Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine >1.5 and < 2.0 mg/dl were dosed with 100 mg QD. (10 patients out of 268 in APEX study).
240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.

Primary endpoint in the sub-group of patients with renal impairment
The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dl and <=2.0 mg/dl). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100mg QD. ADENURIC achieved the primary efficacy endpoint in 44% (80 mgQD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups.

There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58 % in the normal renal function group and 55% in the severe renal dysfunction group).

Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dl
Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dl. In this subgroup ADENURIC achieved the primary efficacy endpoint in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

Clinical Outcomes: proportion of patients requiring treatment for a gout flare and tophi size change
The proportion of subjects requiring treatment for a gout flare (APEX and FACT Study) was numerically lower in the groups that achieved an average post-baseline serum urate level <6.0 mg/dl, <5.0 mg/dl, or <4.0 mg/dl compared to the group that achieved an average post-

baseline serum urate level ≥6.0 mg/dl during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 48 - 52 intervals).

Two years of data from the Phase 3 Open Label Extension study showed that the maintenance of serum urate levels <6 mg/dl (<357 µmol/l) resulted in a decrease in the incidence of gout flares with less than 3 % of subjects requiring treatment for a flare (i.e. more than 97 % of patients did not require treatment for a flare) at Month 16-24. This was associated with a reduction of tophus size leading to complete resolution in 54% of subjects at Month 24.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). These rates were similar to the rates reported on allopurinol (3.6%) (see section 4.4). Increased TSH values (>5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

The total exposure to ADENURIC in phase 3 pivotal studies and long-term extension studies is greater than 2700 patient-years.

5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricemia and gout, treated with ADENURIC 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption
Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.8-3.2 µg/ml, and 5.0-5.3 µg/ml, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in C_{max} and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, ADENURIC may be taken without regard to food.

Distribution
The apparent steady state volume of distribution (V_{ss}/F) of febuxostat ranges from 29 to 75 l after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Metabolism
Febuxostat is extensively metabolized by conjugation *via* uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation *via* the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9

Elimination
Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the active substance (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the faeces as the unchanged febuxostat (12%), the acyl glucuronide of the active substance (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

Special populations
Renal insufficiency
Following multiple doses of 80 mg of ADENURIC in patients with mild, moderate or severe renal insufficiency, the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg·h/ml in the normal renal function group to 13.2 µg.h/ml in the severe renal dysfunction group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
Following multiple doses of 80 mg of ADENURIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Age
There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of ADENURIC in elderly as compared to younger healthy subjects.

Gender
Following multiple oral doses of ADENURIC, the C_{max} and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. No dose adjustment is needed based on gender.

5.3 Preclinical safety data

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, mutagenesis, impairment of fertility

In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Hydroxypropylcellulose
Croscarmellose sodium
Silica, colloidal hydrated

Tablet coating
Opadry II, Yellow, 85F42129 containing:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogols 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Clear (Aclar/PVC/Aluminium) blister of 14 tablets.

ADENURIC 80 mg is available in pack sizes of 28 and 84 film-coated tablets .

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120 mg of febuxostat.

Excipients: Each tablet contains 114.75mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "120" on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

4.2 Posology and method of administration

The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dl (357 µmol/l) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.

ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dl (357µmol/l).

Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

Special populations

Renal insufficiency
No dosage adjustment is necessary in patients with mild or moderate renal impairment. The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 ml/min, see section 5.2).

Hepatic impairment
The recommended dosage in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment. The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

Elderly

No dose adjustment is required in the elderly (see section 5.2).

Children and adolescents
As there has been no experience in children and adolescents, the use of febuxostat in such patients is not recommended.

Organ transplant recipients
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.8).

4.4 Special warnings and precautions for use

Cardio-vascular disorders
Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended (see section 4.8).

Acute gouty attacks (gout flare)
Febuxostat treatment should not be started until an acute attack of gout has completely subsided. As with other urate lowering medicinal products, gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended.
If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Xanthine deposition
As with other urate lowering medicinal products, in patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine (see section 4.5).

Theophylline
Febuxostat should be used with caution in patients concomitantly treated with theophylline and theophylline levels should be monitored in patients starting febuxostat therapy (see section 4.5).

Liver disorders
During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement (see section 5.1).

Thyroid disorders
Increased TSH values (>5.5 μIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

Lactose
Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactase malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine
Although interaction studies with febuxostat have not been performed, inhibition of xanthine oxidase (XO) is known to result in an increase in mercaptopurine or azathioprine levels. On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

Theophylline
Although interaction studies have not been performed with febuxostat, inhibition of XO may cause an increase in the theophylline level (inhibition of the metabolism of theophylline has been reported with other XO inhibitors). Hence caution is advised if these active substances are given concomitantly, and theophylline levels should be monitored in patients starting febuxostat therapy.

Naproxen and other inhibitors of glucuronidation
Febuxostat metabolism depends on UGT enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250mg BID was associated with an increase in febuxostat exposure (C_{max} 28%, AUC 41% and $t_{1/2}$ 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

Inducers of glucuronidation
Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/indometacin/hydrochlorothiazide/warfarin
Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.

No dose adjustment is necessary for warfarin when administered with febuxostat. After initiation of febuxostat therapy, monitoring of anticoagulant activity should be considered in patients receiving warfarin or similar agents.

Desipramine/CYP2D6 substrates.
Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro*. In a study in healthy subjects, 120 mg ADENURIC QD resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo*. Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

Antacids
Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in C_{max}, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

4.6 Pregnancy and lactation

Pregnancy
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breast feeding
It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As with other xanthine oxidase inhibitors adverse reactions such as somnolence, dizziness and paraesthesia have been reported. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADENURIC does not adversely affect performance.

4.8 Undesirable effects

A total of 2531 subjects received at least one dose of ADENURIC (10 mg – 300 mg) in clinical studies.

Phase 3 randomised controlled studies
In randomised controlled phase 3 clinical studies, >,1000 patients have been treated with the recommended doses of 80 mg or 120 mg (536 subjects enrolled in a 28 week study and 507 subjects enrolled in a 52 weeks study). The treatment-related events (ADRs) were mostly mild or moderate in severity.

The most commonly reported ADRs (investigator assessment) are liver function abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%), rash (1.5 %).

