当日配付資料

第21回未承認薬使用問題検討会議
各医薬品の添付文書の掲載ウェブサイトアドレス

- 1. アゴメラチン（agomelatine）
  http://www.emea.europa.eu/humandocs/PDFs/EPAR/valdoxan/H-915-PI-en.pdf

- 2. プラスグレル（prasugrel）
  http://www.emea.europa.eu/humandocs/PDFs/EPAR/Efient/H-984-PI-en.pdf

- 3. アーテメター・ルメファントリン（artemether／lumefantrine）
  http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022268lbl.pdf

- 4. ゴリムマブ（golimumab）
  http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s000lbl.pdf

- 5. ラソフォキシフェン酒石酸塩（lasofoxifene tartrate）
  http://www.emea.europa.eu/humandocs/PDFs/EPAR/fablyn/H-977-PI-en.pdf

- 6. ミファムルチド（mifamurtide）
  http://www.emea.europa.eu/humandocs/PDFs/EPAR/mepact/H-802-PI-en.pdf

  上記のウェブサイトアドレスには PDF ファイルも含まれており、PDF ファイルの閲覧には Adobe Reader 等のソフトウェアが必要となります。

資料 3– 1　アゴメラチン（agomelatine）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Valdoxan 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg of agomelatine.

Excipient: lactose monohydrate 61.84 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet [tablet].
Orange-yellow, oblong, film-coated tablet with blue imprint of company logo on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes in adults

4.2 Posology and method of administration

The recommended dose is 25 mg once daily taken orally at bedtime.
After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime.

Liver function tests should be performed in all patients : at initiation of treatment, and then periodically after around six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated (see also section 4.4).
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

Valdoxan tablets may be taken with or without food.

Children and adolescents:
Valdoxan is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy (see section 4.4).

Elderly patients:
Efficacy has not been clearly demonstrated in the elderly (≥ 65 years). Only limited clinical data is available on the use of Valdoxan in elderly patients ≥ 65 years old with major depressive episodes. Therefore, caution should be exercised when prescribing Valdoxan to these patients (see section 4.4).

Patients with renal impairment:
No relevant modification in agomelatine pharmacokinetic parameters in patients with severe renal impairment has been observed. However, only limited clinical data on the use of Valdoxan in depressed patients with severe or moderate renal impairment with major depressive episodes is available. Therefore, caution should be exercised when prescribing Valdoxan to these patients.

Patients with hepatic impairment:

Valdoxan is contraindicated in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Treatment discontinuation:
No dosage tapering is needed on treatment discontinuation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Hepatic impairment (i.e. cirrhosis or active liver disease) (see sections 4.2 and 4.4).
Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents:
Valdoxan is not recommended in the treatment of depression in patients under 18 years of age since safety and efficacy of Valdoxan have not been established in this age group. In clinical trials among children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with placebo.

Use in elderly patients with dementia:
Valdoxan should not be used for the treatment of major depressive episodes in elderly patients with dementia since the safety and efficacy of Valdoxan have not been established in these patients.

Mania / Hypomania:
Valdoxan should be used with caution in patients with a history of mania or hypomania and should be discontinued if a patient develops manic symptoms.

Suicide/suicidal thoughts:
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Combination with CYP1A2 inhibitors (see sections 4.3 and 4.5)
Combination with potent CYP1A2 inhibitors is contraindicated. Caution should be exercised when prescribing Valdoxan with moderate CYP1A2 inhibitors (*e.g.* propranolol, grepafloxacine, enoxacine) which may result in increased exposure of agomelatine.

Increased serum transaminases:
In clinical studies, elevations of serum transaminases (>3 times the upper limit of the normal range) have been observed in patients treated with Valdoxan particularly on a 50 mg dose (see section 4.8). When Valdoxan was discontinued in these patients, the serum transaminases usually returned to normal levels. Liver function tests should be performed in all patients: at initiation of treatment and then periodically after around six weeks (end of acute phase), after around twelve and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated. Any patient who develops

increased serum transaminases should have his/her liver function tests repeated within 48 hours. Therapy should be discontinued if the increase in serum transaminases exceeds 3X upper limit of normal and liver function tests should be performed regularly until serum transaminases return to normal.
If any patient develops symptoms suggesting hepatic dysfunction liver function tests should be performed. The decision whether to continue the patient on therapy with Valdoxan should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed therapy should be discontinued.
Caution should be exercised when Valdoxan is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury.

Lactose intolerance:
Valdoxan contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions affecting agomelatine:
Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicinal products that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine.
Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12-412) increase of agomelatine exposure.
Consequently, co-administration of Valdoxan with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.
Combination of agomelatine with oestrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure of agomelatine. While there was no specific safety signal in the 800 patients treated in combination with oestrogens, caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol, grepafloxacine, enoxacine) until more experience has been gained (see section 4.4).

Potential for agomelatine to affect other medicinal products:
In vivo, agomelatine does not induce CYP450 isoenzymes. Agomelatine inhibits neither CYP1A2 *in vivo* nor the other CYP450 *in vitro*. Therefore, agomelatine will not modify exposure to medicinal products metabolised by CYP 450.

Medicinal products highly bound to plasma protein:
Agomelatine does not modify free concentrations of medicinal products highly bound to plasma proteins or *vice versa*.

Other medicinal products:
No evidence of pharmacokinetic or pharmacodynamic interaction with medicinal products which could be prescribed concomitantly with Valdoxan in the target population was found in phase I clinical trials: benzodiazepines, lithium, paroxetine, fluconazole and theophylline.

Alcohol:
The combination of Valdoxan and alcohol is not advisable.

Electroconvulsive therapy (ECT):
There is no experience of concurrent use of agomelatine with ECT. Animal studies have not shown proconvulsant properties (see section 5.3). Therefore, clinical consequences of ECT concomitant treatment with Valdoxan are considered to be unlikely.

4.6 Pregnancy and lactation

For agomelatine, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition

or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

It is not known whether agomelatine is excreted into human milk. Agomelatine or its metabolites are excreted in the milk of lactating rats. Potential effects of agomelatine on the breast-feeding infant have not been established. If treatment with Valdoxan is considered necessary, breastfeeding should be discontinued.

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.
However, considering that dizziness and somnolence are common adverse reactions patients should be cautioned about their ability to drive a car or operate machinery.

4.8 Undesirable effects

In clinical trials, over 3,900 depressed patients have received Valdoxan.
Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment.
The most common adverse reactions were nausea and dizziness.
These adverse reactions were usually transient and did not generally lead to cessation of therapy.
Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Valdoxan.
Adverse reactions are listed below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). The frequencies have not been corrected for placebo.

Nervous system disorders:
Common: headache, dizziness, somnolence, insomnia, migraine
Uncommon: paraesthesia

Eye disorders:
Uncommon: blurred vision

Gastrointestinal disorders:
Common: nausea, diarrhoea, constipation, upper abdominal pain

Skin and subcutaneous tissue disorders
Common: hyperhidrosis
Uncommon: eczema
Rare: erythematous rash

Musculoskeletal and connective tissue disorders
Common: back pain

General disorders and administration site conditions:
Common: fatigue

Hepato-biliary disorders:
Common: increases (>3 times the upper limit of the normal range) in ALAT and/or ASAT (i.e. 1.1% on agomelatine 25/50 mg vs. 0.7% on placebo).
Rare: hepatitis

Psychiatric disorders:
Common: anxiety
Frequency not known: Suicidal thoughts or behaviour (see section 4.4)

4.9 Overdose

There is limited experience with agomelatine overdose. During the clinical development, there were a few reports of agomelatine overdose, taken alone (up to 450 mg) or in combination (up to 525 mg) with other psychotropic medicinal products. Signs and symptoms of overdose were limited and included drowsiness and epigastralgia.
No specific antidotes for agomelatine are known. Management of overdose should consist of treatment of clinical symptoms and routine monitoring. Medical follow-up in a specialised environment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants, ATC-code: NO6AX22

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.
Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption.
Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin.
Agomelatine has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress) as well as in models with circadian rhythm desynchronisation and in models related to stress and anxiety.
In humans, Valdoxan has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

The efficacy and safety of Valdoxan in major depressive episodes have been studied in a clinical programme including 5,800 patients of whom 3,900 were treated with Valdoxan.
Six placebo controlled trials have been performed to investigate the short term efficacy of Valdoxan in major depressive disorder: two flexible dose studies and four fixed dose studies. At the end of treatment (over 6 or 8 weeks), significant efficacy of agomelatine 25-50 mg was demonstrated in 3 of the six short-term double-blind placebo-controlled studies. Agomelatine failed to differentiate from placebo in one study where the active control fluoxetine showed assay sensitivity. In two other studies, it was not possible to draw any conclusions because the active controls, paroxetine and fluoxetine, failed to differentiate from placebo.
Efficacy was also observed in more severely depressed patients (baseline HAM-D ≥ 25) in all positive placebo-controlled studies.
Response rates were statistically significantly higher with Valdoxan compared with placebo.
The maintenance of antidepressant efficacy was demonstrated in a relapse prevention study. Patients responding to 8/10-weeks of acute treatment with open-label Valdoxan 25-50 mg once daily were randomised to either Valdoxan 25-50 mg once daily or placebo for further 6-months. Valdoxan 25-50 mg once daily demonstrated a statistically significant superiority compared to placebo ($p=0.0001$) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow up period was 22% and 47% for Valdoxan and placebo, respectively.

Valdoxan does not alter daytime vigilance and memory in healthy volunteers. In depressed patients, treatment with Valdoxan 25 mg increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount or REM latency. Valdoxan 25 mg also induced an advance of the time of sleep onset and of minimum heart rate. From the first week of treatment, onset of sleep and the quality of sleep were significantly improved without daytime clumsiness as assessed by patients.

In a specific sexual dysfunction comparative study with remitted depressed patients, there was a numerical trend (not statistically significant) towards less sexual emergent dysfunction than venlafaxine for Sex Effects Scale (SEXFX) drive arousal or orgasm scores on Valdoxan. The pooled analysis of studies using the Arizona Sexual Experience Scale (ASEX) showed that Valdoxan was not associated with sexual dysfunction. In healthy volunteers Valdoxan preserved sexual function in comparison with paroxetine.

Valdoxan had neutral effect on body weight, heart rate and blood pressure in clinical studies.

In a study designed to assess discontinuation symptoms by the Discontinuation Emergent Signs and Symptoms (DESS) check-list in patients with remitted depression, Valdoxan did not induce discontinuation syndrome after abrupt treatment cessation.
Valdoxan has no abuse potential as measured in healthy volunteer studies on a specific visual analogue scale or the Addiction Research Center Inventory (ARCI) 49 check-list.

5.2 Pharmacokinetic properties

Absorption and bioavailability:
Agomelatine is rapidly and well (≥ 80%) absorbed after oral administration. Absolute bioavailability is low (< 5% at the therapeutic oral dose) and the interindividual variability is substantial. The bioavailability is increased in women compared to men. The bioavailability is increased by intake of oral contraceptives and reduced by smoking. The peak plasma concentration is reached within 1 to 2 hours.

In the therapeutic dose-range, agomelatine systemic exposure increases proportionally with dose. At higher doses, a saturation of the first-pass effect occurs.
Food intake (standard meal or high fat meal) does not modify the bioavailability or the absorption rate. The variability is increased with high fat food.

Distribution:
Steady state volume of distribution is about 35 l and plasma protein binding is 95% irrespective of the concentration and is not modified with age and in patients with renal impairment but the free fraction is doubled in patients with hepatic impairment.

Biotransformation:
Following oral administration, agomelatine is rapidly metabolised mainly via hepatic CYP1A2; CYP2C9 and CYP2C19 isoenzymes are also involved but with a low contribution.
The major metabolites, hydroxylated and demethylated agomelatine, are not active and are rapidly conjugated and eliminated in the urine.

Elimination:
Elimination is rapid, the mean plasma half-life is between 1 and 2 hours and the clearance is high (about 1,100 ml/min) and essentially metabolic.
Excretion is mainly (80%) urinary and in the form of metabolites, whereas unchanged compound recovery in urine is negligible.
Kinetics are not modified after repeated administration.

Renal impairment:
No relevant modification of pharmacokinetic parameters in patients with severe renal impairment has been observed (n=8, single dose of 25 mg), but caution should be exercised in patients with severe or moderate renal impairment as only limited clinical data are available in these patients (see section 4.2).

Hepatic impairment:
In a specific study involving cirrhotic patients with chronic mild (Child-Pugh type A) or moderate (Child-Pugh type B) liver impairment, exposure to agomelatine 25 mg was substantially increased (70-times and 140-times, respectively), compared to matched volunteers (age, weight and smoking habit) with no liver failure (see section 4.2, 4.3 and 4.4).

Ethnic groups:
There is no data on the influence of race on agomelatine pharmacokinetics.

5.3 Preclinical safety data

In mice, rats and monkeys sedative effects were observed after single and repeated administration at high doses.
In rodents, a marked induction of CYP2B and a moderate induction of CYP1A and CYP3A were seen from 125 mg/kg/day whereas in monkeys the induction was slight for CYP2B and CYP3A at 375 mg/kg/day. No hepatotoxicity was observed in rodents and monkeys in the repeat dose toxicity studies.
Agomelatine passes into the placenta and foetuses of pregnant rats.
Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility, embryofoetal development and pre- and post natal development.
A battery of *in vitro* and *in vivo* standard genotoxicity assays concludes to no mutagenic or clastogenic potential of agomelatine.

In carcinogenicity studies agomelatine induced an increase in the incidence of liver tumours in the rat and the mouse, at a dose at least 110-fold higher than the therapeutic dose. Liver tumours are most likely related to enzyme induction specific to rodents. The frequency of benign mammary fibroadenomas observed in the rat was increased with high exposures (60-fold the exposure at the therapeutic dose) but remains in the range of that of controls.

Safety pharmacology studies showed no effect of agomelatine on hERG (human Ether à-go-go Related Gene) current or on dog Purkinje cells action potential. Agomelatine did not show proconvulsive properties at ip doses up to 128 mg/kg in mice and rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Lactose monohydrate
- Maize starch
- Povidone
- Sodium starch glycolate type A
- Stearic acid
- Magnesium stearate
- Silica, colloidal anhydrous

Film-coating:
- Hypromellose
- Yellow iron oxide (E172)
- Glycerol
- Macrogol
- Magnesium stearate
- Titanium dioxide (E171)

Printing ink containing shellac, propylene glycol and indigotine (E132) aluminium lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes (calendar).
Packs containing 7, 14, 28, 42, 56, 84 and 98 film-coated tablets.
Packs of 100 film-coated tablets for hospital use.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
22, rue Garnier
F-92200 Neuilly-sur-Seine
France

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF THE FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING 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 responsible for batch release

Les Laboratoires Servier Industrie, 905, route de Saran - 45520 Gidy, France
Servier (Ireland) Industries Ltd, Gorey Road - Arklow - Co. Wicklow, Ireland
Przedsiebiorstwo Farmaceutyczne ANPHARM S.A., ul. Annopol 6B - 03-236 Warszawa, Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

The Marketing Authorisation Holder (MAH) shall ensure that, at launch, all healthcare professionals who are experienced to prescribe/use Valdoxan are provided with educational materials containing the following:

As described in the RMP, additional risk minimisation activity including educational material will be provided to prescribers.

Objectives of agomelatine Educational Plan:

The prescriber educational material about Valdoxan / Thymanax will be focused on:

- The potential risks of agomelatine
  - Transaminases Elevations
  - Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

- Guidance for hepatic function screening (Need to perform liver function tests in all patients: at initiation of treatment, and then periodically after around six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated;

- Guidance in case of clinical symptoms or liver function tests abnormality;

- Caution to be exercised when therapy is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury;

- Contra-indication in patients with hepatic impairment (i.e. cirrhosis or active liver disease);

- Contra-indication in patients receiving concomitantly potent CYP1A2 inhibitors.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 4.0 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 the version 4.0 of the Risk Management Plan (RMP) presented in the 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

Valdoxan 25 mg film-coated tablets
Agomelatine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg of agomelatine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
42 film-coated tablets
56 film-coated tablets
84 film-coated tablets
98 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

Les Laboratoires Servier
22, rue Garnier
F-92200 Neuilly-sur-Seine
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Valdoxan 25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Valdoxan 25 mg tablets
Agomelatine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot{number}

5. OTHER

MON
TUE
WED
THU
FRI
SAT
SUN

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valdoxan 25 mg film-coated tablets
Agomelatine

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 VALDOXAN IS AND WHAT IT IS USED FOR

Valdoxan belongs to a group of medicines called antidepressants and you have been given Valdoxan to treat your depression.

Depression is a continuing disturbance of mood that interferes with everyday life. The symptoms of depression vary from one person to another, but often include deep sadness, feelings of worthlessness, loss of interest in favourite activities, sleep disturbances, feeling of being slowed down, feelings of anxiety, changes in weight.

2. BEFORE YOU TAKE VALDOXAN

Do not take Valdoxan
- if you are allergic (hypersensitive) to agomelatine or any of the other ingredients of Valdoxan (see '*What Valdoxan contains*' in section 6).
- if you are taking fluvoxamine (another medicine used in the treatment of depression) or ciprofloxacin (an antibiotic).
- if your liver does not work properly (hepatic impairment).

Take special care with Valdoxan
There could be some reasons why Valdoxan may not be suitable for you:
- If you have already experienced or if you develop manic symptoms (a period of abnormally high excitability and emotions) talk to your doctor before you start taking this medicine or continue with this medicine.
- If you are taking medicine known to affect the liver. Ask your doctor for advice on which medicine that is.
  Some patients may get increased levels of liver enzymes in their blood during treatment with Valdoxan. Your doctor will therefore run laboratory tests to check that your liver is working

properly at the initiation of the treatment and then periodically during treatment. Based on the evaluation of these tests the doctor will decide whether you should continue using Valdoxan or not (see also under "*How to take Valdoxan*" in section 3).
- If you are suffering from dementia, your doctor will make an individual evaluation of whether it is safe for you to take Valdoxan.

Valdoxan is not intended for use in children and adolescents (under 18 years old).

Thoughts of suicide and worsening of your depression
If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:
- if you have previously had thoughts about killing or harming yourself.
- if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (aged less than 25 years) with psychiatric conditions who were being treated with an antidepressant.
If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

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.

You should not take Valdoxan together with certain medicines (see also under "*Do not take Valdoxan*" in section 2): fluvoxamine (another medicine used in the treatment of depression), ciprofloxacin (an antibiotic).

Taking Valdoxan with food and drink
Valdoxan can be taken with or without food.
It is not advisable to drink alcohol while you are being treated with Valdoxan.

Pregnancy
Talk to your doctor if you become pregnant (or plan to become pregnant) while you are taking Valdoxan. Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Talk to your doctor if you are breast-feeding or intending to breast-feed as breastfeeding should be discontinued if you take Valdoxan.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You might experience dizziness or sleepiness which could affect your ability to drive or operate machinery. Make sure that your reactions are normal before driving or operating machines.

Important information about some of the ingredients of Valdoxan

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking Valdoxan.

3. HOW TO TAKE VALDOXAN

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

The recommended dose of Valdoxan is one tablet (25 mg) at bedtime. In some cases, your doctor may prescribe a higher dose (50 mg), i.e. two tablets to be taken together at bedtime.

Valdoxan starts to act on symptoms of depression in most depressed people within two weeks of starting treatment. Your doctor may continue to give you Valdoxan when you are feeling better to prevent your depression from returning.

Do not stop taking your medicine without the advice of your doctor even if you feel better.

Valdoxan is for oral use. You should swallow your tablet with a drink of water. Valdoxan can be taken with or without food.

Your doctor will run laboratory tests to check that your liver is working properly at the initiation of treatment and then periodically during treatment, usually after 6 weeks, 12 weeks and 24 weeks. Thereafter tests will be taken if the doctor finds it necessary.
You must not use Valdoxan if your liver does not work properly.

If you have trouble with your kidneys, your doctor will make an individual evaluation of whether it is safe for you to take Valdoxan.

If you take more Valdoxan than you should
If you have taken more Valdoxan than you should, or if for example a child has taken medicine by accident, contact your doctor immediately.
The experience of overdoses with Valdoxan is limited but reported symptoms include pain in the upper part of the stomach and drowsiness.

If you forget to take Valdoxan
Do not take a double dose to make up for a forgotten dose. Just carry on with the next dose at the usual time.
The calendar printed on the blister containing the tablets should help you remembering when you last took a tablet of Valdoxan.

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

4. POSSIBLE SIDE EFFECTS

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

Most side effects are mild or moderate. They usually occur within the first two weeks of the treatment and are usually temporary.

The frequency of possible side effects listed below is defined using the following system:

- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)
- not known (frequency cannot be estimated from the available data)

These side effects include:

- Common side effects: dizziness, sleepiness (somnolence), difficulty in sleeping (insomnia), migraine, headache, feeling sick (nausea), diarrhoea, constipation, upper abdominal pain, excessive sweating (hyperhidrosis), back pain, tiredness, anxiety, increased levels of liver enzymes in your blood.
- Uncommon side effects: pins and needles in the fingers and toes (paraesthesia), blurred vision and eczema.
- Rare side effects: serious skin eruption (erythematous rash), hepatitis.
- Other possible side effects: suicidal thoughts or behaviour (frequency not known).

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 VALDOXAN

Keep out of the reach and sight of children.

Do not use Valdoxan after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.

This medicine 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 Valdoxan contains

- The active substance is agomelatine. Each tablet contains 25 mg of agomelatine.
- The other ingredients are:
    - tablet core: lactose monohydrate, maize starch, povidone, sodium starch glycolate type A, stearic acid, magnesium stearate, colloidal anhydrous silica.
    - tablet film-coating: hypromellose, glycerol, macrogol, magnesium stearate, yellow iron oxide (E172) and titanium dioxide (E171).
    - printing ink : shellac, propylene glycol and indigotine (E132) aluminium lake

What Valdoxan looks like and contents of the pack

Valdoxan 25 mg film-coated tablets are oblong, orange-yellow with a blue imprint of 'company logo' on one side.