A numerically greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the pivotal Phase III (1.3 vs 0.3 events per 100 PYs) and long-term extension studies (1.4 vs 0.7 events per 100 PYs), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

Common ($\geq$ 1/100 to < 1/10), uncommon ($\geq$ 1/1,000 to < 1/100) and rare ($\geq$ 1/10,000 to < 1/1000) adverse reactions suspected (investigator assessment) to be drug related occurring in the 80 mg/120 mg treatment groups and reported more than once in the total febuxostat treatment group are listed below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Treatment related adverse reactions in phase 3 randomized controlled studies

Investigations	Uncommon Blood amylase increase, platelet count decrease, blood creatinine increase, haemoglobin decrease, blood urea increase , LDH increase, triglycerides increase
Cardiac disorders	Rare Palpitations
Nervous system disorders	Common Headache Uncommon Dizziness, paraesthesia, somnolence, altered taste
Gastrointestinal disorders	Common Diarrhoea*, nausea* Uncommon: Abdominal pain, gastro-oesophageal reflux disease, vomiting*, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort,
Renal and urinary disorders	Uncommon Nephrolithiasis, haematuria, pollakiuria Rare Renal insufficiency
Skin and subcutaneous tissue disorders	Common Rash** Uncommon Dermatitis, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Uncommon Arthralgia, arthritis, myalgia, muscle cramp, musculoskeletal pain
Metabolism and nutrition disorders	Uncommon Weight increase, increased appetite
Vascular disorders	Uncommon Hypertension, flushing, hot flush,
General disorders and administration site conditions	Uncommon Fatigue, oedema, influenza like symptoms Rare Asthenia, thirst
Hepato-biliary disorders	Common LFT abnormalities
Psychiatric disorders	Uncommon Libido decreased Rare Nervousness, Insomnia

* Diarrhoea, nausea and vomiting are more frequent in patients concomitantly treated with colchicine

** No serious rashes or severe hypersensitivity reactions were noted in the clinical studies.

Long-term open label extension studies

In the long-term open label extension studies, the number of patients treated with febuxostat 80 mg/120 mg up to 1 year was 906, up to 2 years was 322, up to 3 years was 57, and up 4 years was 53. The treatment-related events reported during the long-term extension studies were similar to those reported in the Phase 3 studies (see Table 1). The most commonly reported treatment-related events (investigator assessment) are: liver function abnormalities, diarrhoea, headache, rash, hypertension.

The following treatment-related events were reported more than once in the total febuxostat treatment group and were reported as uncommon in subjects taking febuxostat 80 mg/120 mg in long-term extension studies (up to 4 years, >1,900 Patient-years of exposure). These treatment-related events were either not reported or reported at a lower frequency for these doses, in the pivotal Phase 3 studies: Diabetes, hyperlipidaemia, insomnia, hypoaesthesia, ECG abnormal, cough, dyspnoea, skin discolouration, skin lesion, bursitis, proteinuria, renal insufficiency, erectile dysfunction, blood potassium increase, blood TSH increase, lymphocyte count decreased, WBC decrease.

4.9 Overdose

No case of overdose has been reported. Patients with an overdose should be managed by symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations inhibiting uric acid production, ATC code: M04AA03

Mechanism of action

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition K_i value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Clinical studies results

The efficacy of ADENURIC was demonstrated in two Phase 3 pivotal studies (APEX study and FACT study described below) that were conducted in 1832 patients with hyperuricemia and gout. In each phase 3 pivotal study, ADENURIC demonstrated superior ability to lower

and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in each study was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). No patients with organ transplant have been included in these studies (see section 4.2).

APEX Study: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: placebo (n=134), ADENURIC 80 mg QD (n=267), ADENURIC 120 mg QD (n=269), ADENURIC 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dl or 100 mg QD [n=10] for patients with a baseline serum creatinine >1.5 mg/dl and ≤2.0 mg/dl). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.

The APEX study showed statistically significant superiority of both the ADENURIC 80 mg QD and the ADENURIC 120 mg QD treatment arms *versus* the conventionnally used doses of allopurinol 300mg (n = 258) /100mg (n = 10) treatment arm in reducing the sUA below 6 mg/dl (357 µmol/l) (see Table 2 and Figure 1).

FACT Study: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred sixty (760) patients were randomized: ADENURIC 80 mg QD (n=256), ADENURIC 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both ADENURIC 80 mg and ADENURIC 120 mg QD treatment arms *versus* the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dl (357 µmol/l).

Table 2 summarises the primary efficacy endpoint results:

Table 2
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)
Last Three Monthly Visits

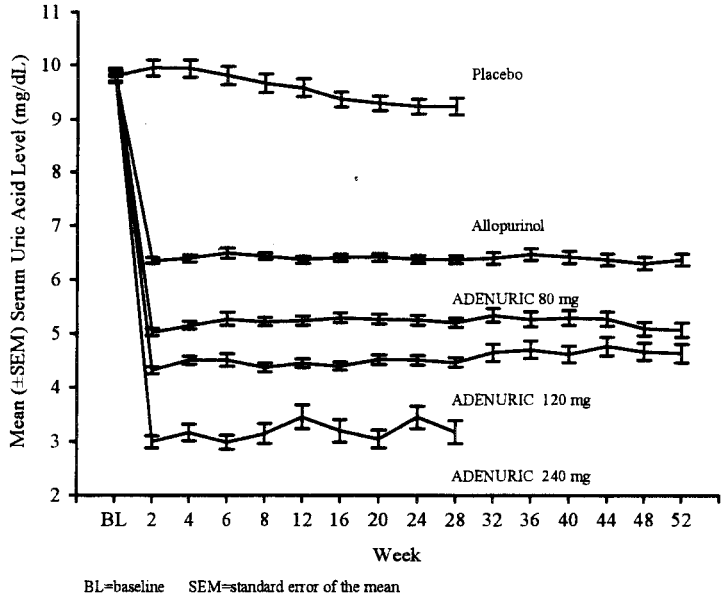
Study	ADENURIC 80 mg QD	ADENURIC 120 mg QD	Allopurinol 300 / 100 mg QD[1]
APEX (28 weeks)	48%* (n=262)	65%*,# (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*,# (n=519)	22% (n=519)

[1] results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤2.0 mg/dl) or 300 mg QD (n=509) were pooled for analyses.
* $p < 0.001$ vs allopurinol, # $p < 0.001$ vs 80 mg

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to <6.0 mg/dl (357 µmol/l) was noted by the Week 2 visit

and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the Phase 3 pivotal studies are shown in Figure 1.

Figure 1 Mean Serum Uric Acid Levels Combined Phase 3 Studies



Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine >1.5 and < 2.0 mg/dl were dosed with 100 mg QD. (10 patients out of 268 in APEX study).
240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.