Valdoxan 25 mg film-coated tablets are available in calendar blisters. Packs contain 7, 14, 28, 42, 56, 84 or 98 tablets. Packs of 100 film-coated tablets are also available for hospital use.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

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Les Laboratoires Servier
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92200 Neuilly sur Seine - France

Manufacturer
Les Laboratoires Servier Industrie
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and

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This leaflet was last approved in {date}

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

資料３－２　プラスグレル（prasugrel）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efient 5 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg prasugrel (as hydrochloride).
Excipient: Each tablet contains 2.7 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow and double-arrow-shaped tablets, debossed with "5 mg" on one side and "4760" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology

Adults
Efient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking Efient should also take ASA daily (75 mg to 325 mg).

In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless the discontinuation of Efient is clinically indicated (see sections 4.4 and 5.1).

Patients ≥ 75 years old
The use of Efient in patients ≥ 75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician (see section 4.4), treatment is deemed necessary in the patients age group ≥ 75 years, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients ≥ 75 years of age have greater sensitivity to bleeding and higher exposure to the active metabolite of prasugrel (see sections 4.4, 4.8, 5.1 and 5.2). The evidence for the 5 mg dose is based only on pharmacodynamic/pharmacokinetic analyses and no clinical data currently exist on the safety of this dose in the patients age group ≥ 75 years.

Patients weighing <60 kg
Efient should be given as a single 60 mg loading dose and then continued at a 5 mg once daily dose.

The 10 mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight <60 kg when given a 10 mg once daily dose compared with patients ≥60 kg. Efficacy and safety of the 5 mg dose have not been prospectively assessed (see sections 4.4, 4.8 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (see section 5.2). There is limited therapeutic experience in patients with renal impairment (see section 4.4).

Hepatic impairment
No dose adjustment is necessary in subjects with mild to moderate hepatic impairment (Child Pugh class A and B) (see section 5.2). There is limited therapeutic experience in patients with mild and moderate hepatic dysfunction (see section 4.4).

Children and adolescents
Efient is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Method of administration
For oral use. Efient may be administered with or without food. Administration of the 60 mg prasugrel loading dose in the fasted state may provide most rapid onset of action (see section 5.2). Do not crush or break the tablet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Active pathological bleeding.
History of stroke or transient ischaemic attack (TIA).
Severe hepatic impairment (Child Pugh class C).

4.4 Special warnings and precautions for use

Bleeding risk
In the phase 3 clinical trial key exclusion criteria included an increased risk of bleeding; anaemia; thrombocytopaenia; a history of pathological intracranial findings. Patients with acute coronary syndromes undergoing PCI treated with Efient and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Efient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleedings. This concern applies especially to patients:
• ≥75 years of age (see below).
• with a propensity to bleed (e.g. due to recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, or active peptic ulcer disease)
• with body weight <60 kg (see sections 4.2 and 4.8). In these patients the 10 mg maintenance dose is not recommended. A 5 mg maintenance dose should be used.
• with concomitant administration of medicinal products that may increase the risk of bleeding, including oral anticoagulants, clopidogrel, non-steroidal anti-inflammatory drugs (NSAIDs), and fibrinolytics.

For patients with active bleeding for whom reversal of the pharmacological effects of Efient is required, platelet transfusion may be appropriate.

The use of Efient in patients ≥75 years of age is generally not recommended and should only be undertaken with caution after a careful individual benefit/risk evaluation by the prescribing physician indicates that benefits in terms of prevention of ischaemic events outweigh the risk of serious bleedings. In the phase 3 clinical trial these patients were at greater risk of bleeding, including fatal

bleeding, compared to patients <75 years of age. If prescribed, a lower maintenance dose of 5 mg should be used; the 10 mg maintenance dose is not recommended (see sections 4.2 and 4.8).

Therapeutic experience with prasugrel is limited in patients with renal impairment (including ESRD) and in patients with moderate hepatic impairment. These patients may have an increased bleeding risk. Therefore, prasugrel should be used with caution in these patients.

Therapeutic experience with prasugrel is limited in Asian patients. Therefore, prasugrel should be used with caution in these patients.

Patients should be told that it might take longer than usual to stop bleeding when they take prasugrel (in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Surgery
Patients should be advised to inform physicians and dentists that they are taking prasugrel before any surgery is scheduled and before any new medicinal product is taken. If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, Efient should be discontinued at least 7 days prior to surgery. Increased frequency (3-fold) and severity of bleeding may occur in patients undergoing CABG surgery within 7 days of discontinuation of prasugrel (see 4.8). The benefits and risks of prasugrel should be carefully considered in patients in whom the coronary anatomy has not been defined and urgent CABG is a possibility.

Thrombotic Thrombocytopaenic Purpura (TTP)
TTP has been reported with the use of other thienopyridines. TTP is a serious condition and requires prompt treatment. Efient was not associated with TTP in clinical trials supporting registration.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Efient.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Concomitant administration of Efient with coumarin derivatives other than warfarin has not been studied. Because of the potential for increased risk of bleeding, warfarin (or other coumarin derivatives) and prasugrel should be co-administered with caution (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs): Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs (including COX-2 inhibitors) and Efient should be co-administered with caution (see section 4.4).

Efient can be concomitantly administered with medicinal products metabolised by cytochrome P450 enzymes (including statins), or medicinal products that are inducers or inhibitors of cytochrome P450 enzymes. Efient can also be concomitantly administered with ASA, heparin, digoxin, and medicinal products that elevate gastric pH, including proton pump inhibitors and H_2 blockers. Although not studied in specific interaction studies, Efient has been co-administered in the phase 3 clinical trial with low molecular weight heparin, bivalirudin, and GP IIb/IIIa inhibitors (no information available regarding the type of GP IIb/IIIa inhibitor used) without evidence of clinically significant adverse interactions.

Effects of other medicinal products on Efient:

Acetylsalicylic acid: Efient is to be administered concomitantly with acetylsalicylic acid (ASA). Although a pharmacodynamic interaction with ASA leading to an increased risk of bleeding is possible, the demonstration of the efficacy and safety of prasugrel comes from patients concomitantly treated with ASA.

Heparin: A single intravenous bolus dose of unfractionated heparin (100 U/kg) did not significantly alter the prasugrel-mediated inhibition of platelet aggregation. Likewise, prasugrel did not significantly alter the effect of heparin on measures of coagulation. Therefore, both medicinal products can be administered concomitantly. An increased risk of bleeding is possible when Efient is co-administered with heparin.

Statins: Atorvastatin (80 mg daily) did not alter the pharmacokinetics of prasugrel and its inhibition of platelet aggregation. Therefore, statins that are substrates of CYP3A are not anticipated to have an effect on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.

Medicinal products that elevate gastric pH: Daily co-administration of ranitidine (an H_2 blocker) or lansoprazole (a proton pump inhibitor) did not change the prasugrel active metabolite's AUC and T_{max}, but decreased the C_{max} by 14% and 29%, respectively. In the phase 3 clinical trial, Efient was administered without regard to co-administration of a proton pump inhibitor or H_2 blocker. Administration of the 60 mg prasugrel loading dose without concomitant use of proton pump inhibitors may provide most rapid onset of action.

Inhibitors of CYP3A: Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated inhibition of platelet aggregation or the prasugrel active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as azol antifungals, HIV protease inhibitors, clarithromycin, telithromycin, verapamil, diltiazem, indinavir, ciprofloxacin, and grapefruit juice are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.

Inducers of cytochromes P450: Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6, and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of prasugrel. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not anticipated to have significant effect on the pharmacokinetics of the active metabolite.

Effects of Efient on other medicinal products:

Digoxin: prasugrel has no clinically significant effect on the pharmacokinetics of digoxin.

Medicinal products metabolised by CYP2C9: prasugrel did not inhibit CYP2C9, as it did not affect the pharmacokinetics of S-warfarin. Because of the potential for increased risk of bleeding, warfarin and Efient should be co-administered with caution (see section 4.4).

Medicinal products metabolised by CYP2B6: prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%. This effect is likely to be of clinical concern only when prasugrel is co-administered with medicinal products for which CYP2B6 is the only metabolic pathway and have a narrow therapeutic window (e.g. cyclophosphamide, efavirenz).

4.6 Pregnancy and lactation

No clinical study has been conducted in pregnant or lactating women.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Because animal reproduction studies are not always predictive of a human response, Efient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

It is unknown whether prasugrel is excreted in human breast milk. Animal studies have shown excretion of prasugrel in breast milk. The use of prasugrel during breastfeeding is not recommended.

Prasugrel had no effect on fertility of male and female rats at oral doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m^2).

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Prasugrel is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one clopidogrel-controlled study (TRITON) in which 6741 patients were treated with prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5802 patients were treated for over 6 months, 4136 patients were treated for more than 1 year). The rate of study drug discontinuation due to adverse events was 7.2% for prasugrel and 6.3% for clopidogrel. Of these, bleeding was the most common adverse reaction for both drugs leading to study drug discontinuation (2.5% for prasugrel and 1.4% for clopidogrel).

Bleeding

Non-Coronary Artery Bypass Graft (CABG) related bleeding
In TRITON, the frequency of patients experiencing a non-CABG related bleeding event is shown in Table 1. The incidence of Non-CABG-related TIMI major bleeding, including life-threatening and fatal, as well as TIMI minor bleeding, was statistically significantly higher in subjects treated with prasugrel compared to clopidogrel in the UA/NSTEMI and All ACS populations. No significant difference was seen in the STEMI population. The most common site of spontaneous bleeding was the gastrointestinal tract (1.7% rate with prasugrel and 1.3% rate with clopidogrel); the most frequent site of provoked bleeding was the arterial puncture site (1.3% rate with prasugrel and 1.2% with clopidogrel).

Table 1: Incidence of Non-CABG related bleeding[a] (% Patients)

Event	All ACS		UA/NSTEMI		STEMI	
	Prasugrel[b] +ASA (N=6741)	**Clopidogrel[b] +ASA (N=6716)**	**Prasugrel[b] +ASA (N=5001)**	**Clopidogrel[b] +ASA (N=4980)**	**Prasugrel[b] +ASA (N=1740)**	**Clopidogrel[b] +ASA (N=1736)**
TIMI major bleeding[c]	2.2	1.7	2.2	1.6	2.2	2.0
Life-threatening[d]	1.3	0.8	1.3	0.8	1.2	1.0
Fatal	0.3	0.1	0.3	0.1	0.4	0.1
Symptomatic ICH[e]	0.3	0.3	0.3	0.3	0.2	0.2
Requiring inotropes	0.3	0.1	0.3	0.1	0.3	0.2
Requiring surgical intervention	0.3	0.3	0.3	0.3	0.1	0.2
Requiring transfusion (≥4 units)	0.7	0.5	0.6	0.3	0.8	0.8
TIMI minor bleeding[f]	2.4	1.9	2.3	1.6	2.7	2.6

a Centrally adjudicated events defined by the Thrombolysis in Myocardial Infarction (TIMI) Study Group criteria.

b Other standard therapies were used as appropriate.

c Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥5 g/dL.

d Life-threatening bleeding is a subset of TIMI major bleeding and includes the types indented below. Patients may be counted in more than one row.

e ICH=intracranial haemorrhage.

f Clinically overt bleeding associated with a fall in haemoglobin of ≥3 g/dL but <5 g/dL.

Patients ≥ 75 years old

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two age groups were as follows:

Age	Prasugrel	Clopidogrel
≥75 years (N=1785)	9.0% (1.0% fatal)	6.9% (0.1% fatal)
<75 years (N=11672)	3.8% (0.2% fatal)	2.9% (0.1% fatal)

Patients < 60 kg

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two weight groups were as follows:

Weight	Prasugrel	Clopidogrel
<60 kg (N=664)	10.1% (0% fatal)	6.5% (0.3% fatal)
≥60 kg (N=12672)	4.2% (0.3% fatal)	3.3% (0.1% fatal)

In patients ≥60 kg *and* age <75 years, non-CABG-related TIMI major or minor bleeding rates were 3.6% for prasugrel and 2.8% for clopidogrel; rates for fatal bleeding were 0.2% for prasugrel and 0.1% for clopidogrel.

CABG-related bleeding

In the phase 3 clinical trial, 437 patients underwent CABG during the course of the study. Of those patients, the rate of CABG-related TIMI major or minor bleeding was 14.1% for the prasugrel group and 4.5% in the clopidogrel group. The higher risk for bleeding events in subjects treated with prasugrel persisted up to 7 days from the most recent dose of study drug. For patients who received their thienopyridine within 3 days prior to CABG, the frequencies of TIMI major or minor bleeding were 26.7% (12 of 45 patients) in the prasugrel group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.3% (3 of 90 patients) in the clopidogrel group. Beyond 7 days after drug discontinuation, the observed rates of CABG-related bleeding were similar between treatment groups (see section 4.4).

Adverse Reactions

Table 2 summarises haemorrhagic and non-haemorrhagic adverse reactions in TRITON classified by frequency and system organ class. Frequencies are defined as follows:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100);
rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 2: Haemorrhagic and Non-haemorrhagic adverse reactions

System Organ Class	Common	Uncommon	Rare
Blood and Lymphatic System disorders	Anaemia		
Eye disorders		Eye haemorrhage	
Vascular Disorders	Haematoma		
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis	
Gastrointestinal disorders	Gastrointestinal haemorrhage	Retroperitoneal haemorrhage Rectal haemorrhage Haematochezia	

		Gingival bleeding	
Skin and subcutaneous tissue disorders	Rash Ecchymosis		
Renal and urinary disorders	Haematuria		
General disorders and administration site conditions	Vessel puncture site haematoma Puncture site haemorrhage		
Injury, poisoning and procedural complications	Contusion	Post-procedural haemorrhage	Subcutaneous haematoma

In patients with or without a history of TIA or stroke, the incidence of stroke in the phase 3 clinical trial was as follows (see section 4.4):

History of TIA or stroke	Prasugrel	Clopidogrel
Yes (N=518)	6.5% (2.3% ICH*)	1.2% (0% ICH*)
No (N=13090)	0.9% (0.2% ICH*)	1.0% (0.3% ICH*)

* *ICH=intracranial haemorrhage.*

4.9 Overdose

Overdose of Efient may lead to prolonged bleeding time and subsequent bleeding complications. No data are available on the reversal of the pharmacological effect of prasugrel; however, if prompt correction of prolonged bleeding time is required, platelet transfusion and/or other blood products may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned. ATC code: Not yet assigned.

Pharmacodynamics
Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke.

Following a 60 mg loading dose of prasugrel, inhibition of ADP-induced platelet aggregation occurs at 15 minutes with 5 µM ADP and 30 minutes with 20 µM ADP. The maximum inhibition by prasugrel of ADP-induced platelet aggregation is 83% with 5 µM ADP and 79% with 20 µM ADP, in both cases with 89% of healthy subjects and patients with stable atherosclerosis achieving at least 50% inhibition of platelet aggregation by 1 hour. Prasugrel-mediated inhibition of platelet aggregation exhibits low between-subject (12%) and within-subject (9%) variability with both 5 µM and 20 µM ADP. Mean steady-state inhibition of platelet aggregation was 74% and 69% respectively for 5 µM ADP and 20 µM ADP, and was achieved following 3 to 5 days of administration of the 10 mg prasugrel maintenance dose preceded by a 60 mg loading dose. More than 98% of subjects had ≥20% inhibition of platelet aggregation during maintenance dosing.

Platelet aggregation gradually returned to baseline values after treatment in 7 to 9 days after administration of a single 60 mg loading dose of prasugrel and in 5 days following discontinuation of maintenance dosing at steady-state.

Clopidogrel: Following administration of 75 mg clopidogrel once daily for 10 days, 40 healthy subjects were switched to prasugrel 10 mg once daily with or without a loading dose of 60 mg. Similar or higher inhibition of platelet aggregation was observed with prasugrel. Switching directly to prasugrel 60 mg loading dose resulted in the most rapid onset of higher platelet inhibition. Following administration of a 900 mg loading dose of clopidogrel (with ASA), 56 subjects with ACS were treated for 14 days with either prasugrel 10 mg once daily or clopidogrel 150 mg once daily, and then switched to either clopidogrel 150 mg or prasugrel 10 mg for another 14 days. Higher inhibition of platelet aggregation was observed in patients switched to prasugrel 10 mg compared with those treated with clopidogrel 150 mg. No data are available on switching from a clopidogrel loading dose directly to a prasugrel loading dose.

Efficacy and Safety in Acute Coronary Syndrome (ACS)
The phase 3 TRITON study compared Efient (prasugrel) with clopidogrel, both co-administered with ASA and other standard therapy. TRITON was a 13,608 patient, multicentre international, randomised, double blind, parallel group study. Patients had ACS with moderate to high risk UA, NSTEMI, or STEMI and were managed with PCI.

Patients with UA/NSTEMI within 72 hours of symptoms or STEMI between 12 hours to 14 days of symptoms were randomised after knowledge of coronary anatomy. Patients with STEMI within 12 hours of symptoms and planned for primary PCI could be randomised without knowledge of coronary anatomy. For all patients, the loading dose could be administered anytime between randomisation and 1 hour after the patient left the catheterisation lab.

Patients randomised to receive prasugrel (60 mg loading dose followed by 10 mg once daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily) were treated for a median of 14.5 months (maximum of 15 months with a minimum of 6 months follow-up). Patients also received ASA (75 mg to 325 mg once daily). Use of any thienopyridine within 5 days before enrolment was an exclusion criterion. Other therapies, such as heparin and GPIIb/IIIa inhibitors, were administered at the discretion of the physician. Approximately 40% of patients (in each of the treatment groups) received GPIIb/IIIa inhibitors in support of PCI (no information available regarding the type of GP IIb/IIIa inhibitor used). Approximately 98% of patients (in each of the treatment groups) received antithrombins (heparin, low molecular weight heparin, bivalirudin, or other agent) directly in support of PCI.

The trial's primary outcome measure was the time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. Analysis of the composite endpoint in the All ACS population (combined UA/NSTEMI and STEMI cohorts) was contingent on showing statistical superiority of prasugrel versus clopidogrel in the UA/NSTEMI cohort ($p<0.05$).

All ACS population: Efient showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (see Table 3). The benefit of prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding (see sections 4.4 and 4.8). The patient population was 92% Caucasian, 26% female, and 39% ≥65 years of age. The benefits associated with prasugrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/low molecular weight heparin, bivalirudin, intravenous GPIIb/IIIa inhibitors, lipid-lowering medicinal products, beta-blockers, and angiotensin converting enzyme inhibitors. The efficacy of prasugrel was independent of the ASA dose (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet medicinal products and chronic NSAIDs was not allowed in TRITON. In the All ACS population, prasugrel was associated with a lower incidence of CV death, non-fatal MI, or non-fatal stroke compared to clopidogrel, regardless of baseline characteristics such as age, sex, body weight, geographical region, use of GPIIb/IIIa inhibitors, and stent type. The benefit was primarily due to a significant decrease in non-fatal MI (see table 3). Subjects with diabetes had significant reductions in the primary and all secondary composite endpoints.

The observed benefit of prasugrel in patients ≥ 75 years was less than that observed in patients <75 years. Patients ≥ 75 years were at increased risk of bleeding, including fatal (see sections 4.2, 4.4, and 4.8). Patients ≥ 75 years in whom the benefit with prasugrel was more evident included those with diabetes, STEMI, higher risk of stent thrombosis, or recurrent events.

Patients with a history of TIA or a history of ischaemic stroke more than 3 months prior to prasugrel therapy had no reduction in the primary composite endpoint.

Table 3: Patients with Outcome Events in TRITON Primary Analysis

Outcome Events	**Prasugrel + ASA**	**Clopidogrel +ASA**	**Hazard Ratio (HR) (95% CI)**	**p-value**
All ACS	**(N=6813) %**	**(N=6795) %**		
Primary Composite Outcome Events Cardiovascular (CV) death, non fatal MI, or non fatal stroke	9.4	11.5	0.812 (0.732, 0.902)	<0.001
Primary Individual Outcome Events				
CV death	2.0	2.2	0.886 (0.701, 1.118)	0.307
Nonfatal MI	7.0	9.1	0.757 (0.672, 0.853)	<0.001
Nonfatal stroke	0.9	0.9	1.016 (0.712, 1.451)	0.930
UA/NSTEMI Primary Composite Outcome Events	**(N= 5044) %**	**(N=5030) %**		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	0.820 (0.726, 0.927)	0.002
CV death	1.8	1.8	0.979 (0.732,1.309)	0.885
Nonfatal MI	7.1	9.2	0.761 (0.663,0.873)	<0.001
Nonfatal stroke	0.8	0.8	0.979 (0.633,1.513)	0.922
STEMI Primary Composite Outcome Events	**(N= 1769) %**	**(N=1765) %**		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	0.793 (0.649, 0.968)	0.019
CV death	2.4	3.3	0.738 (0.497,1.094)	0.129
Nonfatal MI	6.7	8.8	0.746 (0.588,0.948)	0.016
Nonfatal stroke	1.2	1.1	1.097 (0.590,2.040)	0.770

In the All ACS population, analysis of each of the secondary endpoints showed a significant benefit (p<0.001) for prasugrel versus clopidogrel. These included definite or probable stent thrombosis at study end (0.9% vs 1.8%; HR 0.498; CI 0.364, 0.683); CV death, nonfatal MI, or urgent target vessel revascularisation through 30 days (5.9% vs 7.4%; HR 0.784; CI 0.688,0.894); all cause death, nonfatal MI, or nonfatal stroke through study end (10.2% vs 12.1%; HR 0.831; CI 0.751, 0.919); CV death, nonfatal MI, nonfatal stroke or rehospitalisation for cardiac ischaemic event through study end (11.7 % vs 13.8%; HR 0.838; CI 0.762, 0.921). Analysis of all cause death did not show any significant difference between prasugrel and clopidogrel in the All ACS population (2.76% vs 2.90%), in the UA/NSTEMI population (2.58% vs 2.41%), and in the STEMI population (3.28% vs 4.31%).

Prasugrel was associated with a 50% reduction in stent thrombosis through the 15 month follow-up period. The reduction in stent thrombosis with Efient was observed both early and beyond 30 days for both bare metal and drug eluting stents.

In an analysis of patients who survived an ischaemic event, prasugrel was associated with a reduction in the incidence of subsequent primary endpoint events (7.8% for prasugrel vs 11.9% for clopidogrel).