Primary endpoint in the sub-group of patients with renal impairment
The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dl and <=2.0 mg/dl). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100mg QD. ADENURIC achieved the primary efficacy endpoint in 44% (80 mgQD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups.

There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58 % in the normal renal function group and 55% in the severe renal dysfunction group).

Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dl
Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dl. In this subgroup ADENURIC achieved the primary efficacy endpoint in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

Clinical Outcomes: proportion of patients requiring treatment for a gout flare and tophi size change
The proportion of subjects requiring treatment for a gout flare (APEX and FACT Study) was numerically lower in the groups that achieved an average post-baseline serum urate level <6.0 mg/dl, <5.0 mg/dl, or <4.0 mg/dl compared to the group that achieved an average post-

baseline serum urate level ≥6.0 mg/dl during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 48 - 52 intervals).

Two years of data from the Phase 3 Open Label Extension study showed that the maintenance of serum urate levels <6 mg/dl (<357 µmol/l) resulted in a decrease in the incidence of gout flares with less than 3 % of subjects requiring treatment for a flare (i.e. more than 97 % of patients did not require treatment for a flare) at Month 16-24. This was associated with a reduction of tophus size leading to complete resolution in 54% of subjects at Month 24.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). These rates were similar to the rates reported on allopurinol (3.6%) (see section 4.4). Increased TSH values (>5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

The total exposure to ADENURIC in phase 3 pivotal studies and long-term extension studies is greater than 2700 patient-years.

5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricemia and gout, treated with ADENURIC 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption
Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.8-3.2 µg/ml, and 5.0-5.3 µg/ml, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in C_{max} and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, ADENURIC may be taken without regard to food.

Distribution
The apparent steady state volume of distribution (V_{ss}/F) of febuxostat ranges from 29 to 75 l after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Metabolism
Febuxostat is extensively metabolized by conjugation *via* uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation *via* the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9

Elimination
Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the active substance (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the faeces as the unchanged febuxostat (12%), the acyl glucuronide of the active substance (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

Special populations
Renal insufficiency
Following multiple doses of 80 mg of ADENURIC in patients with mild, moderate or severe renal insufficiency, the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 μg·h/ml in the normal renal function group to 13.2 μg.h/ml in the severe renal dysfunction group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
Following multiple doses of 80 mg of ADENURIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Age
There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of ADENURIC in elderly as compared to younger healthy subjects.

Gender
Following multiple oral doses of ADENURIC, the C_{max} and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. No dose adjustment is needed based on gender.

5.3 Preclinical safety data

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, mutagenesis, impairment of fertility

In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Hydroxypropylcellulose
Croscarmellose sodium
Silica, colloidal hydrated

Tablet coating
Opadry II, Yellow, 85F42129 containing:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogols 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Clear (Aclar/PVC/Aluminium) blister of 14 tablets.

ADENURIC 120 mg is available in pack sizes of 28 and 84 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Patheon France
40 Boulevard de Champaret
FR-38300 Bourgoin Kallieu
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.0 (19 February 2008) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 80 mg film-coated tablets
Febuxostat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg febuxostat.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADENURIC 80 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 80 mg film-coated tablets
Febuxostat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg febuxostat.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADENURIC 80 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 80 mg tablets
Febuxostat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon
Tue
Wed
Thurs
Fri
Sat
Sun

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 120 mg film-coated tablets
Febuxostat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 120 mg febuxostat.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADENURIC 120 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 120 mg film-coated tablets
Febuxostat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 120 mg febuxostat.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADENURIC 120 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 120 mg tablets
Febuxostat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon
Tue
Wed
Thurs
Fri
Sat
Sun

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ADENURIC 80 mg film-coated tablets
Febuxostat

ADENURIC 120 mg film-coated tablets
Febuxostat

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ADENURIC IS AND WHAT IT IS USED FOR

ADENURIC tablets are used to treat gout, which is associated with an excess of a chemical called uric acid (urate) in the body. In some people, the amount of uric acid builds up in the blood and may become too high to remain soluble. When this happens, urate crystals may form in and around the joints and kidneys. These crystals can cause sudden, severe pain, redness, warmth and swelling in a joint (known as a gout attack). Left untreated, larger deposits called tophi (TOE-FI) may form in and around joints. These tophi may cause joint and bone damage.

ADENURIC works by reducing uric acid levels. Keeping uric acid levels low by taking ADENURIC once every day stops crystals building up, and over time it reduces symptoms. Keeping uric acid levels sufficiently low for a long enough period can also shrink tophi.

2. BEFORE YOU TAKE ADENURIC

Do not take ADENURIC if you are:
- If you are allergic (hypersensitive) to febuxostat, the active ingredient of ADENURIC, or any of the other ingredients in these tablets.

Take special care with ADENURIC
Tell your doctor before you start to take this medicine:
- If you have or have had heart failure or heart problems
- If you are being treated for high uric acid levels as a result of cancer disease or Lesch-Nyhan syndrome (a rare inherited condition in which there is too much uric acid in the blood)
- If you have thyroid problems

If you are having a gout attack at the moment (a sudden onset of severe pain, tenderness, redness, warmth and swelling in a joint), wait for the gout attack to subside before first starting treatment with ADENURIC.

For some people, gout attacks may flare up when starting certain medicines that control uric acid levels. Not everyone gets flares, but you could get a flare-up even if you are taking ADENURIC, and

especially during the first weeks or months of treatment. It is important to keep taking ADENURIC even if you have a flare, as ADENURIC is still working to lower uric acid. Over time, gout flares will occur less often and be less painful if you keep taking ADENURIC every day.

Your doctor will often prescribe other medicines, if they are needed, to help prevent or treat the symptoms of flares (such as pain and swelling in a joint).

Your doctor may ask you to have blood tests to check that your liver is working normally.

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.

It is especially important to tell your doctor or pharmacist if you are taking medicines containing any of the following substances as they may interact with ADENURIC and your doctor may wish to consider necessary measures:

- Mercaptopurine (used to treat cancer)
- Azathioprine (used to reduce immune response)
- Theophylline (used to treat asthma)
- Warfarin (used to thin your blood if you have a heart condition)

Taking ADENURIC with food and drink
The tablets should be taken by mouth and can be taken with or without food.

Pregnancy and breast-feeding
It is not known if ADENURIC may harm your unborn child. Tell your doctor if you think you are pregnant or if you are planning to become pregnant as ADENURIC should not be used during pregnancy. It is not known if ADENURIC may pass into human breast milk. You should not use ADENURIC if you are breast feeding, or if you are planning to breastfeed.

Driving and using machines
No studies on the effects of ADENURIC on the ability to drive and use machines have been performed. However, you should be aware that you may experience dizziness, sleepiness and numbness or tingling sensation during treatment and should not drive or operate machines if affected.

Important information about some of the ingredients of ADENURIC
ADENURIC tablets contain lactose (a type of sugar). If you have been told that you have an intolerance to some sugars contact your doctor before taking this medicine.

3. HOW TO TAKE ADENURIC

Always take ADENURIC exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

ADENURIC is available as either an 80 mg tablet or a 120 mg tablet. Your doctor will have prescribed the strength most suitable for you.

- The usual dose is one tablet daily. The back of the blister pack is marked with the days of the week to help you check that you have taken a dose each day.
- The tablets should be taken by mouth and can be taken with or without food.

It is important that you do not stop taking ADENURIC unless your doctor tells you to.

Continue to take ADENURIC every day even when you are not experiencing gout flare or attack.

If you take more ADENURIC than you should

In the event of an accidental overdose ask your doctor what to do, or contact your nearest accident and emergency department.

If you forget to take ADENURIC
If you miss a dose of ADENURIC take it as soon as you remember unless it is almost time for your next dose, in which case miss out the forgotten dose and take your next dose at the normal time. Do not take a double dose to make up for a forgotten dose.

If you stop taking ADENURIC
Do not stop taking ADENURIC without the advice of your doctor even if you feel better. If you stop taking ADENURIC your uric acid levels may begin to rise and your symptoms may worsen due to the formation of new crystals of urate in and around your joints and kidneys.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ADENURIC can cause side effects, although not everybody gets them.

Common side effects (more than 1 in 100 patients but less than 1 in 10 patients) are:
- abnormal liver test results
- diarrhoea
- headache
- rashes
- feeling sick

Uncommon side effects (more than 1 in 1,000 patients but less than 1 in 100 patients) are:
- weight gain, increased appetite, change in blood sugar levels (diabetes) of which a symptom may be excessive thirst, increased blood fat levels
- erectile difficulties and/or loss of sex drive
- difficulty in sleeping
- dizziness, numbness or tingling sensation, sleepiness, impaired sense of taste, reduction in sensation of touch
- abnormal ECG heart tracing
- hot flushes or blushing (e.g. redness of the face or neck), increased blood pressure
- cough, shortness of breath, flu-like symptoms
- dry mouth, abdominal pain/discomfort or wind, heartburn/indigestion, constipation, more frequent passing of stools
- vomiting
- itching, hives, skin inflammation or discolouration, other type of skin conditions
- muscle cramp, pain/ache in muscles/joints, bursitis or arthritis (inflammation of joints usually accompanied by pain, swelling and/or stiffness)
- blood in the urine, abnormal frequent urination, kidney stones, abnormal urine tests (increased level of proteins in urine), a reduction in the ability of the kidneys to function properly
- fatigue, localised swelling due to the retention of fluids in the tissues (oedema)
- changes in blood chemistry or amount of blood cells (abnormal blood test results)

Rare side effects (more than 1 in 10,000 patients but less than 1 in 1,000 patients) are:
- weakness
- nervousness
- feeling thirsty
- feeling your heartbeat

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ADENURIC

- Keep out of the reach and sight of children.
- Do not use after the expiry date which is stated on the carton and the tablet blister foil after 'EXP.' The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ADENURIC contains

The active substance is febuxostat.
Each tablet contains 80 mg or 120 mg of febuxostat.

The other ingredients are:
Tablet core: lactose monohydrate, microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, croscarmellose sodium, colloidal hydrated silica.
Film-coating: Opadry II yellow, 85F42129 containing: polyvinyl alcohol, titanium dioxide (E171), macrogols 3350, talc, iron oxide yellow (E172)

What ADENURIC looks like and contents of the pack

ADENURIC film-coated tablets are pale yellow to yellow in colour and capsule shaped.
The 80 mg film-coated tablets are marked on one side with '80'. The 120 mg film-coated tablets are marked on one side with '120'.

ADENURIC is supplied in 2 blisters of 14 tablets (28 tablet pack), or 6 blisters of 14 tablets (84 tablet pack). Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

Manufacturer
Patheon France
40 boulevard de Champaret
38300 Bourgoin Jallieu
France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Luxembourg/Luxemburg
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) website http://www.emea.europa.eu/

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTEREG safely and effectively. See full prescribing information for ENTEREG.

ENTEREG® (alvimopan) Capsules
Initial U.S. Approval: 2008

WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.) program may use ENTEREG.

----------INDICATIONS AND USAGE----------

ENTEREG is a peripherally acting μ-opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. (1)

---------- DOSAGE AND ADMINISTRATION ----------

12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

Capsules: 12 mg (3)

----------CONTRAINDICATIONS----------

Therapeutic doses of opioids for more than 7 consecutive days prior to ENTEREG (4)

---------- WARNINGS AND PRECAUTIONS----------

- A higher number of myocardial infarctions was reported in patients treated with alvimopan 0.5 mg twice daily compared with placebo in a 12-month study in patients treated with opioids for chronic pain, although a causal relationship has not been established. (5.1)
- Patients recently exposed to opioids are expected to be more sensitive to the effects of ENTEREG and therefore may experience abdominal pain, nausea and vomiting, and diarrhea. (5.3)
- Not recommended in patients with severe hepatic impairment. (5.4)
- Not recommended in patients with end stage renal disease. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥3% and ≥1% placebo) in patients undergoing bowel resection were anemia, dyspepsia, hypokalemia, back pain, and urinary retention. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Adolor Corporation at 1-866-4ADOLOR (1-866-423-6567) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Hepatic impairment: Patients with mild-to-moderate hepatic impairment do not require dosage adjustment, but they should be monitored for adverse effects. ENTEREG is not recommended for patients with severe hepatic impairment.(8.5)

Renal impairment: Alvimopan has not been studied in patients with end stage renal disease. ENTEREG is not recommended for use in these patients. Dosage adjustment is not required in patients with mild to severe renal impairment but they should be monitored for adverse effects. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: May 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.) program may use ENTEREG. *[see Warnings and Precautions (5.1 and 5.2)]*

1 INDICATIONS AND USAGE

ENTEREG is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

For hospital use only. The recommended adult dosage of ENTEREG is 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge. Patients should not receive more than 15 doses of ENTEREG.

2.2 Special Populations

Geriatric Use: No dosage adjustment is necessary in elderly patients *[see Use in Specific Populations (8.4)]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild-to-moderate hepatic impairment (Child-Pugh Class A and B). ENTEREG is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*.