Although bleeding was increased with prasugrel, an analysis of the composite endpoint of death from any cause, nonfatal myocardial infarction, nonfatal stroke, and non-CABG-related TIMI major haemorrhage favoured Efient compared to clopidogrel (Hazard ratio, 0.87; 95% CI, 0.79 to 0.95; p=0.004). In TRITON, for every 1000 patients treated with Efient, there were 22 fewer patients with myocardial infarction, and 5 more with non–CABG-related TIMI major haemorrhages, compared with patients treated with clopidogrel.

5.2 Pharmacokinetic properties

Prasugrel is a prodrug and is rapidly metabolised *in vivo* to an active metabolite and inactive metabolites. The active metabolite's exposure (AUC) has moderate to low between-subject (27%) and within-subject (19%) variability. Prasugrel's pharmacokinetics are similar in healthy subjects, patients with stable atherosclerosis, and patients undergoing percutaneous coronary intervention.

Absorption
The absorption and metabolism of prasugrel are rapid, with peak plasma concentration (C_{max}) of the active metabolite occurring in approximately 30 minutes. The active metabolite's exposure (AUC) increases proportionally over the therapeutic dose range. In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and the time to reach C_{max} (T_{max}) was increased from 0.5 to 1.5 hours. Efient was administered without regard to food in TRITON. Therefore, Efient can be administered without regard to food; however, the administration of prasugrel loading dose in the fasted state may provide most rapid onset of action (see section 4.2).

Distribution
Active metabolite binding to human serum albumin (4% buffered solution) was 98%.

Metabolism
Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step of cytochrome P450 metabolism, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite is further metabolised to two inactive compounds by S-methylation or conjugation with cysteine.

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Efient, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.

Elimination
Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the faeces, as inactive metabolites. The active metabolite has an elimination half-life of about 7.4 hours (range 2 to 15 hours).

Special Populations:

Elderly: In a study of healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel or its inhibition of platelet aggregation. In the large phase 3 clinical trial, the mean estimated exposure (AUC) of the active metabolite was 19% higher in very elderly patients (≥75 years of age) compared to subjects <75 years of age. Prasugrel should be used with caution in patients ≥ 75 years of age due to the potential risk of bleeding in this population (see sections 4.2 and 4.4).

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderate impaired hepatic function (Child Pugh Class A and B). Pharmacokinetics of prasugrel and its inhibition of platelet aggregation were similar in subjects with mild to moderate hepatic impairment compared to healthy subjects. Pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic impairment have not been studied. Prasugrel must not be used in patients with severe hepatic impairment (see section 4. 3).

Renal impairment: No dosage adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (ESRD). Pharmacokinetics of prasugrel and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (GFR 30-<50 ml/min/1.73m^2) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also

similar in patients with ESRD who required haemodialysis compared to healthy subjects, although C_{max} and AUC of the active metabolite decreased 51% and 42%, respectively, in ESRD patients.

Body weight: The mean exposure (AUC) of the active metabolite of prasugrel is approximately 30 to 40% higher in healthy subjects and patients with a body weight of <60 kg compared to those weighing ≥60 kg. Prasugrel should be used with caution in patients with a body weight of <60 kg due to the potential risk of bleeding in this population (see section 4.4).

Ethnicity: In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects compared to that of Caucasians, predominantly related to higher exposure in Asian subjects <60 kg. There is no difference in exposure among Chinese, Japanese, and Korean subjects. Exposure in subjects of African and Hispanic descent is comparable to that of Caucasians. No dose adjustment is recommended based on ethnicity alone.

Gender: In healthy subjects and patients, the pharmacokinetics of prasugrel are similar in men and women.

Children and adolescents: Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a paediatric population (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Embryo-foetal developmental toxicology studies in rats and rabbits showed no evidence of malformations due to prasugrel. At a very high dose (>240 times the recommended daily human maintenance dose on a mg/m^2 basis) that caused effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight (relative to controls). In pre- and post-natal rat studies, maternal treatment had no effect on the behavioural or reproductive development of the offspring at doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m^2).

No compound-related tumours were observed in a 2-year rat study with prasugrel exposures ranging to greater than 75 times the recommended therapeutic exposures in humans (based on plasma exposures to the active and major circulating human metabolites). There was an increased incidence of tumours (hepatocellular adenomas) in mice exposed for 2 years to high doses (>75 times human exposure), but this was considered secondary to prasugrel-induced enzyme-induction. The rodent-specific association of liver tumours and drug-induced enzyme induction is well documented in the literature. The increase in liver tumours with prasugrel administration in mice is not considered a relevant human risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose
Mannitol (E421)
Croscarmellose sodium
Hypromellose (E464)
Magnesium stearate

Film-Coat:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide yellow (E172)
Talc

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 temperature storage conditions. Store in the original package to protect from air and moisture.

6.5 Nature and contents of container

Aluminium foil blisters in cartons of 14, 28, 30 (x1), 56, 84, 90 (x1) and 98 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

Efient 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg prasugrel (as hydrochloride).
Excipient: Each tablet contains 2.1 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Beige and double-arrow shaped tablets, debossed with "10 mg"on one side and "4759" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology

Adults
Efient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking Efient should also take ASA daily (75 mg to 325 mg).

In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless the discontinuation of Efient is clinically indicated (see sections 4.4 and 5.1).

Patients ≥ 75 years old
The use of Efient in patients ≥ 75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician (see section 4.4), treatment is deemed necessary in the patients age group ≥ 75 years, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients ≥ 75 years of age have greater sensitivity to bleeding and higher exposure to the active metabolite of prasugrel (see sections 4.4, 4.8, 5.1 and 5.2). The evidence for the 5 mg dose is based only on pharmacodynamic/pharmacokinetic analyses and no clinical data currently exist on the safety of this dose in the patients age group ≥ 75 years.

Patients weighing <60 kg
Efient should be given as a single 60 mg loading dose and then continued at a 5 mg once daily dose.

The 10 mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight <60 kg when given a 10 mg once daily dose compared with patients ≥60 kg. Efficacy and safety of the 5 mg dose have not been prospectively assessed (see sections 4.4, 4.8 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (see section 5.2). There is limited therapeutic experience in patients with renal impairment (see section 4.4).

Hepatic impairment
No dose adjustment is necessary in subjects with mild to moderate hepatic impairment (Child Pugh class A and B) (see section 5.2). There is limited therapeutic experience in patients with mild and moderate hepatic dysfunction (see section 4.4).

Children and adolescents
Efient is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Method of administration
For oral use. Efient may be administered with or without food. Administration of the 60 mg prasugrel loading dose in the fasted state may provide most rapid onset of action (see section 5.2). Do not crush or break the tablet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Active pathological bleeding.
History of stroke or transient ischaemic attack (TIA).
Severe hepatic impairment (Child Pugh class C).

4.4 Special warnings and precautions for use

Bleeding risk
In the phase 3 clinical trial key exclusion criteria included an increased risk of bleeding; anaemia; thrombocytopaenia; a history of pathological intracranial findings. Patients with acute coronary syndromes undergoing PCI treated with Efient and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Efient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleedings. This concern applies especially to patients:
- ≥75 years of age (see below).
- with a propensity to bleed (e.g. due to recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, or active peptic ulcer disease)
- with body weight <60 kg (see sections 4.2 and 4.8). In these patients the 10 mg maintenance dose is not recommended. A 5 mg maintenance dose should be used.
- with concomitant administration of medicinal products that may increase the risk of bleeding, including oral anticoagulants, clopidogrel, non-steroidal anti-inflammatory drugs (NSAIDs), and fibrinolytics.

For patients with active bleeding for whom reversal of the pharmacological effects of Efient is required, platelet transfusion may be appropriate.

The use of Efient in patients ≥75 years of age is generally not recommended and should only be undertaken with caution after a careful individual benefit/risk evaluation by the prescribing physician indicates that benefits in terms of prevention of ischaemic events outweigh the risk of serious bleedings. In the phase 3 clinical trial these patients were at greater risk of bleeding, including fatal

bleeding, compared to patients <75 years of age. If prescribed, a lower maintenance dose of 5 mg should be used; the 10 mg maintenance dose is not recommended (see sections 4.2 and 4.8).

Therapeutic experience with prasugrel is limited in patients with renal impairment (including ESRD) and in patients with moderate hepatic impairment. These patients may have an increased bleeding risk. Therefore, prasugrel should be used with caution in these patients.

Therapeutic experience with prasugrel is limited in Asian patients. Therefore, prasugrel should be used with caution in these patients.

Patients should be told that it might take longer than usual to stop bleeding when they take prasugrel (in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Surgery
Patients should be advised to inform physicians and dentists that they are taking prasugrel before any surgery is scheduled and before any new medicinal product is taken. If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, Efient should be discontinued at least 7 days prior to surgery. Increased frequency (3-fold) and severity of bleeding may occur in patients undergoing CABG surgery within 7 days of discontinuation of prasugrel (see 4.8). The benefits and risks of prasugrel should be carefully considered in patients in whom the coronary anatomy has not been defined and urgent CABG is a possibility.

Thrombotic Thrombocytopaenic Purpura (TTP)
TTP has been reported with the use of other thienopyridines. TTP is a serious condition and requires prompt treatment. Efient was not associated with TTP in clinical trials supporting registration.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Efient.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Concomitant administration of Efient with coumarin derivatives other than warfarin has not been studied. Because of the potential for increased risk of bleeding, warfarin (or other coumarin derivatives) and prasugrel should be co-administered with caution (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs): Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs (including COX-2 inhibitors) and Efient should be co-administered with caution (see section 4.4).

Efient can be concomitantly administered with medicinal products metabolised by cytochrome P450 enzymes (including statins), or medicinal products that are inducers or inhibitors of cytochrome P450 enzymes. Efient can also be concomitantly administered with ASA, heparin, digoxin, and medicinal products that elevate gastric pH, including proton pump inhibitors and H_2 blockers. Although not studied in specific interaction studies, Efient has been co-administered in the phase 3 clinical trial with low molecular weight heparin, bivalirudin, and GP IIb/IIIa inhibitors (no information available regarding the type of GP IIb/IIIa inhibitor used) without evidence of clinically significant adverse interactions.

Effects of other medicinal products on Efient:

Acetylsalicylic acid: Efient is to be administered concomitantly with acetylsalicylic acid (ASA). Although a pharmacodynamic interaction with ASA leading to an increased risk of bleeding is possible, the demonstration of the efficacy and safety of prasugrel comes from patients concomitantly treated with ASA.

Heparin: A single intravenous bolus dose of unfractionated heparin (100 U/kg) did not significantly alter the prasugrel-mediated inhibition of platelet aggregation. Likewise, prasugrel did not significantly alter the effect of heparin on measures of coagulation. Therefore, both medicinal products can be administered concomitantly. An increased risk of bleeding is possible when Efient is co-administered with heparin.

Statins: Atorvastatin (80 mg daily) did not alter the pharmacokinetics of prasugrel and its inhibition of platelet aggregation. Therefore, statins that are substrates of CYP3A are not anticipated to have an effect on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.

Medicinal products that elevate gastric pH: Daily co-administration of ranitidine (an H_2 blocker) or lansoprazole (a proton pump inhibitor) did not change the prasugrel active metabolite's AUC and T_{max}, but decreased the C_{max} by 14% and 29%, respectively. In the phase 3 clinical trial, Efient was administered without regard to co-administration of a proton pump inhibitor or H_2 blocker. Administration of the 60 mg prasugrel loading dose without concomitant use of proton pump inhibitors may provide most rapid onset of action.

Inhibitors of CYP3A: Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated inhibition of platelet aggregation or the prasugrel active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as azol antifungals, HIV protease inhibitors, clarithromycin, telithromycin, verapamil, diltiazem, indinavir, ciprofloxacin, and grapefruit juice are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.

Inducers of cytochromes P450: Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6, and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of prasugrel. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not anticipated to have significant effect on the pharmacokinetics of the active metabolite.

Effects of Efient on other medicinal products:

Digoxin: prasugrel has no clinically significant effect on the pharmacokinetics of digoxin.

Medicinal products metabolised by CYP2C9: prasugrel did not inhibit CYP2C9, as it did not affect the pharmacokinetics of S-warfarin. Because of the potential for increased risk of bleeding, warfarin and Efient should be co-administered with caution (see section 4.4).

Medicinal products metabolised by CYP2B6: prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%. This effect is likely to be of clinical concern only when prasugrel is co-administered with medicinal products for which CYP2B6 is the only metabolic pathway and have a narrow therapeutic window (e.g. cyclophosphamide, efavirenz).

4.6 Pregnancy and lactation

No clinical study has been conducted in pregnant or lactating women.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Because animal reproduction studies are not always predictive of a human response, Efient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

It is unknown whether prasugrel is excreted in human breast milk. Animal studies have shown excretion of prasugrel in breast milk. The use of prasugrel during breastfeeding is not recommended.

Prasugrel had no effect on fertility of male and female rats at oral doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m^2).

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Prasugrel is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one clopidogrel-controlled study (TRITON) in which 6741 patients were treated with prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5802 patients were treated for over 6 months, 4136 patients were treated for more than 1 year). The rate of study drug discontinuation due to adverse events was 7.2% for prasugrel and 6.3% for clopidogrel. Of these, bleeding was the most common adverse reaction for both drugs leading to study drug discontinuation (2.5% for prasugrel and 1.4% for clopidogrel).

Bleeding

Non-Coronary Artery Bypass Graft (CABG) related bleeding
In TRITON, the frequency of patients experiencing a non-CABG related bleeding event is shown in Table 1. The incidence of Non-CABG-related TIMI major bleeding, including life-threatening and fatal, as well as TIMI minor bleeding, was statistically significantly higher in subjects treated with prasugrel compared to clopidogrel in the UA/NSTEMI and All ACS populations. No significant difference was seen in the STEMI population. The most common site of spontaneous bleeding was the gastrointestinal tract (1.7% rate with prasugrel and 1.3% rate with clopidogrel); the most frequent site of provoked bleeding was the arterial puncture site (1.3% rate with prasugrel and 1.2% with clopidogrel).

Table 1: Incidence of Non-CABG related bleeding[a] (% Patients)

Event	All ACS		UA/NSTEMI		STEMI	
	Prasugrel[b] +ASA (N=6741)	**Clopidogrel[b] +ASA (N=6716)**	**Prasugrel[b] +ASA (N=5001)**	**Clopidogrel[b] +ASA (N=4980)**	**Prasugrel[b] +ASA (N=1740)**	**Clopidogrel[b] +ASA (N=1736)**
TIMI major bleeding[c]	2.2	1.7	2.2	1.6	2.2	2.0
Life-threatening[d]	1.3	0.8	1.3	0.8	1.2	1.0
Fatal	0.3	0.1	0.3	0.1	0.4	0.1
Symptomatic ICH[e]	0.3	0.3	0.3	0.3	0.2	0.2
Requiring inotropes	0.3	0.1	0.3	0.1	0.3	0.2
Requiring surgical intervention	0.3	0.3	0.3	0.3	0.1	0.2
Requiring transfusion (≥4 units)	0.7	0.5	0.6	0.3	0.8	0.8
TIMI minor bleeding[f]	2.4	1.9	2.3	1.6	2.7	2.6

a Centrally adjudicated events defined by the Thrombolysis in Myocardial Infarction (TIMI) Study Group criteria.
b Other standard therapies were used as appropriate.
c Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥5 g/dL.

d Life-threatening bleeding is a subset of TIMI major bleeding and includes the types indented below. Patients may be counted in more than one row.

e ICH=intracranial haemorrhage.

f Clinically overt bleeding associated with a fall in haemoglobin of ≥3 g/dL but <5 g/dL.

Patients ≥ 75 years old

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two age groups were as follows:

Age	Prasugrel	Clopidogrel
≥75 years (N=1785)	9.0% (1.0% fatal)	6.9% (0.1% fatal)
<75 years (N=11672)	3.8% (0.2% fatal)	2.9% (0.1% fatal)

Patients < 60 kg

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two weight groups were as follows:

Weight	Prasugrel	Clopidogrel
<60 kg (N=664)	10.1% (0% fatal)	6.5% (0.3% fatal)
≥60 kg (N=12672)	4.2% (0.3% fatal)	3.3% (0.1% fatal)

In patients ≥60 kg *and* age <75 years, non-CABG-related TIMI major or minor bleeding rates were 3.6% for prasugrel and 2.8% for clopidogrel; rates for fatal bleeding were 0.2% for prasugrel and 0.1% for clopidogrel.

CABG-related bleeding

In the phase 3 clinical trial, 437 patients underwent CABG during the course of the study. Of those patients, the rate of CABG-related TIMI major or minor bleeding was 14.1% for the prasugrel group and 4.5% in the clopidogrel group. The higher risk for bleeding events in subjects treated with prasugrel persisted up to 7 days from the most recent dose of study drug. For patients who received their thienopyridine within 3 days prior to CABG, the frequencies of TIMI major or minor bleeding were 26.7% (12 of 45 patients) in the prasugrel group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.3% (3 of 90 patients) in the clopidogrel group. Beyond 7 days after drug discontinuation, the observed rates of CABG-related bleeding were similar between treatment groups (see section 4.4).

Adverse Reactions

Table 2 summarises haemorrhagic and non-haemorrhagic adverse reactions in TRITON classified by frequency and system organ class. Frequencies are defined as follows:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100);
rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 2: Haemorrhagic and Non-haemorrhagic adverse reactions

System Organ Class	Common	Uncommon	Rare
Blood and Lymphatic System disorders	Anaemia		
Eye disorders		Eye haemorrhage	
Vascular Disorders	Haematoma		
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis	
Gastrointestinal disorders	Gastrointestinal haemorrhage	Retroperitoneal haemorrhage Rectal haemorrhage Haematochezia	

		Gingival bleeding	
Skin and subcutaneous tissue disorders	Rash Ecchymosis		
Renal and urinary disorders	Haematuria		
General disorders and administration site conditions	Vessel puncture site haematoma Puncture site haemorrhage		
Injury, poisoning and procedural complications	Contusion	Post-procedural haemorrhage	Subcutaneous haematoma

In patients with or without a history of TIA or stroke, the incidence of stroke in the phase 3 clinical trial was as follows (see section 4.4):

History of TIA or stroke	Prasugrel	Clopidogrel
Yes (N=518)	6.5% (2.3% ICH*)	1.2% (0% ICH*)
No (N=13090)	0.9% (0.2% ICH*)	1.0% (0.3% ICH*)

** ICH=intracranial haemorrhage.*

4.9 Overdose

Overdose of Efient may lead to prolonged bleeding time and subsequent bleeding complications. No data are available on the reversal of the pharmacological effect of prasugrel; however, if prompt correction of prolonged bleeding time is required, platelet transfusion and/or other blood products may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned. ATC code: Not yet assigned.

Pharmacodynamics
Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke.

Following a 60 mg loading dose of prasugrel, inhibition of ADP-induced platelet aggregation occurs at 15 minutes with 5 µM ADP and 30 minutes with 20 µM ADP. The maximum inhibition by prasugrel of ADP-induced platelet aggregation is 83% with 5 µM ADP and 79% with 20 µM ADP, in both cases with 89% of healthy subjects and patients with stable atherosclerosis achieving at least 50% inhibition of platelet aggregation by 1 hour. Prasugrel-mediated inhibition of platelet aggregation exhibits low between-subject (12%) and within-subject (9%) variability with both 5 µM and 20 µM ADP. Mean steady-state inhibition of platelet aggregation was 74% and 69% respectively for 5 µM ADP and 20 µM ADP, and was achieved following 3 to 5 days of administration of the 10 mg prasugrel maintenance dose preceded by a 60 mg loading dose. More than 98% of subjects had ≥20% inhibition of platelet aggregation during maintenance dosing.

Platelet aggregation gradually returned to baseline values after treatment in 7 to 9 days after administration of a single 60 mg loading dose of prasugrel and in 5 days following discontinuation of maintenance dosing at steady-state.

Clopidogrel: Following administration of 75 mg clopidogrel once daily for 10 days, 40 healthy subjects were switched to prasugrel 10 mg once daily with or without a loading dose of 60 mg. Similar or higher inhibition of platelet aggregation was observed with prasugrel. Switching directly to prasugrel 60 mg loading dose resulted in the most rapid onset of higher platelet inhibition. Following administration of a 900 mg loading dose of clopidogrel (with ASA), 56 subjects with ACS were treated for 14 days with either prasugrel 10 mg once daily or clopidogrel 150 mg once daily, and then switched to either clopidogrel 150 mg or prasugrel 10 mg for another 14 days. Higher inhibition of platelet aggregation was observed in patients switched to prasugrel 10 mg compared with those treated with clopidogrel 150 mg. No data are available on switching from a clopidogrel loading dose directly to a prasugrel loading dose.

Efficacy and Safety in Acute Coronary Syndrome (ACS)
The phase 3 TRITON study compared Efient (prasugrel) with clopidogrel, both co-administered with ASA and other standard therapy. TRITON was a 13,608 patient, multicentre international, randomised, double blind, parallel group study. Patients had ACS with moderate to high risk UA, NSTEMI, or STEMI and were managed with PCI.

Patients with UA/NSTEMI within 72 hours of symptoms or STEMI between 12 hours to 14 days of symptoms were randomised after knowledge of coronary anatomy. Patients with STEMI within 12 hours of symptoms and planned for primary PCI could be randomised without knowledge of coronary anatomy. For all patients, the loading dose could be administered anytime between randomisation and 1 hour after the patient left the catheterisation lab.

Patients randomised to receive prasugrel (60 mg loading dose followed by 10 mg once daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily) were treated for a median of 14.5 months (maximum of 15 months with a minimum of 6 months follow-up). Patients also received ASA (75 mg to 325 mg once daily). Use of any thienopyridine within 5 days before enrolment was an exclusion criterion. Other therapies, such as heparin and GPIIb/IIIa inhibitors, were administered at the discretion of the physician. Approximately 40% of patients (in each of the treatment groups) received GPIIb/IIIa inhibitors in support of PCI (no information available regarding the type of GP IIb/IIIa inhibitor used). Approximately 98% of patients (in each of the treatment groups) received antithrombins (heparin, low molecular weight heparin, bivalirudin, or other agent) directly in support of PCI.

The trial's primary outcome measure was the time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. Analysis of the composite endpoint in the All ACS population (combined UA/NSTEMI and STEMI cohorts) was contingent on showing statistical superiority of prasugrel versus clopidogrel in the UA/NSTEMI cohort ($p<0.05$).

All ACS population: Efient showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (see Table 3). The benefit of prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding (see sections 4.4 and 4.8). The patient population was 92% Caucasian, 26% female, and 39% ≥65 years of age. The benefits associated with prasugrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/low molecular weight heparin, bivalirudin, intravenous GPIIb/IIIa inhibitors, lipid-lowering medicinal products, beta-blockers, and angiotensin converting enzyme inhibitors. The efficacy of prasugrel was independent of the ASA dose (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet medicinal products and chronic NSAIDs was not allowed in TRITON. In the All ACS population, prasugrel was associated with a lower incidence of CV death, non-fatal MI, or non-fatal stroke compared to clopidogrel, regardless of baseline characteristics such as age, sex, body weight, geographical region, use of GPIIb/IIIa inhibitors, and stent type. The benefit was primarily due to a significant decrease in non-fatal MI (see table 3). Subjects with diabetes had significant reductions in the primary and all secondary composite endpoints.

The observed benefit of prasugrel in patients ≥ 75 years was less than that observed in patients <75 years. Patients ≥ 75 years were at increased risk of bleeding, including fatal (see sections 4.2, 4.4, and 4.8). Patients ≥ 75 years in whom the benefit with prasugrel was more evident included those with diabetes, STEMI, higher risk of stent thrombosis, or recurrent events.

Patients with a history of TIA or a history of ischaemic stroke more than 3 months prior to prasugrel therapy had no reduction in the primary composite endpoint.

Table 3: Patients with Outcome Events in TRITON Primary Analysis

Outcome Events	Prasugrel + ASA	Clopidogrel +ASA	Hazard Ratio (HR) (95% CI)	p-value
All ACS	**(N=6813) %**	**(N=6795) %**		
Primary Composite Outcome Events Cardiovascular (CV) death, non fatal MI, or non fatal stroke	9.4	11.5	0.812 (0.732, 0.902)	<0.001
Primary Individual Outcome Events				
CV death	2.0	2.2	0.886 (0.701, 1.118)	0.307
Nonfatal MI	7.0	9.1	0.757 (0.672, 0.853)	<0.001
Nonfatal stroke	0.9	0.9	1.016 (0.712, 1.451)	0.930
UA/NSTEMI Primary Composite Outcome Events	**(N= 5044) %**	**(N=5030) %**		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	0.820 (0.726, 0.927)	0.002
CV death	1.8	1.8	0.979 (0.732,1.309)	0.885
Nonfatal MI	7.1	9.2	0.761 (0.663,0.873)	<0.001
Nonfatal stroke	0.8	0.8	0.979 (0.633,1.513)	0.922
STEMI Primary Composite Outcome Events	**(N= 1769) %**	**(N=1765) %**		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	0.793 (0.649, 0.968)	0.019
CV death	2.4	3.3	0.738 (0.497,1.094)	0.129
Nonfatal MI	6.7	8.8	0.746 (0.588,0.948)	0.016
Nonfatal stroke	1.2	1.1	1.097 (0.590,2.040)	0.770

In the All ACS population, analysis of each of the secondary endpoints showed a significant benefit (p<0.001) for prasugrel versus clopidogrel. These included definite or probable stent thrombosis at study end (0.9% vs 1.8%; HR 0.498; CI 0.364, 0.683); CV death, nonfatal MI, or urgent target vessel revascularisation through 30 days (5.9% vs 7.4%; HR 0.784; CI 0.688,0.894); all cause death, nonfatal MI, or nonfatal stroke through study end (10.2% vs 12.1%; HR 0.831; CI 0.751, 0.919); CV death, nonfatal MI, nonfatal stroke or rehospitalisation for cardiac ischaemic event through study end (11.7 % vs 13.8%; HR 0.838; CI 0.762, 0.921). Analysis of all cause death did not show any significant difference between prasugrel and clopidogrel in the All ACS population (2.76% vs 2.90%), in the UA/NSTEMI population (2.58% vs 2.41%), and in the STEMI population (3.28% vs 4.31%).

Prasugrel was associated with a 50% reduction in stent thrombosis through the 15 month follow-up period. The reduction in stent thrombosis with Efient was observed both early and beyond 30 days for both bare metal and drug eluting stents.

In an analysis of patients who survived an ischaemic event, prasugrel was associated with a reduction in the incidence of subsequent primary endpoint events (7.8% for prasugrel vs 11.9% for clopidogrel).

Although bleeding was increased with prasugrel, an analysis of the composite endpoint of death from any cause, nonfatal myocardial infarction, nonfatal stroke, and non-CABG-related TIMI major haemorrhage favoured Efient compared to clopidogrel (Hazard ratio, 0.87; 95% CI, 0.79 to 0.95; p=0.004). In TRITON, for every 1000 patients treated with Efient, there were 22 fewer patients with myocardial infarction, and 5 more with non–CABG-related TIMI major haemorrhages, compared with patients treated with clopidogrel.

5.2 Pharmacokinetic properties

Prasugrel is a prodrug and is rapidly metabolised *in vivo* to an active metabolite and inactive metabolites. The active metabolite's exposure (AUC) has moderate to low between-subject (27%) and within-subject (19%) variability. Prasugrel's pharmacokinetics are similar in healthy subjects, patients with stable atherosclerosis, and patients undergoing percutaneous coronary intervention.

Absorption
The absorption and metabolism of prasugrel are rapid, with peak plasma concentration (C_{max}) of the active metabolite occurring in approximately 30 minutes. The active metabolite's exposure (AUC) increases proportionally over the therapeutic dose range. In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and the time to reach C_{max} (T_{max}) was increased from 0.5 to 1.5 hours. Efient was administered without regard to food in TRITON. Therefore, Efient can be administered without regard to food; however, the administration of prasugrel loading dose in the fasted state may provide most rapid onset of action (see section 4.2).

Distribution
Active metabolite binding to human serum albumin (4% buffered solution) was 98%.

Metabolism
Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step of cytochrome P450 metabolism, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite is further metabolised to two inactive compounds by S-methylation or conjugation with cysteine.

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Efient, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.

Elimination
Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the faeces, as inactive metabolites. The active metabolite has an elimination half-life of about 7.4 hours (range 2 to 15 hours).

Special Populations:

Elderly: In a study of healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel or its inhibition of platelet aggregation. In the large phase 3 clinical trial, the mean estimated exposure (AUC) of the active metabolite was 19% higher in very elderly patients (≥75 years of age) compared to subjects <75 years of age. Prasugrel should be used with caution in patients ≥ 75 years of age due to the potential risk of bleeding in this population (see sections 4.2 and 4.4).

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderate impaired hepatic function (Child Pugh Class A and B). Pharmacokinetics of prasugrel and its inhibition of platelet aggregation were similar in subjects with mild to moderate hepatic impairment compared to healthy subjects. Pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic impairment have not been studied. Prasugrel must not be used in patients with severe hepatic impairment (see section 4. 3).

Renal impairment: No dosage adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (ESRD). Pharmacokinetics of prasugrel and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (GFR 30-<50 ml/min/1.73m^2) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also

similar in patients with ESRD who required haemodialysis compared to healthy subjects, although C_{max} and AUC of the active metabolite decreased 51% and 42%, respectively, in ESRD patients.

Body weight: The mean exposure (AUC) of the active metabolite of prasugrel is approximately 30 to 40% higher in healthy subjects and patients with a body weight of <60 kg compared to those weighing ≥60 kg. Prasugrel should be used with caution in patients with a body weight of <60 kg due to the potential risk of bleeding in this population (see section 4.4).

Ethnicity: In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects compared to that of Caucasians, predominantly related to higher exposure in Asian subjects <60 kg. There is no difference in exposure among Chinese, Japanese, and Korean subjects. Exposure in subjects of African and Hispanic descent is comparable to that of Caucasians. No dose adjustment is recommended based on ethnicity alone.

Gender: In healthy subjects and patients, the pharmacokinetics of prasugrel are similar in men and women.

Children and adolescents: Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a paediatric population (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Embryo-foetal developmental toxicology studies in rats and rabbits showed no evidence of malformations due to prasugrel. At a very high dose (>240 times the recommended daily human maintenance dose on a mg/m^2 basis) that caused effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight (relative to controls). In pre- and post-natal rat studies, maternal treatment had no effect on the behavioural or reproductive development of the offspring at doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m^2).

No compound-related tumours were observed in a 2-year rat study with prasugrel exposures ranging to greater than 75 times the recommended therapeutic exposures in humans (based on plasma exposures to the active and major circulating human metabolites). There was an increased incidence of tumours (hepatocellular adenomas) in mice exposed for 2 years to high doses (>75 times human exposure), but this was considered secondary to prasugrel-induced enzyme-induction. The rodent-specific association of liver tumours and drug-induced enzyme induction is well documented in the literature. The increase in liver tumours with prasugrel administration in mice is not considered a relevant human risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose
Mannitol (E421)
Croscarmellose sodium
Hypromellose (E464)
Magnesium stearate

Film-Coat:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide red (E172)
Iron oxide yellow (E172)
Talc

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 temperature storage conditions. Store in the original package to protect from air and moisture.

6.5 Nature and contents of container

Aluminium foil blisters in cartons of 14, 28, 30 (x1), 56, 84, 90 (x1) and 98 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

ANNEX II

A. MANUFACTURING 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 responsible for batch release

Lilly S.A.
Avda de la Industria 30
E-28108 Alcobendas (Madrid)
Spain

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

The MAH should provide educational material to all physicians who may be involved in treating patients with prasugrel. The format and means of dissemination, of this material should be discussed with the appropriate learned societies. The results of the discussion, and where appropriate the material, should be agreed with the national competent authority and be available prior to launch in each member state.

The educational material should include:

- A copy of the SPC
- Emphasis that:
    - Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg
    - Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.
    - If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5mg should be prescribed.
    - Patients weighing < 60 kg should have a reduced maintenance dose of 5mg
    - The evidence for a 5mg dose is based only on PK/PD analyses and no clinical data currently exist on the safety of this dose in the at risk sub groups.

• OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version v2.1 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 Revision 1.4 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

CARTON OF 5mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Efient 5 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg prasugrel (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablet
56 film-coated tablets
84 film-coated tablets
90x1 film-coated tablet
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

Store in the original package to protect from air and moisture.

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

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX 14 film-coated tablets
EU/X/XX/XXX/XXX 28 film-coated tablets
EU/X/XX/XXX/XXX 30x1 film-coated tablet
EU/X/XX/XXX/XXX 56 film-coated tablets
EU/X/XX/XXX/XXX 84 film-coated tablets
EU/X/XX/XXX/XXX 90x1 film-coated tablet
EU/X/XX/XXX/XXX 98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Efient 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 5 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Efient 5 mg film-coated tablets
prasugrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

<MON, TUE, WED, THU, FRI, SAT, SUN, >

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 10 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Efient 10 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg prasugrel (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablet
56 film-coated tablets
84 film-coated tablets
90x1 film-coated tablet
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral 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

Store in the original package to protect from air and moisture.

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

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX 14 film-coated tablets
EU/X/XX/XXX/XXX 28 film-coated tablets
EU/X/XX/XXX/XXX 30x1 film-coated tablet
EU/X/XX/XXX/XXX 56 film-coated tablets
EU/X/XX/XXX/XXX 84 film-coated tablets
EU/X/XX/XXX/XXX 90x1 film-coated tablet
EU/X/XX/XXX/XXX 98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

16. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Efient 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 10 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Efient 10 mg film-coated tablets
prasugrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot:

5. OTHER

<MON, TUE, WED, THU, FRI, SAT, SUN, >

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Efient 10 mg film-coated tablets
Efient 5 mg film-coated tablets
Prasugrel

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

In this leaflet:

1. WHAT EFIENT IS AND WHAT IT IS USED FOR

Efient, belongs to a group of medicines called anti-platelet agents. Platelets are very small cell particles that circulate in the blood. When a blood vessel is damaged, for example if it is cut, platelets clump together to help form a blood clot (thrombus). Therefore, platelets are essential to help stop bleeding. If clots form within a hardened blood vessel such as an artery they can be very dangerous as they can cut off the blood supply, causing a heart attack (myocardial infarction), stroke or death. Clots in arteries supplying blood to the heart may also reduce the blood supply, causing unstable angina (a severe chest pain).

Efient inhibits the clumping of platelets and so reduces the chance of a blood clot forming.

You have been prescribed Efient because you have already had a heart attack or unstable angina and you have been treated with a procedure to open blocked arteries in the heart. You may also have had one or more stents placed to keep open a blocked or narrowed artery supplying blood to the heart. Efient reduces the chances of you having a further heart attack or stroke or of dying from one of these atherothrombotic events. Your doctor will also give you acetylsalicylic acid (e.g. aspirin), another anti-platelet agent.

2. BEFORE YOU TAKE EFIENT

Do not take Efient
- If you are allergic (hypersensitive) to prasugrel or any of the other ingredients of Efient. An allergic reaction may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your doctor.
- If you have a medical condition that is currently causing bleeding, such as bleeding from your stomach or intestines.
- If you have ever had a stroke or a transient ischaemic attack (TIA).
- If you have severe liver disease.

Take special care with Efient
You should tell your doctor before taking Efient if any of the situations mentioned below apply to you:

- If you have an increased risk of bleeding such as:
    - age of 75 years or older. Your doctor should prescribe a daily dose of 5 mg as there is a greater risk of bleeding in patients older than 75 years
    - a recent serious injury
    - recent surgery (including some dental procedures)
    - recent or recurrent bleeding from the stomach or intestines (e.g. a stomach ulcer, colon polyps)
    - body weight of less than 60 kg. Your doctor should prescribe a daily dose of 5 mg of Efient if you weigh less than 60 kg
    - renal (kidney) disease or moderate liver problems
    - taking certain types of medicines (see 'Taking other medicines' below)
    - planned surgery (including some dental procedures) in the next seven days. Your doctor may wish you to stop taking Efient temporarily due to the increased risk of bleeding
- If you are Asian- there is limited experience of Efient use in Asians
- Although no cases have been seen with Efient, with certain other antiplatelet agents a very rare condition called Thrombotic Thrombocytopenic Purpura (TTP) can occur. TTP is associated with fever, tiny round pin-point purplish-red bruises, small to medium-sized bruises, confusion, headaches and a decrease in the number of platelets. If you notice tiny round pin-point purplish-red bruises, please contact your doctor immediately.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, dietary supplements and herbal remedies. It is particularly important to tell your doctor if you are being treated with clopidogrel (an anti-platelet agent), warfarin (an anti-coagulant), or "non steroidal anti inflammatory drugs" for pain and fever (such as ibuprofen, naproxen, etoricoxib). If given together with Efient these medicines may increase the risk of bleeding

Only take other medicines while you are on Efient if your doctor tells you that you can.

Taking Efient with food and drink
Efient may be taken with or without food.

Pregnancy and breast-feeding
Tell your doctor if you become pregnant or are trying to become pregnant while you are taking Efient. You should use Efient only after discussing with your doctor the potential benefits and any potential risks to your unborn child.
If you are breast-feeding, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects of Efient on the ability to drive and use machines have been performed. Efient is unlikely to affect your ability to drive or use machines.

Important information about some of the ingredients of Efient
Efient contains lactose. If you have been told by a doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE EFIENT

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

Your doctor will tell you how many Efient tablets to take. The usual dose of Efient is 10 mg per day. You will start the treatment with a single dose of 60 mg.
If you weigh less than 60 kg or are more than 75 years of age, the dose is 5 mg Efient per day.
Your doctor will also tell you to take acetylsalicylic acid- (s)he will tell you the exact dose to take (usually between 75 mg and 325 mg daily).

You may take Efient with or without food. Take your dose at around the same time every day. Do not break or crush the tablet.

It is important that you tell your doctor, dentist and pharmacist, that you are taking Efient.
Efient should not be used in children and adolescents below 18 years of age.

If you take more Efient than you should
Contact your doctor or hospital straight away, as you may be at risk of excessive bleeding. You should show the doctor your pack of Efient.

If you forget to take Efient
If you miss your scheduled daily dose, take Efient when you remember. If you forget your dose for an entire day, just resume taking Efient at its usual dose the next day. Do not take two doses in one day. For the 14, 28, 56 84 and 98 tablet pack sizes, you can check the day on which you last took a tablet of Efient by referring to the calendar printed on the blister.

If you stop taking Efient
Do not stop taking Efient without consulting your doctor. It is especially important to discuss with your doctor before stopping Efient because both the risks and the benefits are based on regular use.

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

4. POSSIBLE SIDE EFFECTS

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

- Frequencies of the observed side effects are defined as:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

Contact your doctor **immediately** if you notice any of the following:

- Sudden numbness or weakness of the arm, leg or face, especially if only on one side of the body
- sudden confusion, difficulty speaking or understanding others
- sudden difficulty in walking or loss of balance or co-ordination
- sudden dizziness or sudden severe headache with no known cause

All of the above may be signs of a stroke. Stroke is an uncommon side effect of Efient in patients who have never had a stroke or transient ischaemic attack (TIA).

Tell your doctor **promptly** if you notice any of the following:

- Blood in your urine
- Bleeding from your rectum, blood in your stools or black stools
- Uncontrollable bleeding, for example from a cut

All of the above may be signs of bleeding, the most common side effect with Efient. Although uncommon, severe bleeding can be life-threatening.

Side effects seen in clinical trials with Efient include:

Common side effects
Bleeding in the stomach or bowels
Bleeding from a needle puncture site
Nose bleeds
Skin rash
Small red bruises on the skin (ecchymoses)
Blood in urine
Haematoma (bleeding under the skin at the site of an injection, or into a muscle, causing swelling)
Low haemoglobin or red blood cell count (anaemia)
Bruising

Uncommon side effects
Spontaneous bleeding from the eye, rectum, gums or in the abdomen around the internal organs
Bleeding after surgery
Coughing up blood
Blood in stools

Rare side effects
Subcutaneous haematoma (bleeding under the skin causing a swelling)

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

5. HOW TO STORE EFIENT

Keep out of the reach and sight of children.

Do not use Efient after the expiry date, which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Store in the original package to protect from air and moisture.

6. FURTHER INFORMATION

What Efient contains
- The active substance is prasugrel.
  Efient 10 mg: Each tablet contains 10 mg of prasugrel (as hydrochloride).
  Efient 5 mg: Each tablet contains 5 mg of prasugrel (as hydrochloride).

- The other ingredients are microcrystalline cellulose, mannitol (E421), croscarmellose sodium, hypromellose (E464) magnesium stearate, lactose monohydrate, titanium dioxide (E171), triacetin (E1518), iron oxide red (10 mg tablets only) (E172), iron oxide yellow (E172) and talc.

What Efient looks like and contents of the pack
Efient 10 mg :The tablets are beige and double-arrow shaped, with "10 mg" debossed on one side and "4759" on the other.

Efient 5 mg: The tablets are yellow and double-arrow-shaped, with "5 mg" debossed on one side and "4760" on the other.

Efient is available in packs of 14, 28, 30, 56, 84, 90 and 98 tablets.
Not all pack sizes may be marketed.

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This leaflet was last approved in

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

資料3－3　アーテメター/ルメファントリン（artemether/lumefantrine）

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Coartem (artemether/lumefantrine) Tablets
Initial U.S. Approval: 2009

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

- Coartem (artemether and lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above (1)
- Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported (1)
- Coartem Tablets should not be used to treat severe malaria or to prevent malaria (1)

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

- Coartem Tablets should be taken with food. (2.1, 5.2)
- Tablets may be crushed and mixed with one to two teaspoons of water immediately prior to administration to patients, including children (2.1)
- Coartem Tablets should be administered over 3-days for a total of 6 doses: an initial dose, second dose after 8 hours and then twice daily (morning and evening) for the following two days (2.2, 2.3)
- The adult dosage for patients with bodyweight of 35 kg and above is 4 tablets per dose for a total of 6 doses (2.2)
- The number of tablets per dose for children is determined by bodyweight, as shown in the chart below (2.3):

Tablets per dose by bodyweight; total of 6 doses over 3 days

5 to < 15 kg	1 tablet
15 to < 25 kg	2 tablets
25 to < 35 kg	3 tablets
35 kg and over	4 tablets

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

Tablets are scored and contain 20 mg artemether and 120 mg lumefantrine. (3)

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

- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients (4.1)

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

- Avoid use in patients with known QT prolongation, those with hypokalemia or hypomagnesemia, and those taking other drugs that prolong the QT interval (5.1, 12.5)
- Halofantrine and Coartem Tablets should not be administered within one month of each other due to potential additive effects on the QT interval. (5.1, 5.2, 12.3)
- Antimalarials should not be given concomitantly, unless there is no other treatment option, due to limited safety data. (5.2)
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Coartem Tablets; (5.1, 5.2, 7.6, 12.3)
- Substrates, inhibitors, or inducers of CYP3A4, including antiretroviral medications, should be used cautiously with Coartem Tablets, due to a potential loss of efficacy of the concomitant drug or additive QT prolongation (5.3, 7.1, 7.3)

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

The most common adverse reactions in adults (> 30%) are headache, anorexia, dizziness, asthenia, arthralgia and myalgia. The most common adverse reactions in children (> 12%) are pyrexia, cough, vomiting, anorexia and headache. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- CYP3A4 Inhibitors: Use cautiously due to potential for QT prolongation (5.3, 7.1)
- Mefloquine: If used immediately before treatment, monitor for decreased efficacy of Coartem Tablets and encourage food consumption (2.1, 7.2)
- Hormonal Contraceptives: Effectiveness may be reduced; use an additional method of birth control (5.3, 7.3)
- Anti-Retrovirals: Use cautiously due to potential for QT prolongation, loss of anti-viral efficacy, or loss of antimalarial efficacy of Coartem Tablets (5.3, 7.3)
- CYP2D6 Substrates: Monitor for adverse reactions and potential QT prolongation (5.1, 5.4, 7.4)

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

- Pregnancy: Based on animal data, may increase fetal loss. (8.1)
- Nursing Mothers: Use caution when administering to a nursing woman (8.3)
- Pediatric Use: Studied in children 2 months of age and older with a bodyweight of 5 kg and greater. (8.4)
- Geriatric Use: Not studied in geriatric patients (8.5)

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

Revised: 4/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Coartem (artemether/lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above. Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported [see *Clinical Studies (14.1)*].