Renal Impairment: No dosage adjustment is necessary in patients with mild-to-severe renal impairment, but they should be monitored for adverse effects. ENTEREG is not recommended for use in patients with end-stage renal disease. *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

12 mg blue, hard gelatin capsules with "ADL2698" printed on both the body and the cap of the capsule.

4 CONTRAINDICATIONS

ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG.

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Infarction in a 12 Month Study in Patients treated with Opioids for Chronic Pain

There were more reports of myocardial infarctions in patients treated with alvimopan

0.5 mg twice daily compared with placebo-treated patients in a 12-month study of patients treated with opioids for chronic pain. In this study, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment. This imbalance has not been observed in other studies of alvimopan, including studies in patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily for up to 7 days. A causal relationship with alvimopan has not been established.

5.2 Distribution Program for ENTEREG

ENTEREG is available only to hospitals that enroll in the E.A.S.E. program. To enroll in the E.A.S.E. program, the hospital must acknowledge that:

-hospital staff who prescribe, dispense, or administer ENTEREG have been provided the educational materials on the need to limit use of ENTEREG to short-term, inpatient use;
-patients will not receive more than 15 doses of alvimopan; and
-ENTEREG will not be dispensed to patients after they have been discharged from the hospital.

Contact the E.A.S.E. program at 1-866-4ADOLOR (1-866-423-6567).

5.3 Opioid Tolerance and Gastrointestinal-Related Adverse Effects

Patients recently exposed to opioids are expected to be more sensitive to the effects of μ-opioid receptor antagonists. Since ENTEREG acts peripherally, clinical signs and symptoms of increased sensitivity would likely be limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea). Patients receiving more than 3 doses of an opioid within the week prior to surgery were not studied in the postoperative ileus clinical trials; therefore, ENTEREG 12 mg capsules should be administered with caution to these patients.

5.4 Severe Hepatic Impairment

In patients with severe hepatic impairment, there is a potential for 10-fold higher plasma levels of drug *[see Clinical Pharmacology (12.3)]*. There are no studies of ENTEREG in patients with severe hepatic impairment undergoing bowel resection. Because of the limited data available, ENTEREG is not recommended for use in patients with severe hepatic impairment.

5.5 End-Stage Renal Disease

No studies have been conducted with end-stage renal disease. ENTEREG is not recommended for use in these patients.

5.6 Bowel Obstruction

Use of ENTEREG in patients undergoing surgery for correction of complete bowel obstruction is not recommended.

6 ADVERSE REACTIONS

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 clinical practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to ENTEREG in 1,650 patients in 9 placebo-controlled studies worldwide. The population was 19 to 97 years old, 68% were female, and 83% were Caucasian; 61% were undergoing bowel resection surgery. The first dose of ENTEREG was administered 30 minutes to 5 hours before the scheduled start of surgery and then twice daily until hospital discharge (or for a maximum of 7 days of postoperative treatment).

Table 1 presents treatment-emergent adverse reactions reported in ≥3% patients treated with ENTEREG and for which the rate for ENTEREG was ≥1% than placebo. Treatment-emergent adverse reactions are those events occurring after the first dose of study medication treatment and within 7 days of the last dose of study medication or those events present at baseline that increased in severity after the start of study medication treatment.

Table 1. Treatment-Emergent Adverse Reactions That Were Reported in ≥3% of Either Bowel Resection Patients Treated With ENTEREG or All Surgical Patients Treated With ENTEREG and for Which the Rate for ENTEREG Was ≥1% Than Placebo

	Bowel Resection Patients		All Surgical Patients	
System Organ Class	Placebo (n = 986) %	ENTEREG (n = 999) %	Placebo (n = 1,365) %	ENTEREG (n = 1,650) %
Blood and lymphatic system disorders				
Anemia	4.2	5.2	5.4	5.4
Gastrointestinal disorders				
Constipation	3.9	4.0	7.6	9.7
Dyspepsia	4.6	7.0	4.8	5.9
Flatulence	4.5	3.1	7.7	8.7
Metabolism and nutrition disorders				
Hypokalemia	8.5	9.5	7.5	6.9
Musculoskeletal and connective tissue disorders				
Back pain	1.7	3.3	2.6	3.4
Renal and urinary disorders				
Urinary retention	2.1	3.2	2.3	3.5

7 DRUG INTERACTIONS

7.1 Potential for Drugs to Affect Alvimopan Pharmacokinetics

Based on *in vitro* data, alvimopan is not a substrate of CYP enzymes. Therefore, concomitant administration of ENTEREG with inducers or inhibitors of CYP enzymes is unlikely to alter the metabolism of alvimopan. No clinical studies have been performed to assess the effect of concomitant administration of inducers or inhibitors of cytochrome P450 enzymes on alvimopan pharmacokinetics.

In vitro studies suggest that alvimopan and its 'metabolite' are substrates for p-glycoprotein. A population PK analysis did not reveal any evidence that alvimopan or 'metabolite' pharmacokinetics were influenced by concomitant medications that are mild-to-moderate p-glycoprotein inhibitors. No clinical studies of concomitant administration of alvimopan and strong inhibitors of p-glycoprotein (e.g., verapamil, cyclosporine, amiodorone, itraconazole, quinine, spirinolactone, quinidine, diltiazem, bepridil) have been conducted.

A population PK analysis suggests that the pharmacokinetics of alvimopan were not affected by concomitant administration of acid blockers or antibiotics. However, plasma concentrations of the 'metabolite' were lower in patients receiving acid blockers or preoperative oral antibiotics (49% and 81%, respectively). Because the 'metabolite' is not required for efficacy, no dosage adjustments are necessary in these patients.

7.2 Potential for Alvimopan to Affect the Pharmacokinetics of Other Drugs

Alvimopan and its 'metabolite' are not inhibitors of CYP 1A2, 2C9, 2C19, 3A4, 2D6, and 2E1 *in vitro* at concentrations far in excess of those observed clinically. Alvimopan and its 'metabolite' are not inducers of CYP 1A2, 2B6, 2C9, 2C19 and 3A4. *In vitro* studies also suggest that alvimopan and its 'metabolite' are not inhibitors of p-glycoprotein. These *in vitro* findings suggest that ENTEREG is unlikely to alter the pharmacokinetics of coadministered drugs through inhibition or induction of CYP enzymes or inhibition of p-glycoprotein.