Limitations of Use:

- Coartem Tablets are not approved for patients with severe or complicated *P. falciparum* malaria.
- Coartem Tablets are not approved for the prevention of malaria.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Coartem Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

For patients who are unable to swallow the tablets such as infants and children, Coartem Tablets may be crushed and mixed with a small amount of water (one to two teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

2.2 Dosage in Adult Patients (>16 years of age)

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

For patients weighing less than 35 kg, see Dosage in Pediatric Patients (2.3).

2.3 Dosage in Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended as below:

5 kg to less than 15 kg bodyweight: One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) for the following two days (total course of 6 tablets).

15 kg to less than 25 kg bodyweight: Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) for the following two days (total course of 12 tablets).

25 kg to less than 35 kg bodyweight: Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) for the following two days (total course of 18 tablets).

35 kg bodyweight and above: Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

2.4 Dosage in Patients with Hepatic or Renal Impairment

No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

In clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in clinical studies. No specific dose adjustments are needed for patients with mild to moderate renal impairment.

Caution should be exercised when administering Coartem Tablets in patients with severe hepatic or renal impairment [see *Warnings and Precautions (5.6)*].

3 DOSAGE FORMS AND STRENGTHS

Coartem Tablets contain 20 mg of artemether and 120 mg of lumefantrine. Coartem Tablets are supplied as yellow, round, flat tablets with beveled edges and scored on one side. Tablets are imprinted with N/C on one side and CG on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients of Coartem Tablets [see *Adverse Reactions (6.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Prolongation of the QT Interval

Some antimalarials (e.g., halofantrine, quinine, quinidine) including Coartem Tablets have been associated with prolongation of the QT interval on the electrocardiogram.

Coartem Tablets should be avoided in patients:

- with congenital prolongation of the QT interval (e.g., long QT syndrome) or any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- with a family history of congenital prolongation of the QT interval or sudden death.
- with known disturbances of electrolyte balance, e.g., hypokalemia or hypomagnesemia.
- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistaminics (terfenadine, astemizole), or cisapride [see *Clinical Pharmacology (12.5)*].
- receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.4), Drug Interactions (7.4)* and *Clinical Pharmacology (12.3)*].

5.2 Use of QT Prolonging Drugs and Other Antimalarials

Halofantrine and Coartem Tablets should not be administered within one month of each other due to the long elimination half-life of lumefantrine (3-6 days) and potential additive effects on the QT interval [see *Warnings and Precautions (5.1),* and *Clinical Pharmacology (12.3)*].

Antimalarials should not be given concomitantly with Coartem Tablets, unless there is no other treatment option, due to limited safety data.

Drugs that prolong the QT interval, including antimalarials such as quinine and quinidine, should be used cautiously following Coartem Tablets, due to the long elimination half-life of lumefantrine (3-6 days) and the potential for additive effects on the QT interval. [see *Warnings and Precautions (5.1), Drug Interactions (7.5),* and *Clinical Pharmacology (12.3)*].

If mefloquine is administered immediately prior to Coartem Tablets there may be a decreased exposure to lumefantrine, possibly due to a mefloquine-induced decrease in bile production. Therefore, patients should be monitored for decreased efficacy and food consumption should be encouraged while taking Coartem Tablets [see *Dosage and Administration (2.1), Drug Interactions (7.2),* and *Clinical Pharmacology (12.3)*].

5.3 Drug Interactions with CYP3A4

When Coartem Tablets are co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Coartem Tablets are co-administered with an inhibitor of CYP3A4, including grapefruit juice it may result in increased concentrations of artemether and/or lumefantrine and

potentiate QT prolongation. When Coartem Tablets are co-administered with inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy [see *Drug Interactions (7.1)*].

Drugs that have a mixed effect on CYP3A4, especially Anti-Retroviral drugs, and those that have an effect on the QT interval should be used with caution in patients taking Coartem Tablets [see *Drug Interactions (7.3)*].

Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control [see *Drug Interactions (7.3)*].

5.4 Drug Interactions with CYP2D6

Administration of Coartem Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1), Drug Interactions (7.4)* and *Clinical Pharmacology (12.3)*].

5.5 Recrudescence

Food enhances absorption of artemether and lumefantrine following administration of Coartem Tablets. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater [see *Dosage and Administration (2.1)*].

In the event of recrudescent *P. falciparum* infection after treatment with Coartem Tablets, patients should be treated with a different antimalarial drug.

5.6 Hepatic and Renal Impairment

Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment [see *Dosage and Administration (2.4)*].

5.7 *Plasmodium vivax* Infection

Coartem Tablets have been shown in limited data (43 patients) to be effective in treating the erythrocytic stage of *P. vivax* infection. However, relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoites forms that may remain dormant in the liver.

6 ADVERSE REACTIONS

6.1 Serious Adverse Reactions

The following serious and otherwise important adverse reactions are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions [see *Contraindications (4.1)* and *Postmarketing Experience (6.3)*].

6.2 Clinical Studies 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 rate observed in practice.

The data described below reflect exposure to a 6-dose regimen of Coartem Tablets in 1,979 patients including 647 adults (older than 16 years) and 1,332 children (16 years and younger). For the 6-dose regimen, Coartem Tablets was studied in active-controlled (366 patients) and non-controlled, open-label trials (1,613 patients). The 6-dose Coartem Tablets population was patients with malaria between ages 2 months and 71 years: 67% (1,332) were 16 years and younger and 33% (647) were older than 16 years. Males represented 73% and 53% of the adult and pediatric populations, respectively. The majority of adult patients were enrolled in studies in Thailand, while the majority of pediatric patients were enrolled in Africa.

Tables 1 and 2 show the most frequently reported adverse reactions (≥3%) in adults and children respectively who received the 6-dose regimen of Coartem Tablets. Adverse reactions collected in clinical trials included signs and symptoms at baseline but only treatment emergent adverse events, defined as events that appeared or worsened after the start of treatment, are presented below. In adults, the most frequently reported adverse reactions were headache, anorexia, dizziness, and asthenia. In children, the adverse reactions were pyrexia, cough, vomiting, anorexia, and headache. Most adverse reactions were mild, did not lead to discontinuation of study medication, and resolved.

In limited comparative studies, the adverse reaction profile of Coartem Tablets appeared similar to that of another antimalarial regimen.

Discontinuation of Coartem Tablets due to adverse drug reactions occurred in 1.1% of patients treated with the 6-dose regimen overall: 0.2% (1/647) in adults and 1.6% (21/1,332) in children.

Table 1: Adverse Reactions Occurring in 3% or More of Adult Patients Treated in Clinical Trials with the 6-dose Regimen of Coartem Tablets

System Organ Class	Preferred term	Adults* N=647 (%)
Nervous system disorders	Headache	360 (56)
	Dizziness	253 (39)
Metabolism and nutrition disorders	Anorexia	260 (40)
General disorders and administration site conditions	Asthenia	243 (38)
	Pyrexia	159 (25)
	Chills	147 (23)
	Fatigue	111 (17)

System Organ Class	Preferred term	Adults* N=647 (%)
	Malaise	20 (3)
Musculoskeletal and connective tissue disorders	Arthralgia	219 (34)
	Myalgia	206 (32)
Gastrointestinal disorders	Nausea	169 (26)
	Vomiting	113 (17)
	Abdominal pain	112 (17)
	Diarrhea	46 (7)
Psychiatric disorders	Sleep disorder	144 (22)
	Insomnia	32 (5)
Cardiac disorders	Palpitations	115 (18)
Hepatobiliary disorders	Hepatomegaly	59 (9)
Blood and lymphatic system disorders	Splenomegaly	57 (9)
	Anemia	23 (4)
Respiratory, thoracic and mediastinal disorders	Cough	37 (6)
Skin and subcutaneous tissue disorders	Pruritus	24 (4)
	Rash	21 (3)
Ear and labyrinth disorders	Vertigo	21 (3)
Infections and infestations	Malaria	18 (3)
	Nasopharyngitis	17 (3)

* Adult patients defined as >16 years of age

Table 2: Adverse Reactions Occurring in 3% or More of Pediatric Patients Treated in Clinical Trials with the 6-dose Regimen of Coartem Tablets

System organ class	Preferred Term	Children* N=1,332 (%)
General disorders and administration site conditions	Pyrexia	381 (29)
	Chills	72 (5)
	Asthenia	63 (5)
	Fatigue	46 (3)
Respiratory, thoracic and mediastinal disorders	Cough	302 (23)
Gastrointestinal disorders	Vomiting	242 (18)
	Abdominal pain	112 (8)
	Diarrhea	100 (8)

System organ class	Preferred Term	Children* N=1,332 (%)
	Nausea	61 (5)
Infections and infestations	Plasmodium falciparum infection	224 (17)
	Rhinitis	51 (4)
Metabolism and nutrition disorders	Anorexia	175 (13)
Nervous system disorders	Headache	168 (13)
	Dizziness	56 (4)
Blood and lymphatic system disorders	Splenomegaly	124 (9)
	Anemia	115 (9)
Hepatobiliary disorders	Hepatomegaly	75 (6)
Investigations	Aspartate aminotransferase increased	51 (4)
Musculoskeletal and connective tissue disorders	Arthralgia	39 (3)
	Myalgia	39 (3)
Skin and subcutaneous tissue disorders	Rash	38 (3)

* Children defined as patients ≤ 16 years of age

Clinically significant adverse reactions reported in adults and/or children treated with the 6-dose regimen of Coartem Tablets which occurred in clinical studies at < 3% regardless of causality are listed below:

Blood and lymphatic system disorders: eosinophilia

Ear and labyrinth disorders: tinnitus

Eye disorders: conjunctivitis

Gastrointestinal disorders: constipation, dyspepsia, dysphagia, peptic ulcer

General disorders: gait disturbance

Infections and infestations: abscess, acrodermatitis, bronchitis, ear infection, gastroenteritis, helminthic infection, hookworm infection, impetigo, influenza, lower respiratory tract infection, malaria, nasopharyngitis, oral herpes, pneumonia, respiratory tract infection, subcutaneous abscess, upper respiratory tract infection, urinary tract infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased hematocrit decreased, lymphocyte morphology abnormal, platelet count decreased, platelet count increased, white blood cell count decreased, white blood cell count increased

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: back pain

Nervous system disorders: ataxia, clonus, fine motor delay, hyperreflexia, hypoaesthesia, nystagmus, tremor

Psychiatric disorders: agitation, mood swings

Renal and urinary disorders: hematuria, proteinuria

Respiratory, thoracic and mediastinal disorders: asthma, pharyngo-laryngeal pain

Skin and subcutaneous tissue disorders: urticaria

6.3 Postmarketing Experience

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

- Hypersensitivity including urticaria and angioedema. Serious skin reactions (bullous eruption) have been rarely reported.

7 DRUG INTERACTIONS

7.1 Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Coartem Tablets resulted in a moderate increase in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether), and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Coartem Tablets is necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Coartem Tablets should be used cautiously with drugs that inhibit CYP3A4 [see *Warnings and Precautions (5.1, 5.3)*].

7.2 Prior Use of Mefloquine

Administration of three doses of mefloquine followed 12 hours later by a 6-dose regimen of Coartem Tablets in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio. However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of Coartem Tablets [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

7.3 CYP3A4 Metabolism: Hormonal Contraceptives and Anti-Retroviral Drugs

Artemether induces CYP3A4 and both artemether and lumefantrine are metabolized primarily by CYP3A4.

Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should

be advised to use an additional non-hormonal method of birth control [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

Anti-Retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. No formal drug-drug interaction studies between Coartem Tablets and ARTs have been performed. However, Coartem Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation or a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Coartem Tablets [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

7.4 CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 *in vitro*. Administration of Coartem Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1, 5.4)* and *Clinical Pharmacology (12.3)*].

7.5 Sequential Use of Quinine

A single dose of intravenous quinine (10 mg/kg bodyweight) concurrent with the final dose of a 6-dose regimen of Coartem Tablets demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with Coartem Tablets due to the long elimination half life of lumefantrine and the potential for additive QT effects. [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Coartem Tablets (including a third of patients who were exposed in the first trimester), and published data of over 1000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate.

The efficacy of Coartem Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Coartem Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant rats dosed during the period of organogenesis at or higher than a dose of about half the highest clinical dose of 1120 mg artemether-lumefantrine per day (based on body surface area comparisons), showed increases in fetal loss, early resorptions and post implantation loss. No adverse effects were observed in animals dosed at about one-third the highest clinical dose. Similarly, dosing in pregnant rabbits at about three times the clinical dose (based on body surface area comparisons) resulted in abortions, preimplantation loss, post implantation loss and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at two times the clinical dose. Embryo-fetal loss is a significant reproductive toxicity. Other artemisinins are known to be embryotoxic in animals. However, because metabolic profiles in animals and humans are dissimilar, artemether exposures in animals may not be predictive of human exposures [see *Nonclinical Toxicology (13.2)*]. These data cannot rule out an increased risk for early pregnancy loss or fetal defects in humans.

8.3 Nursing Mothers

It is not known whether artemether or lumefantrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Coartem Tablets are administered to a nursing woman. Animal data suggest both artemether and lumefantrine are excreted into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

8.4 Pediatric Use

The safety and effectiveness of Coartem Tablets have been established for the treatment of acute, uncomplicated malaria in studies involving pediatric patients weighing 5 kg or more [see *Clinical Studies (14.1)*]. The safety and efficacy have not been established in pediatric patients who weigh less than 5 kg. Children from non-endemic countries were not included in clinical trials.

8.5 Geriatric Use

Clinical studies of Coartem Tablets did not include sufficient numbers of subjects aged 65 years and over to determine they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Coartem Tablets.

8.6 Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic and/or renal impairment [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.6)*].

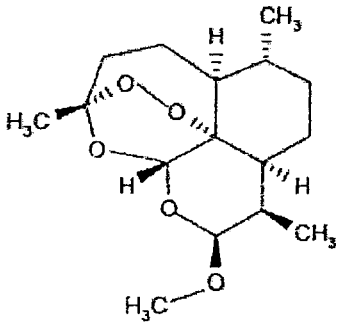
10 OVERDOSAGE

There is no information on overdoses of Coartem Tablets higher than the doses recommended for treatment.

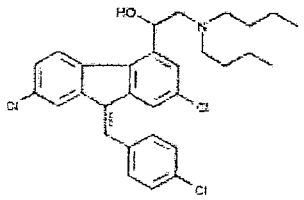
In cases of suspected overdosage, symptomatic and supportive therapy, which would include ECG and blood electrolyte monitoring, should be given as appropriate.

11 DESCRIPTION

Coartem Tablets contain a fixed combination of two antimalarial active ingredients, artemether, an artemisinin derivative, and lumefantrine. Both components are blood schizontocides. The chemical name of artemether is (3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine. Artemether is a white, crystalline powder that is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. It has the empirical formula $C_{16}H_{26}O_5$ with a molecular weight of 298.4, and the following structural formula:



The chemical name of lumefantrine is (±)-2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluorene-4-yl]ethanol. Lumefantrine is a yellow, crystalline powder that is freely soluble in N,N-dimethylformamide, chloroform, and ethyl acetate; soluble in dichloromethane; slightly soluble in ethanol and methanol; and insoluble in water. It has the empirical formula $C_{30}H_{32}Cl_3NO$ with a molecular weight of 528.9, and the following structural formula:



Coartem Tablets are for oral administration. Each Coartem Tablet contains 20 mg of artemether and 120 mg lumefantrine. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Coartem Tablets, a fixed dose combination of artemether and lumefantrine in the ratio of 1:6, is an antimalarial agent [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Absorption

Following administration of Coartem Tablets to healthy volunteers and patients with malaria, artemether is absorbed with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentrations about 6 to 8 hours after administration. The single dose (4 tablets) pharmacokinetic parameters for artemether, dihydroartemisinin (DHA), an active antimalarial metabolite of artemether, and lumefantrine in adult Caucasian healthy volunteers are given in Table 3. Multiple dose data after the 6-dose regimen of Coartem Tablets in adult malaria patients are given in Table 4.

Table 3: Single Dose Pharmacokinetic Parameters[a] for Artemether, Dihydroartemisinin (DHA), and Lumefantrine under Fed Conditions

	Study 2102 (n=50)	Study 2104 (n=48)
Artemether		
C_{max} (ng/mL)	60.0 ± 32.5	83.8 ± 59.7
t_{max} (h)	1.50	2.00
AUC_{last} (ng·h/mL)	146 ± 72.2	259 ± 150
$t_{½}$ (h)	1.6 ± 0.7	2.2 ± 1.9
DHA		
C_{max} (ng/mL)	104 ± 35.3	90.4 ± 48.9
t_{max} (h)	1.76	2.00
AUC_{last} (ng·h/mL)	284 ± 83.8	285 ± 98.0
$t_{½}$ (h)	1.6 ± 0.6	2.2 ± 1.5
Lumefantrine		
C_{max} (µg/mL)	7.38 ± 3.19	9.80 ± 4.20

t_{max} (h)	6.01	8.00
AUC_{last} (µg·h/mL)	158 ± 70.1	243 ± 117
$t_{½}$ (h)	101 ± 35.6	119 ± 51.0

[a]Mean ± SD C_{max}, AUC_{last}, $t_{½}$ and Median t_{max}

Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers, the relative bioavailability of artemether was increased between two- to three-fold, and that of lumefantrine sixteen-fold when Coartem Tablets were taken after a high-fat meal compared under fasted conditions. . Patients should be encouraged to take Coartem Tablets with a meal as soon as food can be tolerated [see *Dosage and Administration (2.1)*].

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47% to 76%). Protein binding to human plasma proteins is linear.

Biotransformation

In human liver microsomes and recombinant CYP450 enzymes, the metabolism of artemether was catalyzed predominantly by CYP3A4/5. Dihydroartemisinin (DHA) is an active metabolite of artemether. The metabolism of artemether was also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19. *In vitro* studies with artemether at therapeutic concentrations revealed no significant inhibition of the metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11.

During repeated administration of Coartem Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHA AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. This suggests that there was induction of CYP3A4/5 responsible for the metabolism of artemether.

In human liver microsomes and in recombinant CYP450 enzymes, lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine. The systemic exposure to the metabolite desbutyl-lumefantrine was less than 1% of the exposure to the parent compound. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Caution is recommended when combining Coartem Tablets with substrates, inhibitors, or inducers of CYP3A4, especially anti-retroviral drugs and those that prolong the QT interval (e.g., macrolide antibiotics, pimozide, terfenadine, astemizole, cisapride) [see *Warnings and Precautions (5.1, 5.3)*].

Co-administration of Coartem Tablets with CYP2D6 substrates may result in increased plasma concentrations of the CYP2D6 substrate and increase the risk of adverse reactions. In addition, many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1, 5.4)*].

Elimination

Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with a terminal half-life of 3-6 days in healthy volunteers and in patients with *falciparum* malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

No urinary excretion data are available for humans. In animal studies, artemether metabolites were largely excreted in the urine. However, urinary excretion of artemether, lumefantrine and lumefantrine metabolites was negligible. While animal data are informative, they do not always predict human results.

Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment [see *Dosage and Administration (2.4)*].

Pediatric Patients

The PK of artemether, DHA, and lumefantrine were obtained in two pediatric studies by sparse sampling using a population based approach. PK estimates derived from a composite plasma concentration profile for artemether, DHA, and lumefantrine are provided in Table 4.

Systemic exposure to artemether, DHA, and lumefantrine, when dosed on a mg/kg body weight basis in pediatric patients ($\geq$5 to <35 kg body weight), is comparable to that of the recommended dosing regimen in adult patients.

Table 4: Summary of Pharmacokinetic Parameters for Lumefantrine, Artemether and DHA in Pediatric and Adult Patients with Malaria Following Administration of a 6-dose Regimen of Coartem Tablets

		Pediatric patients (body weight, kg)[1]		
Drug	Adults[2]	5 - < 15	15 - < 25	25 - < 35
Lumefantrine				
Mean Cmax, range (µg/mL)	5.60 - 9.0	4.71 – 12.6		Not Available
Mean AUClast, range (µg·h/mL)	410 - 561	372 – 699		Not Available
Artemether				
Mean Cmax ± SD (ng/mL)	186 ± 125	223 ± 309	198 ± 179	174 ± 145
Dihydroartemisinin				
Mean Cmax ± SD (ng/mL)	101 ± 58	54.7 ± 58.9	79.8 ± 80.5	65.3 ± 23.6

[1] There are 477 children for the lumefantrine pharmacokinetic parameters; for artemether and dihydroartemisinin pharmacokinetic parameters there are 55, 29, and 8 children for the 5 to < 15, 15 to < 25 and the 25 to < 35 kg groups, respectively.

[2] There are a total of 181 adults for lumefantrine pharmacokinetic parameters and a total of 25 adults for artemether and dihydroarthemisin pharmacokinetic parameters.

Geriatric Patients

No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

Drug Interactions

Ketoconazole (potent CYP3A4 inhibitor)

Concurrent oral administration of ketoconazole (400 mg on Day 1 followed by 200 mg on days 2, 3, 4 and 5) with Coartem Tablets (single dose of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet) with a meal led to an increase in exposure, in terms of area under the curve (AUC), of artemether (2.3-fold), DHA (1.5 fold), and lumefantrine (1.6-fold) in 13 healthy subjects. The pharmacokinetics of ketoconazole were not evaluated. Based on this study, dose adjustment of Coartem Tablets is considered unnecessary when administered with ketoconazole or other CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Coartem Tablets should be used cautiously with other drugs that inhibit CYP3A4 (e.g., anti-retroviral drugs, macrolide antibiotics, antidepressants, imidazole antifungal agents) [see *Warnings and Precautions (5.1, 5.3)*].