Coadministration of alvimopan does not appear to alter the pharmacokinetics of morphine and its metabolite, morphine-6-glucuronide, to a clinically significant degree when morphine is administered intravenously. Dosage adjustment for intravenously administered morphine is not necessary when it is coadministered with alvimopan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in pregnant rats at about 68 to 136 times the recommended human oral dose based on the body surface area and intravenous doses of about 3.4 to 6.8 times the recommended human oral dose based on the body surface area and in pregnant rabbits at intravenous doses at about 5 to 10 times the recommended human oral dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Nursing Mothers

Alvimopan and its 'metabolite' are detected in the milk of lactating rats. It is not known whether alvimopan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENTEREG is administered to a nursing woman.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

Of the total number of patients in 5 clinical efficacy studies treated with ENTEREG or placebo, 45% were 65 years of age and over, while 18% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment based on increased age is required *[see Clinical Pharmacology (12.3)]*.

8.5 Hepatic Impairment

Although there is a potential for higher plasma levels of drug in patients with mild-to-moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*, dosage adjustment in these patients is not required. Patients with mild-to-moderate hepatic impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur. ENTEREG is not recommended for use in patients with severe hepatic impairment. *[See Dosage and Administration (2.2), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)]*

8.6 Renal Impairment

Alvimopan has not been studied in patients with end-stage renal disease and ENTEREG is not recommended for use in these patients. Patients with mild-to-severe renal impairment do not require dosage adjustment, but they should be monitored for adverse effects. *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. Patients with severe impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur.

9 DRUG ABUSE AND DEPENDENCE

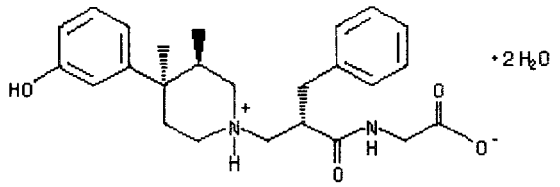
ENTEREG has no known potential for abuse or dependence.

10 OVERDOSAGE

There is no specific antidote for overdosage with ENTEREG. Patients should be managed with appropriate supportive therapy. Single doses up to 120 mg and multiple doses up to 48 mg for 7 days have been administered to normal, healthy subjects in clinical studies and were well tolerated.

11 DESCRIPTION

ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist. Chemically, alvimopan is the single stereoisomer [[2(S)-[[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate. It has the following structural formula:



Alvimopan is a white to light beige powder with a molecular weight of 460.6, and the empirical formula is $C_{25}H_{32}N_2O_4 \bullet 2H_2O$. It has a solubility of <0.1 mg/mL in water or buffered solutions between pH 3.0 and 9.0, 1 to 5 mg/mL in buffered solutions at pH 1.2, and 10 to 25 mg/mL in aqueous 0.1 N sodium hydroxide. At physiological pH, alvimopan is zwitterionic, a property that contributes to its low solubility.

ENTEREG Capsules for oral administration contain 12 mg of alvimopan on an anhydrous basis suspended in the inactive ingredient polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alvimopan is a selective antagonist of the cloned human μ-opioid receptor with a Ki of 0.4 nM (0.2 ng/mL) and no measurable opioid-agonist effects in standard pharmacologic assays. The dissociation of [^{3}H]-alvimopan from the human μ-opioid receptor is slower than that of other opioid ligands, consistent with its higher affinity for the receptor. At concentrations of 1 to 10 μM, alvimopan demonstrated no activity at any of over 70 non-opioid receptors, enzymes, and ion channels.

Postoperative ileus is the impairment of gastrointestinal motility after intra-abdominal surgery or other non-abdominal surgeries. Postoperative ileus affects all segments of the gastrointestinal tract and may last from 5 to 6 days, or even longer. This may potentially delay gastrointestinal recovery and hospital discharge until its resolution. It is characterized by abdominal distention and bloating, nausea, vomiting, pain, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation. Postoperative ileus is the result of a multifactorial process that includes inhibitory sympathetic input, release of hormones, neurotransmitters, and other mediators (e.g., endogenous opioids). A component of postoperative ileus also results from an inflammatory reaction and the effects of opioid analgesics. Morphine and other μ-opioid receptor agonists are universally used for the treatment of acute postsurgical pain; however, they are known to have an inhibitory effect on gastrointestinal motility and may prolong the duration of postoperative ileus.

Following oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors. The antagonism produced by alvimopan at opioid receptors is evident in isolated guinea pig ileum preparations where alvimopan competitively antagonizes the effects of morphine on contractility. Alvimopan achieves this selective gastrointestinal opioid antagonism without reversing the central analgesic effects of μ-opioid agonists.

12.2 Pharmacodynamics

In exploratory studies in healthy volunteers, alvimopan 3 mg three times daily appeared to reduce the delay in gastrointestinal transit produced by morphine 30 mg twice daily as measured by radio-opaque markers.

In a study designed to evaluate potential effects on cardiac conduction, alvimopan did not cause clinically significant QTc prolongation at doses up to 24 mg twice daily for 7 days. The potential for QTc effects at higher doses has not been studied.

12.3 Pharmacokinetics

Following oral administration of alvimopan, an amide hydrolysis compound is present in the systemic circulation, which is considered a product exclusively of intestinal flora metabolism. This compound is referred to as the 'metabolite'. It is also a μ-opioid receptor antagonist with a Ki of 0.8 nM (0.3 ng/mL).

Absorption: Following oral administration of Entereg capsules in healthy volunteers, plasma alvimopan concentration peaked at approximately 2 hours postdose. No significant accumulation in alvimopan concentration was observed following twice daily (BID) dosing. The mean peak plasma concentration was 10.98 (±6.43) ng/mL and mean $AUC_{0\text{-}12h}$ was 40.2 (±22.5) ng•h/mL after dosing of alvimopan at 12 mg BID for 5 days. The absolute bioavailability was estimated to be 6% (range, 1% to 19%). Plasma concentrations of alvimopan increased approximately proportionally with increasing doses between 6 and 18 mg, but less than proportionally from 18 to 24 mg.

There was a delay in the appearance of the 'metabolite', which had a median T_{max} of 36 hours following administration of a single dose of alvimopan. Concentrations of the 'metabolite' were highly variable between subjects and within a subject. The 'metabolite' accumulated after multiple doses of ENTEREG. The mean C_{max} for the 'metabolite' after alvimopan 12 mg twice daily for 5 days was 35.73±35.29 ng/mL.

Concentrations of alvimopan and its metabolite are higher (~1.9-fold and ~1.4-fold, respectively) in POI patients than in healthy volunteers.