Antimalarials

The oral administration of mefloquine in 14 healthy volunteers administered as three doses of 500 mg, 250 mg and 250 mg, followed 12 hours later by Coartem Tablets (6 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet), had no effect on plasma concentrations of artemether or the artemether/DHA ratio. In the same study, there was a 30% reduction in C_{max} and 40% reduction in AUC of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production.

Intravenous administration of a single dose of quinine (10 mg/kg bodyweight) concurrent with the last dose of a 6-dose regimen of Coartem Tablets had no effect on systemic exposure of DHA, lumefantrine or quinine in 14 healthy volunteers. Mean AUC of artemether were 46% lower when administered with quinine compared to Coartem Tablets alone. This decrease in artemether exposure is not thought to be clinically significant. However, quinine should be used cautiously in patients following treatment with Coartem Tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval [see *Warnings and Precautions (5.2)*].

Anti-Retroviral Drugs

No formal drug-drug interaction studies between Coartem Tablets and Anti-Retroviral drugs (ARTs), such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors, have been performed. Due to variable patterns of inhibition, induction or competition for CYP3A4 with anti-retroviral drugs, Coartem Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation, a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Coartem Tablets [see *Warnings and Precautions (5.3)*].

Hormonal Contraceptives

No formal drug-drug interaction studies between Coartem Tablets and hormonal contraceptives have been performed. However, artemether may induce CYP3A4/5, reducing the effectiveness of hormonal contraceptives [see *Warnings and Precautions (5.3)*].

12.4 Microbiology

Mechanism of Action

Coartem Tablets, a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively, is an antimalarial agent. Artemether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). The anti-malarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine, exerts its anti-malarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of β-hematin by forming a complex with hemin. Both artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis.

Activity In Vitro and In Vivo

Artemether and lumefantrine are active against the erythrocytic stages of *Plasmodium falciparum*.

Drug Resistance

Strains of *P. falciparum* with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected *in vitro* or *in vivo*, but not maintained in the case of artemether. The clinical relevance of such an effect is not known.

12.5 Effects on the Electrocardiogram

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the 6-dose regimen of Coartem Tablets was associated with prolongation of QTcF (Fridericia). Following administration of a 6-dose regimen of Coartem Tablets consisting of 4 tablets per dose (total of 4 tablets of 80 mg artemether/480 mg lumefantrine) taken with food, the maximum mean change from baseline and placebo adjusted QTcF was 7.5 msec (1-sided 95% Upper CI: 11 msec). There was a concentration-dependent increase in QTcF for lumefantrine.

In clinical trials conducted in children, no patient had QTcF >500 msec. Over 5% of patients had an increase in QTcF of over 60 msec.

In clinical trials conducted in adults, QTcF prolongation of >500 msec was reported in 3 (0.3%) of patients. Over 6% of adults had a QTcF increase of over 60 msec from baseline.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were not conducted.

Mutagenesis

No evidence of mutagenicity was detected. The artemether: lumefantrine combination was evaluated using the *Salmonella* and *Escherichia*/mammalian-microsome mutagenicity test, the gene mutation test with Chinese hamster cells V79, the cytogenetic test on Chinese hamster cells *in vitro*, and the rat micronucleus test, *in vivo*.

Impairment of Fertility

Pregnancy rates were reduced by about one half in female rats dosed for 2 to 4 weeks with the artemether-lumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on body surface area comparisons). Male rats dosed for 70 days showed increases in abnormal sperm (87 % abnormal) and increased testes weights at 30 mg/kg doses (about one third the clinical dose). Higher doses (about 9 times the clinical dose) resulted in decreased sperm motility and 100 % abnormal sperm cells.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicity

Pregnant rats dosed during the period of organogenesis, at or higher than 60 mg/kg/day with the artemether-lumefantrine combination (a dose about half the highest clinical dose based on body surface area comparisons), showed increases in the number of dead fetuses, early resorptions and post implantation losses. No adverse effects were observed in animals dosed at 40 mg/kg (about one third the clinical dose). Similarly, dosing in pregnant rabbits at 175 mg/kg/day (about three times the highest clinical dose based on body surface area comparisons) resulted in abortions, preimplantation losses, post

implantation losses, and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at 105 mg/kg/day, about two times the clinical dose based on body surface area comparisons.

Other artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives (e.g, artesunate) demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. Similar findings were not seen in animal reproductive studies using artemether.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis, and dark neurons. Lesions were observed in rats dosed with artemether at 25 mg/kg for 7 or 14 days and dogs dosed at 20 mg/kg for 8 days or longer, but lesions were not observed after shorter courses of drug or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7-fold greater than the estimated artemether 24 h AUC in humans on day 1 of the standard 3-day oral treatment regimen; oral exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent to about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study [see *Adverse Reactions (6.2)*].

14 CLINICAL STUDIES

14.1 Treatment of Acute, Uncomplicated *P. falciparum* Malaria

The efficacy of Coartem Tablets was evaluated for the treatment of acute, uncomplicated malaria caused by *P. falciparum* in HIV negative patients in 8 clinical studies. Uncomplicated malaria was defined as symptomatic *P. falciparum* malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction. Baseline parasite density ranged from 500/μL - 200,000/μL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in partially immune and non-immune adults and children (≥5kg body weight) with uncomplicated malaria in China, Thailand, sub-Saharan Africa, Europe, and South America. Patients who had clinical features of severe malaria, severe cardiac, renal, or hepatic impairment were excluded.

The studies include two 4-dose studies assessing the efficacy of the components of the regimen, a study comparing a 4-dose versus a 6-dose regimen, and 5 additional 6-dose regimen studies.

Coartem Tablets were administered at 0, 8, 24, and 48 hours in the 4-dose regimen, and at 0, 8, 24, 36, 48, and 60 hours in the 6-dose regimen. Efficacy endpoints consisted of:

- 28 day cure rate, defined as clearance of asexual parasites (the erythrocytic stage) within 7 days without recrudescence by day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature > 37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28.

Studies 1 and 2: The two studies which assessed the efficacy of Coartem Tablets (4 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine) compared to each component alone were randomized, double-blind, comparative, single center, conducted in China. The efficacy results (Table 5) support that the combination of artemether and lumefantrine in Coartem Tablets had a significantly higher 28-day cure rate compared to artemether and had a significantly faster parasite clearance time (PCT) and fever clearance time (FCT) compared to lumefantrine.

Table 5: Clinical Efficacy of Coartem Tablets versus Components (mITT Population[1]

Study No. **Region/patient ages**	**28-day cure rate[2]** n/N (%) patients	**Median FCT[3]** [25th,75th percentile]	**Median PCT** [25th,75th percentile]
Study 1 China, ages 13 - 57 years			
Coartem Tablets	50/51 (98.0)	24 hours [9, 48]	30 hours [24, 36]
Artemether[4]	24/52 (46.2)	21 hours [12, 30]	30 hours [24, 33]
Lumefantrine[5]	47/52 (90.4)	60 hours [36, 78]	54 hours [45, 66]
Study 2 China, ages 12 - 65 years			
Coartem Tablets	50/52 (96.2)	21 hours [6, 33]	30 hours [24, 36]
Lumefantrine[6]	45/51 (88.2)	36 hours [12, 60]	48 hours [42, 60]

[1]In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[2]Efficacy cure rate based on blood smear microscopy.
[3]For patients who had a body temperature > 37.5°C at baseline only
[4]95% CI (Coartem Tablets – artemether) on 28-day cure rate: 37.8%, 66.0%
[5]P-value comparing Coartem Tablets to lumefantrine on parasite clearance time (PCT) and fever clearance time (FCT): < 0.001
[6]P-value comparing Coartem Tablets to lumefantrine on parasite clearance time (PCT): < 0.001 and on fever clearance time (FCT): < 0.05

Results of 4-dose studies conducted in areas with high resistance such as Thailand during 1995-96 showed lower efficacy results than the above studies. Therefore, Study 3 was conducted.

Study 3: Study 3 was a randomized, double-blind, two-center study conducted in Thailand in adults and children (aged ≥2 years), which compared the 4-dose regimen (administered over 48 hours) of Coartem Tablets to a 6-dose regimen (administered over 60 hours). Twenty-eight day cure rate in mITT subjects was 81% (96/118) for the Coartem Tablets 6-dose arm as compared to 71% (85/120) in the 4-dose arm.

Studies 4, 5, 6, 7, and 8: In these studies, Coartem Tablets were administered as the 6-dose regimen.

In study 4, a total of 150 adults and children aged ≥2 years received Coartem Tablets. In study 5, a total 164 adults and children ≥12 years received Coartem Tablets. Both studies were conducted in Thailand.

Study 6 was a study of 165 non-immune adults residing in regions non-endemic for malaria (Europe and Colombia) who contracted acute uncomplicated *falciparum* malaria when traveling in endemic regions.

Study 7 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5 °C.

Study 8 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to < 35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours.

Results of 28-day cure rate, median parasite clearance time (PCT), and fever clearance time (FCT) for Studies 3 to 8 are reported in Table 6.

Table 6: Clinical Efficacy of 6-dose Regimen of Coartem Tablets

Study No. Region/ages	28-day cure rate[1] n/N (%) patients		Median FCT[2]	Median PCT
	mITT[3]	Evaluable	[25th, 75th percentile]	[25th, 75th percentile]
Study 3 Thailand, ages 3 – 62 years	96/118 (81.4)	93/96 (96.9)	35 hours	44 hours
Early failure[4]	0	0	[20, 46]	[22, 47]
Late failure[5]	4 (3.4)	3 (3.1)		
Lost to follow up	18 (15.3)			
Other[6]	0			
Study 4 Thailand, ages 2 – 63 years	130/149 (87.2)	130/134 (97.0)	22 hours	NA
Early failure[4]	0	0	[19, 44]	
Late failure[5]	4 (2.7)	4 (3.0)		
Lost to follow up	13 (8.7)			
Other[6]	2 (1.3)			
Study 5 Thailand, ages 12 – 71 years	148/164 (90.2)	148/155 (95.5)	29 hours	29 hours
Early failure[4]	0	0	[8, 51]	[18, 40]
Late failure[5]	7 (4.3)	7 (4.5)		
Lost to follow up	9 (5.5)			
Other[6]	0			
Study 6				

Europe/Columbia, ages 16 – 66 years	120/162 (74.1)	119/124 (96.0)	37 hours [18, 44]	42 hours [34, 63]
Early failure[4]	6 (3.7)	1 (0.8)		
Late failure[5]	3 (1.9)	3 (2.4)		
Lost to follow up	17 (10.5)			
Other[6]	16 (9.9)	1 (0.8)		
Study 7 Africa, ages 2 months – 9 years	268/310 (86.5)	267/300 (89.0)	8 hours [8, 24]	24 hours [24, 36]
Early failure[4]	2 (0.6)	0		
Late failure[5]	34 (11.0)	33 (11.0)		
Lost to follow up	2 (0.6)			
Other[6]	4 (1.3)			
Study 8 Africa, ages 3 months – 12 years	374/452 (82.7)	370/419 (88.3)	8 hours [8, 23]	35 hours [24, 36]
Early failure[4]	13 (2.9)	0		
Late failure[5]	49 (10.8)	49 (11.7)		
Lost to follow up	6 (1.3)			
Other[6]	10 (2.2)			

[1] Efficacy cure rate based on blood smear microscopy
[2] For patients who had a body temperature > 37.5°C at baseline only
[3] In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[4] Early failures were usually defined as patients withdrawn for unsatisfactory therapeutic effect within the first 7 days or because they received another antimalarial medication within the first 7 days
[5] Late failures were defined as patients achieving parasite clearance within 7 days but having parasite reappearance including recrudescence or new infection during the 28 day follow-up period
[6] Other includes withdrawn due to protocol violation or non-compliance, received additional medication after day 7, withdrew consent, missing day 7 or 28 assessment

In all studies, patients' signs and symptoms of malaria resolved when parasites were cleared.

In studies conducted in areas with high transmission rates, such as Africa, reappearance of *P. falciparum* parasites may be due to recrudescence or a new infection.

The efficacy by body weight category for studies 7 and 8 is summarized in Table 7.

Table 7: Clinical Efficacy by Weight for Pediatric Studies

Study No. Age category	Coartem Tablets 6-dose Regimen		
	mITT population[1]		Evaluable population
	Median PCT [25th,75th percentile]	28-day cure rate[2] n/N (%) patients	28-day cure rate[2] n/N (%) patients
Study 7			
5 - <10 kg	24 [24, 36]	133/154 (86.4)	133/149 (89.3)
10 - <15 kg	35 [24, 36]	94/110 (85.5)	94/107 (87.9)
15 -25 kg	24 [24, 36]	41/46 (89.1)	40/44 (90.9)
Study 8[3]			
5 - <10 kg	36 [24, 36]	61/83 (73.5)	61/69 (88.4)
10 - <15 kg	35 [24, 36]	160/190 (84.2)	157/179 (87.7)
15 - <25 kg	35 [24, 36]	123/145 (84.8)	123/140 (87.9)

25 - <35 kg	26 [24, 36]	30/34 (88.2)	29/31 (93.5)

[1] In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[2] Efficacy cure rate based on blood smear microscopy
[3] Coartem Tablets administered as crushed tablets

The efficacy of Coartem Tablets for the treatment *P. falciparum* infections mixed with *P. vivax* was assessed in a small number of patients. Coartem Tablets are only active against the erythrocytic phase of *P. vivax* malaria. Of the 43 patients with mixed infections at baseline, all cleared their parasitemia within 48 hours. However, parasite relapse occurred commonly (14 /43; 33%). Relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoite forms that may remain dormant in the liver.

16 HOW SUPPLIED/STORAGE AND HANDLING

Coartem (artemether/lumefantrine) Tablets

20mg/120mg Tablets - yellow, round flat tablets with beveled edges and scored on one side. Tablets are imprinted with N/C on one side and CG on the other.

Bottle of 24	NDC 0078-0568-45
Unit dose carton of 24 tablets (4 x 6-tablet blister cards)	NDC 0078-0568-43

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

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2).

17.1 Information for Safe Use

- Instruct patients to take Coartem Tablets with food. Patients who do not have an adequate intake of food are at risk for recrudescence of malaria.
- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients should not receive Coartem Tablets.
- Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia.
- Instruct patients to inform their physician if they are taking any other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistamines (terfenadine, astemizole), or cisapride.
- Instruct patients to notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

- Instruct patients to avoid medications that are metabolized by the cytochrome enzyme CYP2D6 while receiving Coartem Tablets since these drugs also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).
- Inform patients that based on animal data, Coartem Tablets administered during pregnancy may result in fetal loss. Fetal defects have been reported when artemisinins are administered to animals.
- Halofantrine and Coartem Tablets should not be administered within one month of each other due to potential additive effects on the QT interval.
- Antimalarials should not be given concomitantly with Coartem Tablets, unless there is no other treatment option, due to limited safety data.
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Coartem Tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval.
- Closely monitor food intake in patients who received mefloquine immediately prior to treatment with Coartem Tablets.
- Use Coartem Tablets cautiously in patients receiving other drugs that are substrates, inhibitors or inducers of CYP3A4, including grapefruit juice, especially those that prolong the QT interval or are anti-retroviral drugs.
- Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- Inform patients that Coartem Tablets can cause hypersensitivity reactions. Instruct patients to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

17.2 FDA-Approved Patient Labeling

Patient Information
Coartem®
(co-AR-tem)
(artemether and lumefantrine)
Tablets

Read this patient information before you start taking Coartem. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is Coartem?

Coartem is a prescription medicine used to treat uncomplicated malaria in adults and children who weigh at least 11 pounds (5 kg).

Who should not take Coartem?

Do not take Coartem if you are allergic to any of the ingredients. See the end of this leaflet for a complete list of ingredients in Coartem.

What should I tell my healthcare provider before taking Coartem?

Before you take Coartem, tell your healthcare provider about all your medical conditions including if you have:

- heart disease or a family history of heart problems or heart disease
- liver or kidney problems
- recently taken other medicines used to treat malaria
- if you are pregnant or are planning to become pregnant. Coartem may increase your risk for loss of pregnancy. Fetal defects have been reported when artemisinins are administered to animals. Talk to your healthcare provider before taking Coartem.
- if you are breast-feeding. It is not known if Coartem passes into your breast milk. You and your doctor will decide the best way to feed your baby if you take Coartem.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Coartem and other medicines may affect each other causing side effects. Coartem may affect the way other medicines work and other medicines may affect how Coartem works.

Especially tell your doctor if you take:

- any other medicines to treat or prevent malaria
- medicines for your heart

- antipsychotic medicines
- antidepressants
- antibiotics
- antihistamines
- Cisapride (Propulsid®)
- medicines to treat HIV-infection
- hormonal methods of birth control (for example, birth control pills or patch)

Ask your healthcare provider if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take Coartem?

- Take Coartem exactly as prescribed.
- If you weigh 77 pounds (35 kg) or more, one dose of Coartem is 4 tablets.
- If you weigh less than 77 pounds (35 kg), your healthcare provider will tell you how many tablets to take for each dose.
- A full course of treatment is 6 doses of Coartem taken over 3 days:

  Day 1: take 1 dose; 8 hours later take 1 dose

  Day 2: take 1 dose in the morning, 1 dose in the evening

  Day 3: take 1 dose in the morning, 1 dose in the evening

  Take Coartem for 3 days even if you are feeling better.
- Every dose of Coartem should be taken with food, such as milk, infant formula pudding, porridge, or broth. It is important for you to eat as soon as you can so that your malaria will go away and not get worse.
- Do not drink grapefruit juice while you take Coartem. Drinking grapefruit juice during treatment with Coartem can cause you to have too much medicine in your blood.
- Coartem may be crushed and mixed with one to two teaspoons of water in a clean container.
- If you vomit within 1 hour of taking Coartem you should take another dose of Coartem. If you vomit the second dose, tell your healthcare provider. A different medicine may need to be prescribed for you.

Tell your healthcare provider right away if:

- your malaria does not get better
- you vomited any of your doses of Coartem
- you are not able to eat

- you get flu-like symptoms (chills, fever, muscle pains, or headaches) again after you have finished your treatment with Coartem.
- you have any change in the way your heart beats or a loss of consciousness (fainting).

What are the possible side effects of Coartem?

Coartem can cause serious side effects including:

- **A heart problem called QT prolongation** that can cause an abnormal heartbeat can happen in people who take Coartem. The chance of this happening is higher in people with a family history of prolonged QT interval, low potassium (hypokalemia), and in people who take medicines to control heartbeats.
- **Allergic reactions.** Symptoms of an allergic reaction include: rash, hives, fast heartbeat, trouble swallowing or breathing, swelling of lips, tongue, face, tightness of the throat, or trouble speaking. If you have a serious allergic reaction, stop taking Coartem and get emergency medical help right away.

The most common side effects in adults are:

- headache
- feeling dizzy
- feeling weak
- loss of appetite
- muscle and joint pain or stiffness
- feeling tired
- chills
- fever

The most common side effects in children are:

- fever
- cough
- vomiting
- headache
- loss of appetite

These are not all the possible side effects of Coartem. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Coartem?

Store Coartem between 59°F to 86°F (15°C to 30°C).

Keep Coartem and all medicines out of the reach of children.

General information about the safe and effective use of Coartem.

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

This patient information leaflet summarizes the most important information about Coartem. If you would like more information about Coartem talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Coartem that is written for health professionals. For more information call 1-888-294-6287.

What are the ingredients in Coartem?

Active ingredients include: artemether, lumefantrine

Inactive ingredients include: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate 80

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

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資料3－4　ゴリムマブ（golimumab）

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIMPONI (golimumab) safely and effectively. See full prescribing information for SIMPONI.

SIMPONI (golimumab)
Injection, solution for subcutaneous use
Initial U.S. Approval: 2009

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning

Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal, and other opportunistic infections have occurred in patients receiving SIMPONI (5.1).

SIMPONI should be discontinued if a patient develops a serious infection or sepsis (5.1).

Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI (5.1).

Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)

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

SIMPONI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

Moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate (1.1)

Active Psoriatic Arthritis (PsA) in adults, alone or in combination with methotrexate (1.2)

Active Ankylosing Spondylitis in adults (AS) (1.3)

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

Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis (2.1)

50 mg administered by subcutaneous injection once a month.

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

50 mg/0.5 mL in a single dose prefilled SmartJect autoinjector (3)

50 mg/0.5 mL in a single dose prefilled syringe (3)

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

None (4)

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

Serious Infections – Do not start SIMPONI during an active infection. If an infection develops, monitor carefully, and sto SIMPONI if infection becomes serious (5.1).

Invasive fungal infections – For patients who develop a systen illness on SIMPONI, consider empiric antifungal therapy fo those who reside or travel to regions where mycoses are enden (5.1).

Hepatitis B reactivation – Monitor HBV carriers during anc several months after therapy. If reactivation occurs, stop SIMPONI and begin anti-viral therapy (5.1).

Malignancies – The incidence of lymphoma was seen more oft than in the general U.S. population. Cases of other malignanc have been observed among patients receiving TNF-blockers (5

Heart failure – Worsening, or new onset, may occur. Stop SIMPONI if new or worsening symptoms occur (5.3).

Demyelinating disease, exacerbation or new onset, may occu (5.4).

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

Most common adverse reactions (incidence > 5%): upper respiratory tract infection, nasopharyngitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Centocor Ortho Biotech Inc. at 1-800-457-6399 or FDA at 1-8(FDA-1088 or *www.fda.gov/medwatch.*

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

Abatacept – increased risk of serious infection (5.1, 5.5, 7.2)

Anakinra – increased risk of serious infection (5.1, 5.6, 7.2).

Live vaccines – should not be given with SIMPONI (5.8, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2009

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

FULL PRESCRIBING INFORMATION

WARNING
RISK OF SERIOUS INFECTIONS

Patients treated with SIMPONI™ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

SIMPONI should be discontinued if a patient develops a serious infection.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before SIMPONI use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with SIMPONI should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warning and Precautions (5.1)]*.

1.0 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

SIMPONI, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

1.2 Psoriatic Arthritis

SIMPONI, alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis.

1.3 Ankylosing Spondylitis

SIMPONI is indicated for the treatment of adult patients with active ankylosing spondylitis.

2.0 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis

The SIMPONI dose regimen is 50 mg administered by subcutaneous (SC) injection once a month.