Food Effects: A high-fat meal decreased the extent and rate of alvimopan absorption. The C_{max} and AUC were decreased by approximately 38% and 21%, respectively, and the T_{max} was prolonged by approximately 1 hour. The clinical significance of this decreased bioavailability is unknown. In POI clinical trials, the preoperative dose of ENTEREG was administered in a fasting state. Subsequent doses were given without regard to meals.

Distribution: The steady state volume of distribution of alvimopan was estimated to be 30±10 L. Plasma protein binding of alvimopan and its 'metabolite' was independent of concentration over ranges observed clinically and averaged 80% and 94%, respectively. Both alvimopan and the 'metabolite' were bound to albumin and not to alpha-1 acid glycoprotein.

Metabolism and Elimination: The average plasma clearance for alvimopan was 402 (±89) mL/min. Renal excretion accounted for approximately 35% of total clearance. There was no evidence that hepatic metabolism was a significant route for alvimopan elimination. Biliary secretion was considered the primary pathway for alvimopan elimination. Unabsorbed drug and unchanged alvimopan resulting from biliary excretion were then hydrolyzed to its 'metabolite'

by gut microflora. The 'metabolite' was eliminated in the feces and in the urine as unchanged 'metabolite', the glucuronide conjugate of the 'metabolite', and other minor metabolites. The mean terminal phase half-life of alvimopan after multiple oral doses of ENTEREG ranged from 10 to17 hours. The terminal half-life of the 'metabolite' ranged 10 to 18 hours.

Special Populations:

Age: The pharmacokinetics of alvimopan, but not its 'metabolite', were related to age, but this effect was not clinically significant and does not warrant dosage adjustment based on increased age.

Race: The pharmacokinetic characteristics of alvimopan were not affected by race. Plasma 'metabolite' concentrations were lower in black and in Hispanic patients (by 43% and 82%, respectively) than in Caucasian patients following alvimopan administration. These changes are not considered to be clinically significant in surgical patients; therefore, dosage adjustment based on race is not required.

Gender: There was no effect of gender on the pharmacokinetics of alvimopan or the 'metabolite'.

Hepatic Impairment: Exposure to alvimopan following a single 12-mg dose tended to be higher (1.5 to 2 fold, on average) in patients with mild or moderate hepatic impairment (as defined by Child-Pugh Class A and B, n = 8 each) compared with healthy controls (n = 4). There were no consistent effects on the C_{max} or half-life of alvimopan in patients with hepatic impairment. However, two of 16 patients with mild to moderate impairment had longer than expected half-lives of alvimopan indicating that some accumulation may occur upon multiple dosing. The C_{max} of the 'metabolite' tended to be more variable in patients with mild or moderate hepatic impairment than in matched normal subjects. A study of 3 patients with severe hepatic impairment (Child-Pugh Class C), indicated similar alvimopan exposure in 2 patients and an approximately 10-fold increase in C_{max} and exposure in 1 patient with severe hepatic impairment when compared with healthy control volunteers *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

Renal Impairment: There was no relationship between renal function (i.e., creatinine clearance [CrCl]) and plasma alvimopan pharmacokinetics (C_{max}, AUC, or half-life) in patients with mild (CrCl 51-80 mL/min), moderate (CrCl 31-50 mL/min), or severe (CrCl <30 mL/min) renal impairment (n = 6 each). Renal clearance of alvimopan was related to renal function; however, because renal clearance was only a small fraction (35%) of the total clearance, renal impairment had a small effect on the apparent oral clearance of alvimopan. The half-lives of alvimopan were comparable in the mild, moderate and control renal impairment groups but longer in the severe renal impairment group. Exposure to the 'metabolite' tended to be 2- to 5-fold higher in patients with moderate or severe renal impairment compared to patients with mild renal impairment or control subjects. Thus, there may be accumulation of alvimopan and 'metabolite' in patients with severe renal impairment receiving multiple doses of ENTEREG. Patients with end-stage renal disease were not studied *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.6)]*.

Crohn's Disease: There was no relationship between disease activity in patients with Crohn's disease (measured as Crohn's Disease Activity Index or bowel movement frequency) and alvimopan pharmacokinetics (AUC or C_{max}). Patients with active or quiescent Crohn's disease had increased variability in alvimopan pharmacokinetics and exposure tended to be 2-fold higher in patients with quiescent disease than in those with active disease or normal subjects. Concentrations of the 'metabolite' were lower in patients with Crohn's disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two year carcinogenicity studies have been conducted with alvimopan in CD-1 mice at oral doses up to 4000 mg/kg/day and in Sprague Dawley rats at oral doses up to 500 mg/kg/day. Oral administration of alvimopan for 104 weeks produced significant increases in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcoma in bones of female mice at 4000 mg/kg/day (about 674 times the recommended human dose based on body surface area). In rats, oral administration of alvimopan for 104 weeks did not produce any tumor up to 500 mg/kg/day (about 166 times the recommended human dose based on body surface area).

Alvimopan was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/$TK^{+/-}$) forward mutation test, the Chinese Hamster Ovary (CHO) cell chromosome aberration test or the mouse micronucleus test. The pharmacologically active 'metabolite' ADL 08-0011 was negative in the Ames test, chromosome aberration test in CHO cells and mouse micronucleus test.

Alvimopan at intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

A single oral dose of 500 mg/kg of alvimopan was not lethal to mice and rats.

Reproduction studies have been performed in pregnant rats at oral doses up to 200 mg/kg/day (about 68 to 136 times the recommended human oral dose based on the body surface area) and intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) and in pregnant rabbits at intravenous doses up to 15 mg/kg/day (about 5 to 10 times the recommended human oral dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan.

14 CLINICAL STUDIES

14.1 Postoperative Ileus

The efficacy of ENTEREG in the management of postoperative ileus was evaluated in 5 multicenter, randomized, double-blind, parallel-group, placebo-controlled studies: 4 US studies (Studies 1-4) and 1 non-US study (Study 5). Patients 18 years of age or older undergoing partial large or small bowel resection surgery with primary anastomosis or total abdominal hysterectomy under general anesthesia were randomly assigned to receive oral doses of ENTEREG 12 mg or matching placebo. The initial dose was administered at least 30 minutes

and up to 5 hours prior to the scheduled start of surgery for most patients, and subsequent doses were administered twice daily beginning on the first postoperative day and continued until hospital discharge or a maximum of 7 days. There were no limitations on the type of general anesthesia used, but intrathecal or epidural opioids or anesthetics were prohibited.