For patients with rheumatoid arthritis (RA), SIMPONI should be given in combination with methotrexate and for patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS), SIMPONI may be given with or without methotrexate or other non-biologic DMARDs. For patients with RA, PsA, or AS, corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued during treatment with SIMPONI.

2.2 Monitoring to Assess Safety

Prior to initiating SIMPONI and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection [*see Warnings and Precautions (5.1)*].

2.3 General Considerations for Administration

SIMPONI is intended for use under the guidance and supervision of a physician. After proper training in subcutaneous injection technique, a patient may self inject with SIMPONI if a physician determines that it is appropriate. Patients should be instructed to follow the directions provided in the Medication Guide [*see Medication Guide (17.3)*]. To ensure proper use, allow the prefilled syringe or autoinjector to sit at room temperature outside the carton for 30 minutes prior to subcutaneous injection. Do not warm SIMPONI in any other way.

Prior to administration, visually inspect the solution for particles and discoloration through the viewing window. SIMPONI should be clear to slightly opalescent and colorless to light yellow. The solution should not be used if discolored, or cloudy, or if foreign particles are present. Any leftover product remaining in the prefilled syringe or prefilled autoinjector should not be used. NOTE: The needle cover on the prefilled syringe as well as the prefilled syringe in the autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

3.0 DOSAGE FORMS AND STRENGTHS

SmartJect™ Autoinjector
Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge ½ inch) providing 50 mg of SIMPONI per 0.5 mL of solution.

Prefilled Syringe
Each single dose prefilled glass syringe (27 gauge ½ inch) contains 50 mg of SIMPONI per 0.5 mL of solution.

4.0 CONTRAINDICATIONS

None.

5.0 WARNINGS AND PRECAUTIONS (see Boxed WARNINGS)

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended [*see Warning and Precautions (5.5, 5.6) and Drug Interactions (7.2)*].

Treatment with SIMPONI should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating SIMPONI in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI. SIMPONI should be discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with SIMPONI should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI-treated patients and 1.3% of control-treated patients. In the

controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.4 (95% CI: 4.0, 7.2) for the SIMPONI group and 5.3 (95% CI: 3.1, 8.7) for the placebo group. Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection.

Tuberculosis
Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating SIMPONI and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating SIMPONI, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of SIMPONI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Tuberculosis should be strongly considered in patients who develop a new infection during SIMPONI treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB.

Invasive Fungal Infections
For SIMPONI-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Hepatitis B Virus Reactivation
The use of TNF-blockers including SIMPONI has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers 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, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely.

5.2 Malignancies
The risks and benefits of TNF-blocker treatment including SIMPONI should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy.

In the controlled portions of clinical trials of TNF-blockers including SIMPONI, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In the controlled and uncontrolled portions of these clinical trials in 2347 SIMPONI-treated patients with a median follow-up of 1.4 years, the incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was not elevated in the combined SIMPONI group compared with the placebo group. In the controlled and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in SIMPONI-treated patients was similar to that expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1]

In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory 1-year clinical trial evaluating the use of 50, 100 and 200 mg of SIMPONI in 309 patients with severe persistent asthma, 6 patients developed malignancies other than NMSC in the SIMPONI groups compared to none in the control group. Three of the 6 patients were in the 200 mg SIMPONI group.

5.3 Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI has not been studied in patients with a history of CHF and SIMPONI should be used with caution in patients with CHF. If a decision is made to administer SIMPONI to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear.

5.4 Demyelinating Disorders

Use of TNF-blockers has been associated with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS). While no trials have been performed evaluating SIMPONI in the treatment of patients with MS, another TNF-blocker was associated with increased disease activity in patients with MS. Therefore, prescribers should exercise caution in considering the use of TNF-blockers including SIMPONI in patients with CNS demyelinating disorders including MS.

5.5 Use with Abatacept

In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI and abatacept is not recommended [*see Drug Interactions (7.2)*].

5.6 Use with Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI, is not recommended [*see Drug Interactions 7.2*].

5.7 Hematologic Cytopenias

There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. Although, there were no cases of severe cytopenias seen in the SIMPONI clinical trials, caution should be exercised when using TNF-blockers, including SIMPONI, in patients who have significant cytopenias.

5.8 Vaccinations

Patients treated with SIMPONI may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving SIMPONI. In the Phase 3 PsA study, after pneumococcal vaccination, a similar proportion of SIMPONI-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving MTX compared with patients not receiving MTX. The data suggest that SIMPONI does not suppress the humoral immune response to the pneumococcal vaccine.

6.0 ADVERSE REACTIONS

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.

6.1 Clinical Studies Experience

The safety data described below are based on 5 pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA, and AS) [*see Clinical Studies (14.1, 14.2 and 14.3)*]. These 5 trials included 639 control-treated patients and 1659 SIMPONI-treated patients including 1089 with RA, 292 with PsA, and 278 with AS. The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%).

The most serious adverse reactions were:

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

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and 6% of SIMPONI-treated patients as compared with 6% and 5% of control-treated patients, respectively.

Infections

In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI-treated patients compared to 25% of control-treated patients [for Serious Infections, *see Warnings and Precautions (5.1)*].

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI in patients with RA, PsA, and AS through Week 16, ALT elevations $\geq$ 5 x ULN occurred in 0.2% of control-treated patients and 0.7% of SIMPONI-treated patients and ALT elevations $\geq$ 3 x ULN occurred in 2% of control-treated patients and 2% of SIMPONI-treated patients. Since many of the patients in the Phase 3 trials were also taking

medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between golimumab and liver elevation is not clear.

Autoimmune Disorders and Autoantibodies
The use of TNF-blockers has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI treatment and the development of newly positive anti-dsDNA antibodies.

Injection Site Reactions
In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI-treated patients had injection site reactions compared with 2% of control-treated patients. The majority of the injection site reactions were mild and the most frequent manifestation was injection site erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with SIMPONI developed anaphylactic reactions.

Psoriasis: New-Onset and Exacerbations
Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including SIMPONI. Cases of exacerbation of pre-existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of SIMPONI should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Immunogenicity
Antibodies to SIMPONI were detected in 57 (4%) of SIMPONI-treated patients across the Phase 3 RA, PsA and AS trials through Week 24. Similar rates were observed in each of the three indications. Patients who received SIMPONI with concomitant MTX had a lower proportion of antibodies to SIMPONI than patients who received SIMPONI without MTX (approximately 2% versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a cell-based functional assay. The small number of patients positive for antibodies to SIMPONI limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

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

Other Adverse Reactions

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the combined SIMPONI groups during the controlled period of the 5 pooled Phase 3 trials through Week 16 in patients with RA, PsA, and AS.

Table 1. Adverse Drug Reactions Reported by ≥ 1% of Patients in the Phase 3 Trials of RA, PsA, and AS through Week 16[a]

	Placebo ± DMARDs	SIMPONI ± DMARDs
Patients treated	639	1659
Adverse Reaction (Preferred Term)		
Upper respiratory tract infection	37 (6%)	120 (7%)
Nasopharyngitis	31 (5%)	91 (6%)
Alanine aminotransferase increased	18 (3%)	58 (4%)
Injection site erythema	6 (1%)	56 (3%)
Hypertension	9 (1%)	48 (3%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Bronchitis	9 (1%)	31 (2%)
Dizziness	7 (1%)	32 (2%)
Sinusitis	7 (1%)	27 (2%)
Influenza	7 (1%)	25 (2%)
Pharyngitis	8 (1%)	22 (1%)
Rhinitis	4 (< 1%)	20 (1%)
Pyrexia	4 (< 1%)	20 (1%)
Oral herpes	2 (< 1%)	16 (1%)
Paraesthesia	2 (< 1%)	16 (1%)

a Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids (≤ 10 mg of prednisone/day or equivalent), and/or NSAIDs during the trials).

7.0 DRUG INTERACTIONS

7.1 Methotrexate

For the treatment of RA, SIMPONI should be used with methotrexate (MTX) [*see Clinical Studies (14.1)*]. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI in the treatment of PsA or AS, SIMPONI can be used with or without MTX in the treatment of PsA and AS [*see Clinical Studies (14.1) and Clinical Pharmacology (12.3)*].

7.2 Biologic Products for RA, PsA, and/or AS

An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI with abatacept or anakinra is not recommended [*see Warnings and Precautions (5.5 and 5.6)*]. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. There is insufficient information to provide recommendations regarding the concomitant use of SIMPONI and other biologic products approved to treat RA, PsA, or AS.

7.3 Live Vaccines

Live vaccines should not be given concurrently with SIMPONI [*see Warnings and Precautions (5.8)*].

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8.0 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI should be used during pregnancy only if clearly needed.

An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MHRD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus.

A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants.

8.3 Nursing Mothers

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

In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations.

8.4 Pediatric Use

Safety and effectiveness of SIMPONI in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMPONI-treated patients ages 65 or older (N = 155) compared with younger SIMPONI-treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI.

10.0 OVERDOSAGE

In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMPONI without serious adverse reactions or other significant reactions. The highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000 mg of SIMPONI. There were no SIMPONI overdoses in the clinical studies.

11.0 DESCRIPTION

SIMPONI (golimumab) is a human IgG1κ monoclonal antibody specific for human tumor necrosis factor alpha (TNFα) that exhibits multiple glycoforms with molecular masses of approximately 150 to 151 kilodaltons. SIMPONI was created using genetically engineered mice immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. SIMPONI is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

The SIMPONI drug product is a sterile solution of the golimumab antibody supplied as either a single dose prefilled syringe (with a passive needle safety guard) or a single dose prefilled autoinjector. The Type 1 glass syringe has a coated stopper. The fixed stainless steel needle (5 bevel, 27G, half-inch) is covered with a needle shield to prevent leakage of the solution through the needle and to protect the needle during handling prior to administration. The needle shield is made of a dry natural rubber containing latex.

SIMPONI does not contain preservatives. The solution is clear to slightly opalescent, colorless to light yellow with a pH of approximately 5.5. SIMPONI is provided in one strength: 50 mg of the golimumab antibody in 0.5 mL of solution. Each 0.5 mL of SIMPONI contains 50 mg of the

golimumab antibody, 0.44 mg of L-histidine and L-histidine monohydrochloride monohydrate, 20.5 mg of sorbitol, 0.08 mg of polysorbate 80, and Water for Injection.

12.0 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα (a cytokine protein). There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

Elevated TNFα levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNFα is an important mediator of the articular inflammation that is characteristic of these diseases. Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

12.2 Pharmacodynamics

In clinical studies, decreases in C-reactive protein (CRP), interleukin (IL)-6, matrix metalloproteinase 3 (MMP-3), intercellular adhesion molecule (ICAM)-1 and vascular endothelial growth factor (VEGF) were observed following SIMPONI administration in patients with RA, PsA, and AS.

12.3 Pharmacokinetics

Following subcutaneous (SC) administration of SIMPONI to healthy subjects and patients with active RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A SC injection of 50 mg SIMPONI to healthy subjects produced a mean maximum serum concentration (C_{max}) of approximately 2.5 μg/mL. SIMPONI exhibited dose-proportional pharmacokinetics (PK) in patients with active RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous (IV) dose. Following a single IV administration over the same dose range in patients with active RA, mean systemic clearance of SIMPONI was estimated to be 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg. The volume of distribution for SIMPONI indicates that SIMPONI is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be approximately 2 weeks in healthy subjects and patients with active RA, PsA or AS. By cross-study comparisons of mean AUC_{inf} values following an IV or SC administration of SIMPONI, the absolute bioavailability of SC SIMPONI was estimated to be approximately 53%.

When 50 mg SIMPONI was administered SC to patients with RA, PsA or AS every 4 weeks, serum concentrations appeared to reach steady state by Week 12. With concomitant use of methotrexate (MTX), treatment with 50 mg SIMPONI SC every 4 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4-0.6 μg/mL in patients with active RA, approximately 0.5 μg/mL in patients with active PsA, and approximately 0.8 μg/mL in patients with active AS.

Patients with RA, PsA and AS treated with SIMPONI 50 mg and MTX had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of golimumab, respectively compared with those treated with SIMPONI 50 mg without MTX. The presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% [*see Adverse Reactions (6.1)*]. For RA, SIMPONI should be used with MTX. In the PsA and AS trials, the presence or absence of concomitant MTX did not appear to influence clinical efficacy and safety parameters [*see Drug Interactions (7.1) and Clinical Studies (14.1)*].

Population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of SIMPONI.

Population PK analyses showed there was a trend toward higher apparent clearance of SIMPONI with increasing weight. However, across the PsA and AS populations, no meaningful differences in clinical efficacy were observed among the subgroups by weight quartile. The RA trial in MTX-experienced and TNF-blocker-naïve patients (Study RA-2) did show evidence of a reduction in clinical efficacy with increasing body weight, but this effect was observed for both tested doses of SIMPONI (50 mg and 100 mg). Therefore, there is no need to adjust the dosage of SIMPONI based on a patient's weight.

Population PK analyses suggested no PK differences between male and female patients after body weight adjustment in the RA and PsA trials. In the AS trial, female patients showed 13% higher apparent clearance than male patients after body weight adjustment. Subgroup analysis based on gender showed that both female and male patients achieved clinically significant response at the proposed clinical dose. Dosage adjustment based on gender is not needed.

Population PK analyses indicated that PK parameters of SIMPONI were not influenced by age in adult patients. Patients with age ≥ 65 years had apparent clearance of SIMPONI similar to patients with age < 65 years. No ethnicity-related PK differences were observed between Caucasians and Asians, and there were too few patients of other races to assess for PK differences.

Patients who developed anti-SIMPONI antibodies generally had lower steady-state serum trough concentrations of SIMPONI.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

13.0 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic potential. Mutagenicity studies have not been conducted with golimumab. A fertility study conducted in mice using an analogous anti-mouse TNFα antibody showed no impairment of fertility.

14.0 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of SIMPONI were evaluated in 3 multicenter, randomized, double-blind, controlled trials (Studies RA-1, RA-2, and RA-3) in 1542 patients ≥ 18 years of age with moderately to severely active RA, diagnosed according to the American College of Rheumatology (ACR) criteria, for at least 3 months prior to administration of study agent. Patients were required to have at least 4 swollen and 4 tender joints. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Double-blinded controlled efficacy data were collected and analyzed through Week 24. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials.

Study RA-1 evaluated 461 patients who were previously treated (at least 8 to 12 weeks prior to administration of study agent) with one or more doses of a biologic TNF-blocker without a serious adverse reaction. Patients may have discontinued the biologic TNF-blocker for a variety of reasons. Patients were randomized to receive placebo (n = 155), SIMPONI 50 mg (n = 153), or SIMPONI 100 mg (n = 153). Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

Study RA-2 evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with a biologic TNF-blocker. Patients were randomized to receive background MTX (n = 133), SIMPONI 50 mg + background MTX (n = 89), SIMPONI 100 mg + background MTX (n = 89), or SIMPONI 100 mg monotherapy (n = 133). The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

Study RA-3 evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with a biologic TNF-blocker. Patients were randomized to receive MTX (n = 160), SIMPONI 50 mg + MTX (n = 159), SIMPONI 100 mg + MTX (n = 159), or SIMPONI 100 mg monotherapy (n = 159). For patients receiving MTX, MTX was administered at a dose of 10 mg/week beginning at Week 0 and increased to 20 mg/week by Week 8. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

The primary endpoint in Study RA-1 and Study RA-2 was the percentage of patients achieving an ACR 20 response at Week 14 and the primary endpoint in Study RA-3 was the percentage of patients achieving an ACR 50 response at Week 24.

In Studies RA-1, RA-2, and RA-3, the median duration of RA disease was 9.4, 5.7, and 1.2 years; and 99%, 75%, and 54% of the patients used at least one DMARD in the past, respectively. Approximately 77% and 57% of patients received concomitant NSAIDs and low dose corticosteroids, respectively, in the 3 pooled RA trials.

Clinical Response

In the 3 RA trials, a greater percentage of patients treated with the combination of SIMPONI and MTX achieved ACR responses at Week 14 (Studies RA-1 and RA-2) and Week 24 (Studies RA-1,

RA-2, and RA-3) versus patients treated with the MTX alone. There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). In Studies RA-2 and RA-3, the SIMPONI monotherapy groups were not statistically different from the MTX monotherapy groups in ACR responses. Table 2 shows the proportion of patients with the ACR response for the SIMPONI 50 mg and control groups in Studies RA-1, RA-2, and RA-3. In the subset of patients who received SIMPONI in combination with MTX in Study RA-1, the proportion of patients achieving ACR 20, 50 and 70 responses at Week 14 were 40%, 18%, and 13%, respectively, in the SIMPONI 50 mg + MTX group (N = 103) compared with 17%, 6%, and 2%, respectively, in the placebo + MTX group (N = 107). Table 3 shows the percent improvement in the components of the ACR response criteria for the SIMPONI 50 mg + MTX and MTX groups in Study RA-2. The percent of patients achieving ACR 20 responses by visit for Study RA-2 is shown in Figure 1. ACR 20 responses were observed in 38% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.

Table 2. Studies RA-1, RA-2, and RA-3 Proportion of Patients with an ACR Response[a]

	Study RA-1 Active RA previously treated with one or more doses of TNF-blockers		**Study RA-2 Active RA, despite MTX**		**Study RA-3 Active RA, MTX Naïve**	
	Placebo ± DMARDs[b]	SIMPONI 50 mg ± DMARDs[b]	Background MTX	SIMPONI 50 mg + Background MTX	MTX	SIMPONI 50 mg + MTX
N[c]	155	153	133	89	160	159
ACR 20						
Week 14	18%	35%	33%	55%	NA	NA
Week 24	17%	34%	28%	60%	49%	62%
ACR 50						
Week 14	6%	16%	10%	35%	NA	NA
Week 24	5%	18%	14%	37%	29%	40%
ACR 70						
Week 14	2%	10%	4%	13%	NA	NA
Week 24	3%	12%	5%	20%	16%	24%[d]

a Approximately 78% and 58% of the patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and NSAIDs, respectively, during the 3 pooled RA trials.
b DMARDs in Study RA-1 included MTX, HCQ, and/or SSZ (about 68%, 8%, and 5% of patients received MTX, HCQ,and SSZ, respectively).
c N reflects randomized patients.
d Not significantly different from MTX monotherapy.
NA Not applicable, as data was not collected at Week 14 in Study RA-3.

Table 3. Study RA-2 — Median Percent Improvement from Baseline in the Individual ACR Components at Weeks 14[a]

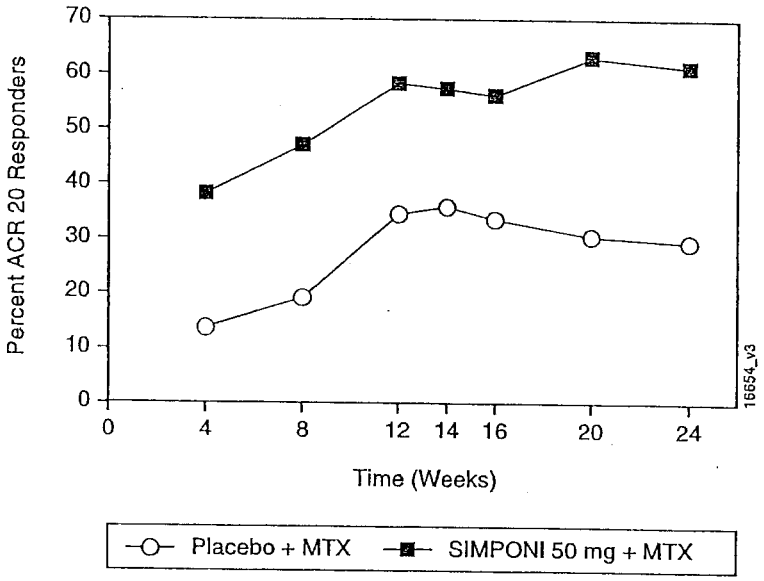
	Background MTX	SIMPONI 50 mg + Background MTX
N[b]	133	89
Number of swollen joints (0-66)		
Baseline	12	13
Week 14	38%	62%
Number of tender joints (0-68)		
Baseline	21	26
Week 14	30%	60%
Patient's assessment of pain (0-10)		
Baseline	5.7	6.1
Week 14	18%	55%
Patient's global assessment of disease activity (0-10)		
Baseline	5.3	6.0
Week 14	15%	45%
Physician's global assessment of disease activity (0-10)		
Baseline	5.7	6.1
Week 14	35%	55%
HAQ score (0-3)		
Baseline	1.25	1.38
Week 14	10%	29%
CRP (mg/dl)		
Baseline	0.8	1.0
Week 14	2%	44%

Note: Baseline values are medians.

a In Study RA-2, about 70% and 85% of patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs during the trials, respectively.

b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.

Figure 1. Study RA- 2 — Percent of Patients Achieving ACR 20 Response by Visit: Randomized Patients*



* The same patients may not have responded at each timepoint.

Physical Function Response in Patients with RA

In Studies RA-1 and RA-2, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24: 0.25 vs. 0.05 in RA-1, 0.47 vs. 0.13 in RA-2, respectively. Also in Studies RA-1 and RA-2, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at Week 24: 44% vs. 28%, 65% vs. 35%, respectively.

14.2 Psoriatic Arthritis

The safety and efficacy of SIMPONI were evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite NSAID or DMARD therapy (Study PsA). Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Previous treatment with a biologic TNF-blocker was not allowed. Patients were randomly assigned to placebo (n = 113), SIMPONI 50 mg (n = 146), or SIMPONI 100 mg (n = 146) given subcutaneously every 4 weeks. Patients were allowed to receive stable doses of concomitant MTX (≤ 25 mg/week), low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). The median duration of

PsA disease was 5.1 years, 78% of patients received at least one DMARD in the past, and approximately 48% of patients received MTX, and 16% received low dose oral steroids.