All patients in the US studies were scheduled to receive intravenous patient-controlled opioid analgesia. In the non-US study, patients were scheduled to receive opioids either by intravenous patient-controlled opioid analgesia or bolus parenteral administration (intravenous or intramuscular). In all studies, there was no restriction on the type of opioid used or the duration of intravenous patient-controlled opioid analgesia. A standardized accelerated postoperative care pathway was implemented: early nasogastric tube removal (end of surgery); early ambulation (day following surgery); early diet advancement (liquids offered the day following surgery) and solids by the second day following surgery, as tolerated.

Patients who received more than 3 doses of an opioid (regardless of route) during the 7 days prior to surgery and patients with complete bowel obstruction or who were scheduled for a total colectomy, colostomy, or ileostomy were excluded.

The primary endpoint for all studies was time to achieve resolution of postoperative ileus, a clinically defined composite measure of both upper and lower gastrointestinal recovery. Although both 2-component (GI2: toleration of solid food and first bowel movement) and 3-component (GI3: toleration of solid food and either first flatus or bowel movement) endpoints were used in all studies, GI2 is presented as it represents the most objective and clinically relevant measure of treatment response in the bowel resection population. The time from the end of surgery to when the discharge order was written represented the length of hospital stay. In the 5 studies, 1,081 patients received placebo (157 for total abdominal hysterectomy) and 1,096 patients received ENTEREG (143 for total abdominal hysterectomy).

The efficacy of ENTEREG following total abdominal hysterectomy has not been established. Therefore, the following data are presented for the bowel resection population only.

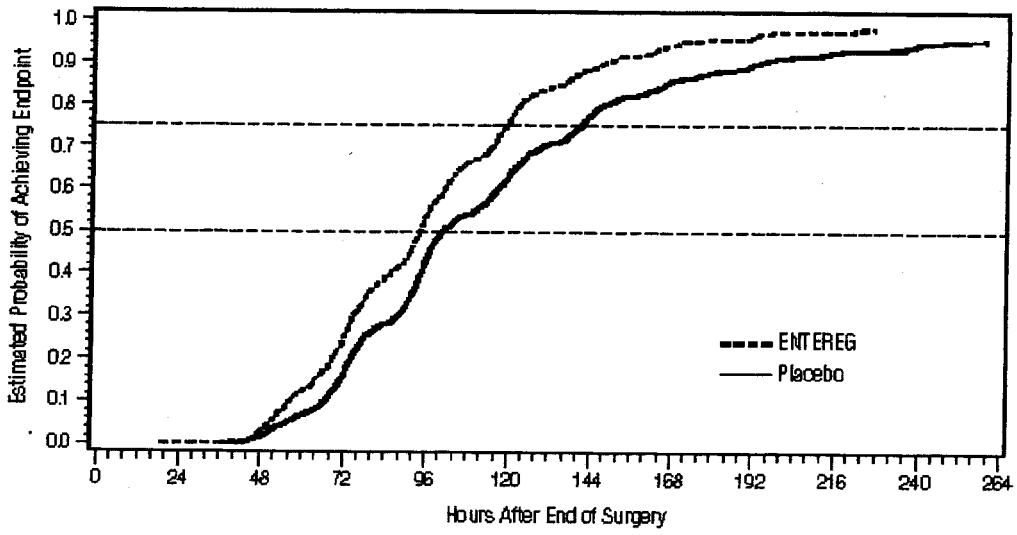
Bowel Resection: A total of 1,877 patients underwent bowel resection. The average age was 61 years with equal proportions of males and females, and 88% were Caucasian. The most common indications for surgery were colon or rectal cancer and diverticular disease. In the non-US study (Study 5), average daily postoperative opioid consumption was approximately 50% lower and the use of non-opioid analgesics substantially higher, as compared with the US studies (Studies 1-4) for both treatment groups. During the first 48 hours postoperatively, the use of non-opioid analgesics was 69% compared with 4% for the non-US and US studies, respectively. In each of the 5 studies, ENTEREG accelerated the time to recovery of gastrointestinal function, as measured by the composite endpoint GI2, and time to discharge order written as compared with placebo. Hazard ratios greater than 1 indicate a higher probability of achieving the event during the study period with treatment with ENTEREG than with placebo. Table 2 provides the Hazard Ratios, Kaplan Meier means and the mean treatment differences (hours) in gastrointestinal recovery between ENTEREG and placebo.

Table 2. GI2 Recovery (Hours) in Bowel Resection Patients

Study No.	ENTEREG 12 mg Mean	Placebo Mean	Treatment Difference Mean	Hazard Ratio (95% CI)
1	92.0	111.8	19.8	1.533 (1.293, 1.816)
2	105.9	132.0	26.1	1.625 (1.256, 2.102)
3	116.4	130.3	14.0	1.365 (1.057, 1.764)
4	106.7	119.9	13.2	1.400 (1.035, 1.894)
5	98.8	109.5	10.7	1.299 (1.070, 1.575)

Gastrointestinal recovery began after approximately 48 hours post surgery. The proportion of patients receiving ENTEREG who achieved GI2 was higher at all times throughout the study observation period compared with those receiving placebo (Figure 1).

Figure 1 Time to GI2 Based on the Combined Data from Five Studies



Across studies 1-4, patients receiving ENTEREG had their discharge order written approximately 13 to 21 hours sooner compared to patients receiving placebo.

ENTEREG did not reverse opioid analgesia as measured by visual analog scale pain

intensity scores and/or amount of postoperative opioids administered across all 5 studies.

There were no gender-, age-, or race-related differences in treatment effect.

The incidence of anastomotic leak was low and comparable in patients receiving either ENTEREG or placebo (0.8% and 1.1%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTEREG Capsules, 12 mg, are blue, hard-gelatin capsules printed with "ADL2698" on both the body and the cap of the capsule. ENTEREG Capsules are available in unit-dose packs of 30 capsules (30 doses) (NDC 11227-010-30) for hospital use only.

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

17 PATIENT COUNSELING INFORMATION

17.1 Recent Use of Opioids

Patients should be informed that they must disclose long-term or intermittent opioid pain therapy, including any use of opioids in the week prior to receiving ENTEREG. They should understand that recent use of opioids may make them more susceptible to adverse reactions to ENTEREG, primarily those limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea).

17.2 Hospital Use Only

Patients should be informed that ENTEREG is for hospital use only for no more than 7 days after their bowel resection surgery.

17.3 Most Common Side Effects

Patients should be informed that the most common side effects with ENTEREG in patients undergoing bowel resection are constipation, dyspepsia, and flatulence.

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