Clinical Response in Patients with PsA

SIMPONI ± MTX, compared with placebo ± MTX, resulted in significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ACR 20 response at Week 14 in Study PsA (see Table 4). There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). ACR responses observed in the SIMPONI-treated groups were similar in patients receiving and not receiving concomitant MTX. Similar ACR 20 responses at Week 14 were observed in patients with different PsA subtypes. However, the number of patients with arthritis mutilans was too small to allow meaningful assessment. SIMPONI 50 mg treatment also resulted in significantly greater improvement compared with placebo for each ACR component in Study PsA (Table 5). Treatment with SIMPONI resulted in improvement in enthesitis and skin manifestations in patients with PsA. However, the safety and efficacy of SIMPONI in the treatment of patients with plaque psoriasis has not been established.

The percent of patients achieving ACR 20 responses by visit for Study PsA is shown in Figure 2. ACR 20 responses were observed in 31% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.

Table 4. Study PsA - Proportion of Patients with ACR Responses

	Placebo ± MTX[a]	**SIMPONI 50 mg ± MTX[a]**
N[b]	113	146
ACR 20		
Week 14	**9 %**	**51 %**
Week 24	12 %	52 %
ACR 50		
Week 14	2 %	30 %
Week 24	4 %	32 %
ACR 70		
Week 14	1 %	12 %
Week 24	1 %	19 %

a In Study PsA, about 48%, 16%, and 72% of the patients received stable doses of MTX (≤ 25 mg/day), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively.
b N reflects randomized patients.
Bold text indicates primary endpoint

Table 5. Study PsA - Percent Improvement in ACR Components at Week 14

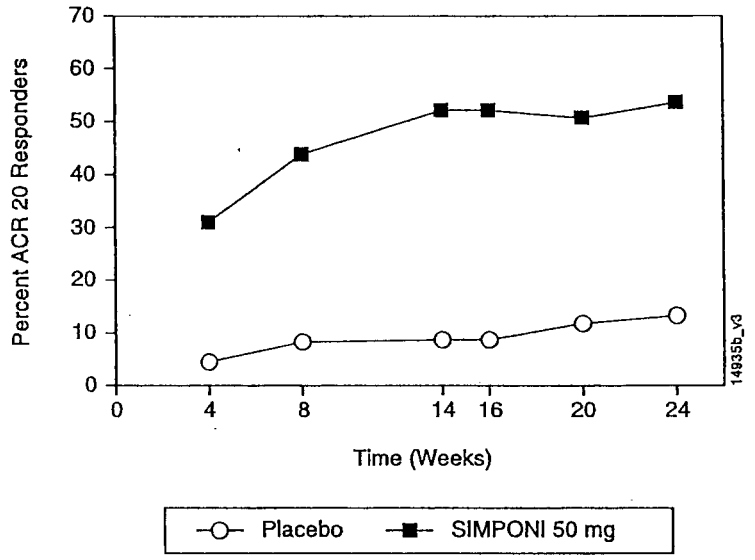
	Placebo± MTX[a]	SIMPONI 50 mg ± MTX[a]
N[b]	113	146
Number of swollen joints (0-66)		
Baseline	10.0	11.0
Week 14	8 %	60 %
Number of tender joints (0-68)		
Baseline	18.0	19.0
Week 14	0 %	54 %
Patient's assessment of pain (0-10)		
Baseline	5.4	5.8
Week 14	-1 %	48 %
Patient's global assessment of disease activity (0-10)		
Baseline	5.2	5.2
Week 14	2 %	49 %
Physician's global assessment of disease activity (0-10)		
Baseline	5.2	5.4
Week 14	7 %	59 %
HAQ score (0-10)		
Baseline	1.0	1.0
Week 14	0 %	28 %
CRP (mg/dL) (0-10)		
Baseline	0.6	0.6
Week 14	0 %	40 %

Note: Baseline are median values

a In Study PsA, about 48%, 16%, and 78% of the patients received stable doses of MTX (≤ 25 mg/day), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively.

b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint

Figure 2. Study PsA – Percent of ACR 20 PsA Responders by Visit: Randomized Patients*



* The same patients may not have responded at each timepoint.

Physical Function Response in Patients with PsA
In Study PsA, SIMPONI 50 mg demonstrated a greater improvement compared to placebo in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24 (0.33 and -0.01, respectively). In addition, the SIMPONI 50 mg group compared to the placebo group had a greater proportion of HAQ responders ($\geq$ 0.3 change from baseline) at Week 24: 43% vs. 22%, respectively.

14.3 Ankylosing Spondylitis

The safety and efficacy of SIMPONI were evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in 356 adult patients with active ankylosing spondylitis according to modified New York criteria for at least 3 months (Study AS). Patients had symptoms of active disease [defined as a Bath AS Disease Activity Index (BASDAI) $\geq$ 4 and VAS for total back pain of $\geq$ 4, on scales of 0 to 10 cm] despite current or previous NSAID therapy. Patients were excluded if they were previously treated with a biologic TNF-blocker or if they had complete ankylosis of the spine. Patients were randomly assigned to placebo (n = 78), SIMPONI 50 mg (n = 138), or SIMPONI 100 mg (n = 140) administered subcutaneously every 4 weeks. Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), low dose corticosteroids (equivalent to < 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint was the percentage of patients achieving an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

In Study AS, the median duration of AS disease was 5.6 years, median duration of inflammatory back pain was 12 years, 83% were HLA-B27 positive, 24% had prior joint surgery or procedure, and 55% received at least one DMARD in the past. During the trial, the use of concomitant DMARDs and/or NSAIDs was as follows: MTX (20%), SSZ (26%), HCQ (1%), low dose oral steroids (16%), and NSAIDs (90%).

Clinical Response in Patients with AS

In Study AS, SIMPONI ± DMARDs treatment, compared with placebo ± DMARDs, resulted in a significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ASAS 20 response at Week 14 (see Table 6). There was no clear evidence of improved ASAS response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). Table 7 shows the percent improvement in the components of the ASAS response criteria for the SIMPONI 50 mg ± DMARDs and placebo ± DMARDs groups in Study AS.

The percent of patients achieving ASAS 20 responses by visit for Study AS is shown in Figure 3. ASAS 20 responses were observed in 48% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.

Table 6. Study AS – Proportion of ASAS Responders at Weeks 14 and 24

	Placebo ± DMARDs[a]	**SIMPONI 50 mg ± DMARDs[a]**
N[b]	78	138
Responders, % of patients		
ASAS 20		
Week 14	22%	**59%**
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%

a During the trial, the concomitant use of stable doses of DMARDS was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively.

b N reflects randomized patients.

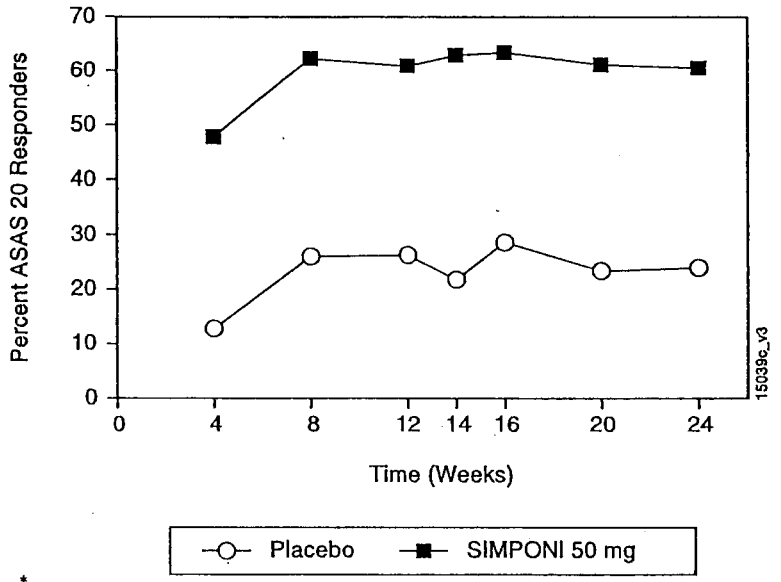
Bold text indicates primary endpoint

Table 7. Study AS — Median Percent Improvement in ASAS Components at Week 14

	Placebo ± DMARDs[a]	SIMPONI 50 mg ± DMARDs[a]
N[b]	78	138
ASAS components		
Patient global assessment (0-10)		
Baseline	7.2	7.0
Week 14	13%	47%
Total back pain (0-10)		
Baseline	7.6	7.5
Week 14	9%	50%
BASFI (0-10)[c]		
Baseline	4.9	5.0
Week 14	-3%	37%
Inflammation (0-10)[d]		
Baseline	7.1	7.1
Week 14	6%	59%

a During the trial, the concomitant use of stable doses of DMARDS was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively.
b N reflects randomized patients
c BASFI is Bath Ankylosing Spondylitis Functional Index
d Inflammation is the mean of two patient-reported stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI)

Figure 3. Study AS – Percent of AS Patients Achieving ASAS 20 Response by Visit: Randomized Patients*



* The same patients may not have responded at each timepoint.

15.0 REFERENCES

1. SEER [database online]. US Population Data – 1969-2004. Bethesda, MD: National Cancer Institute. Release date: January 3, 2007. Available at: http//seer.cancer.gov/popdata/.

16.0 HOW SUPPLIED/STORAGE AND HANDLING

Each SIMPONI prefilled autoinjector or prefilled syringe is packaged in a light-blocking, cardboard outer carton. SIMPONI is available in packs of 1 prefilled syringe NDC 57894-070-01 or 1 prefilled SmartJect autoinjector NDC 57894-070-02.

Prefilled SmartJect Autoinjector

Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge ½ inch) providing 50 mg of SIMPONI per 0.5 mL of solution.

Prefilled Syringe

Each single dose prefilled glass syringe (27 gauge ½ inch) contains 50 mg of SIMPONI per 0.5 mL of solution.

Storage and Stability

SIMPONI must be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI beyond the expiration date (EXP) on the carton or the expiration date on the prefilled syringe (observed through the viewing window) or the prefilled SmartJect autoinjector.

17.0 PATIENT COUNSELING INFORMATION

See Medication Guide (17.3)

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of SIMPONI. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI therapy and to read it each time the prescription is renewed.

Infections

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

Malignancies

Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI.

Allergic Reactions

Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect autoinjector contains dry natural rubber (a derivative of latex).

Other Medical Conditions
Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

17.2 Instruction on Injection Technique
The first self-injection should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer SIMPONI, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of SIMPONI [*see Medication Guide (17.3)*].

Prior to use, remove the prefilled syringe or the prefilled SmartJect autoinjector from the refrigerator and allow SIMPONI to sit at room temperature outside of the carton for 30 minutes and out of the reach of children.

Do not warm SIMPONI in any other way. For example, do not warm SIMPONI in a microwave or in hot water.

Do not remove the prefilled syringe needle cover or SmartJect autoinjector cap while allowing SIMPONI to reach room temperature. Remove these immediately before injection.

Do not pull the autoinjector away from the skin until you hear a first "click" sound and then a second "click" sound (the injection is finished and the needle is pulled back). It usually takes about 3 to 6 seconds but may take up to 15 seconds for you to hear the second "click" after the first "click." If the autoinjector is pulled away from the skin before the injection is completed, a full dose of SIMPONI may not be administered.

A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique of proper syringe and needle disposal, and be advised not to reuse these items.

17.3 Medication Guide
Rx Only

MEDICATION GUIDE
SIMPONI™ (SIM-po-nee)
(golimumab)

Read the Medication Guide that comes with SIMPONI before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. It is important to remain under your doctor's care while using SIMPONI.

What is the most important information I should know about SIMPONI?
SIMPONI is a medicine that affects your immune system. SIMPONI can lower the ability of your immune system to fight infections. Some people have serious infections while taking SIMPONI, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that spread throughout their body. Some people have died from these serious infections.

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

You should not start taking SIMPONI if you have any kind of infection unless your doctor says it is okay.

Before starting SIMPONI, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB
- live, have lived, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become more severe if you use SIMPONI. Ask your doctor, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B

- use the medicine Orencia (abatacept), Kineret (anakinra), or Rituxan (rituximab)

After starting SIMPONI, call your doctor right away if you have any symptoms of an infection. SIMPONI can make you more likely to get infections or make worse any infection that you have.

What is SIMPONI?
SIMPONI is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. SIMPONI is used in adults:

- with the medicine methotrexate to treat moderately to severely active rheumatoid arthritis (RA)
- to treat active psoriatic arthritis (PsA) alone or with methotrexate
- to treat active ankylosing spondylitis (AS)

You may continue to use other medicines that help treat your condition while taking SIMPONI, such as non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your doctor.

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

- have an infection (see "What is the most important information I should know about SIMPONI?").
- have or have had lymphoma or any other type of cancer.
- have or had heart failure.
- have or have had a condition that affects your nervous system, such as multiple sclerosis.
- have recently received or are scheduled to receive a vaccine. People taking SIMPONI should not receive live vaccines. People taking SIMPONI can receive non-live vaccines.
- are allergic to rubber or latex. The needle cover on the prefilled syringe and SmartJect autoinjector contains dry natural rubber.
- are pregnant or planning to become pregnant. It is not known if SIMPONI will harm your unborn baby.
- are breastfeeding. You and your doctor should decide if you will take SIMPONI or breastfeed. You should not do both without talking to your doctor first.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially, tell your doctor if you use:

- ORENCIA (abatacept), KINERET (anakinra), or RITUXAN (rituximab). You should not take SIMPONI while you are also taking ORENCIA or KINERET. Your doctor may not want to give you SIMPONI if you have received RITUXAN recently.
- Another TNF-blocker medicine. You should not take SIMPONI while you are also taking REMICADE (infliximab), HUMIRA (adalimumab), ENBREL (etanercept), or CIMZIA (certolizumab pegol).

Ask your doctor if you are not sure if your medicine is one listed above.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine.

How should I use SIMPONI?

- SIMPONI is given as an injection under the skin (subcutaneous injection or SC).
- SIMPONI should be injected one time each month.
- If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI. Do not try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.
- Use SIMPONI exactly as prescribed by your doctor.
- SIMPONI comes in a prefilled syringe or SmartJect™ autoinjector. Your doctor will prescribe the type that is best for you.
- See the detailed ***Patient Instructions for Use*** at the end of this Medication Guide for instructions about the right way to prepare and give your SIMPONI injections at home.
- Do not miss any doses of SIMPONI. If you forget to use SIMPONI, inject your dose as soon as you remember. Then, take your next dose at your regular scheduled time. In case you are not sure when to inject SIMPONI, call your doctor or pharmacist.

What are the possible side effects with SIMPONI?

SIMPONI can cause serious side effects including:

Serious Infections

(See **"What is the most important information I should know about SIMPONI?"**).

Hepatitis B infection in people who carry the virus in their blood.

- If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use SIMPONI. Your doctor may do blood tests before you start treatment with SIMPONI and while you are using SIMPONI. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:

  - feel very tired
  - skin or eyes look yellow
  - little or no appetite
  - vomiting
  - muscle aches
  - dark urine
  - clay-colored bowel movements
  - fevers
  - chills
  - stomach discomfort
  - skin rash

Cancer

- People with inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, especially those with very active disease, may be more likely to get lymphoma.
- If you use SIMPONI or other TNF-blockers, your risk of getting lymphoma or other cancers may increase.

Heart failure, including new heart failure or worsening of heart failure that you already have.

New or worse heart failure can happen in people who use TNF-blocker medicines like SIMPONI.

- If you have heart failure, your condition should be watched closely while you take SIMPONI.
- Call your doctor right away if you get new or worsening symptoms of heart failure while taking SIMPONI (such as shortness of breath or swelling of your lower legs or feet).

Nervous System Problems
Rarely, people using TNF-blocker medicine have nervous system problems such as multiple sclerosis.
- Tell your doctor right away if you get any of these symptoms:
    - vision changes
    - weakness in your arms or legs
    - numbness or tingling in any part of your body

Liver Problems
Liver problems can happen in people who use TNF-blocker medicines, including SIMPONI. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
- feel very tired
- skin or eyes look yellow
- poor appetite or vomiting
- pain on the right side of your stomach (abdomen)

Blood Problems
Low blood counts have been seen with other TNF-blockers. Your body may not make enough blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding easily, or looking pale. Your doctor will check your blood counts before and during treatment with SIMPONI.

Common side effects with SIMPONI include:

- upper respiratory tract infection
- nausea
- abnormal liver tests
- redness at the site of injection
- high blood pressure
- bronchitis
- dizziness
- sinus infection (sinusitis)
- flu
- runny nose
- fever
- cold sores
- numbness or tingling

Other side effects with SIMPONI include:
- **Immune System Problems.** Rarely, people using TNF-blocker medicines have developed symptoms that are like the symptoms of Lupus. Tell your doctor if you have any of these symptoms:
    - a rash on your cheeks or other parts of the body
    - sensitivity to the sun
    - new joint or muscle pains
    - becoming very tired
    - chest pain or shortness of breath

- swelling of the feet, ankles, and/or legs

- **Psoriasis.** Some people using TNF-blocker medicines including SIMPONI had new psoriasis or worsening of psoriasis that they already had. Symptoms of psoriasis include: red scaly patches or raised bumps that are filled with pus on the skin. Psoriasis may go away or get better after stopping SIMPONI in some people.

- **Allergic Reactions.** Allergic reactions can happen in people who use TNF-blocker medicines. Call your doctor right away if you have any of these symptoms of an allergic reaction:
  - hives
  - swollen face
  - breathing trouble
  - chest pain

These are not all of the side effects with SIMPONI. Tell your doctor about any side effect that bothers you or does not go away. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How do I store SIMPONI?
- Refrigerate SIMPONI at 36°F to 46°F (2°C to 8°C).
- Do not freeze SIMPONI.
- Keep SIMPONI in the carton to protect it from light when not being used.
- Do not shake SIMPONI.

Keep SIMPONI and all medicines out of the reach of children.

General Information about SIMPONI
- Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use SIMPONI for a condition for which it was not prescribed.
- Do not give SIMPONI to other people, even if they have the same condition that you have. It may harm them.
- This Medication Guide summarizes the most important information about SIMPONI. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SIMPONI that is written for health professionals. For more information go to www.simponi.com or call 1-800-457-6399.

What are the ingredients in SIMPONI?
Active ingredient: golimumab.
Inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sorbitol, polysorbate 80, and water for injection. SIMPONI does not contain preservatives.

Patient Instructions for Use
SIMPONI™ (SIM-po-nee)
(golimumab)
SmartJect™ autoinjector

If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI. **Do not** try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.

It is important to read, understand, and follow these instructions so that you inject SIMPONI the right way. Call your doctor if you or your caregiver has any questions about the right way to inject SIMPONI.

Important information about your SmartJect autoinjector:

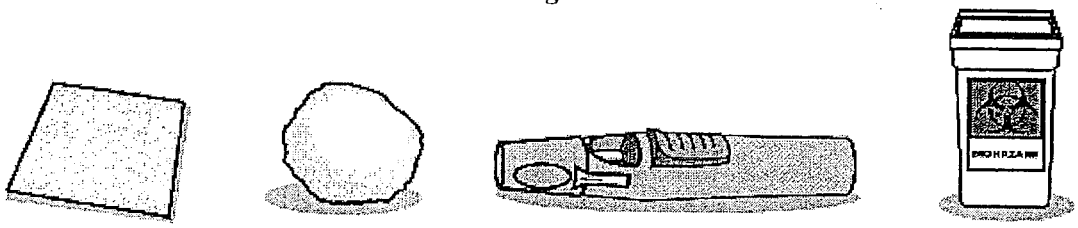
- When the button on the SmartJect autoinjector is pressed to give the dose of SIMPONI you will hear a loud 'click' sound. It is very important that you practice injecting SIMPONI with your doctor or nurse so that you are not startled by this click when you start giving the injections to yourself at home.
- If you pull the SmartJect autoinjector away from the skin before the injection is completed, you may not get your full dose of medicine and may lose some of the medicine.

Do not:
- shake the SmartJect autoinjector at any time
- remove the SmartJect autoinjector cap until you get to that step

Step 1: Gather and inspect the supplies for your injection

You will need these supplies for an injection of SIMPONI. See Figure 1.
- 1 alcohol swab
- 1 cotton ball or gauze
- 1 SIMPONI prefilled SmartJect autoinjector
- sharps container for autoinjector disposal

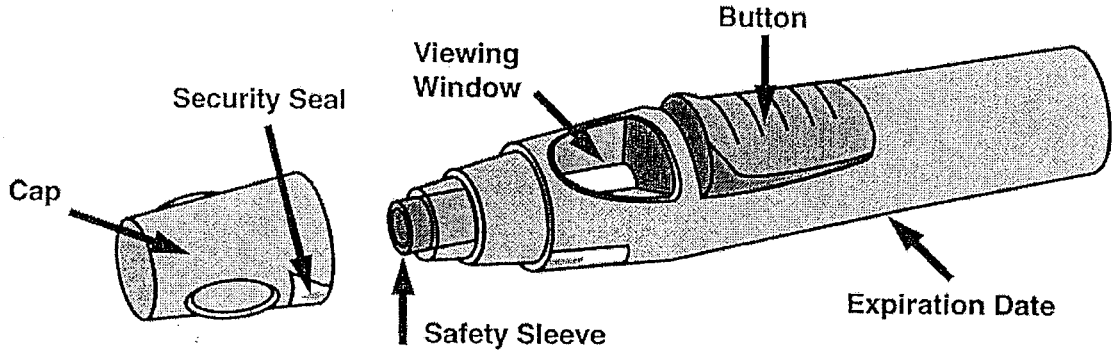
Figure 1



1 alcohol swab | 1 cotton ball or gauze | 1 SIMPONI single use SmartJect autoinjector | sharps container for syringe disposal

The figure below shows what the SmartJect autoinjector looks like. See Figure 2.

Figure 2



1.1 Check Expiration Date

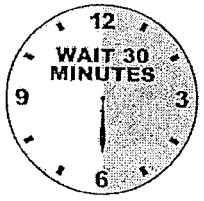
- Check the expiration date ("EXP") on the SmartJect autoinjector.
- You can also check the expiration date printed on the carton.
- If the expiration date has passed, do not use the SmartJect autoinjector. Call your doctor or pharmacist, or call 1-800-457-6399 for help.

1.2 Check Security Seal

- Check the security seal around the cap of the SmartJect autoinjector. If the security seal is broken, do not use the SmartJect autoinjector.

1.3 Wait 30 minutes

- To ensure proper injection, allow the autoinjector to sit at room temperature outside the carton for 30 minutes and out of the reach of children.

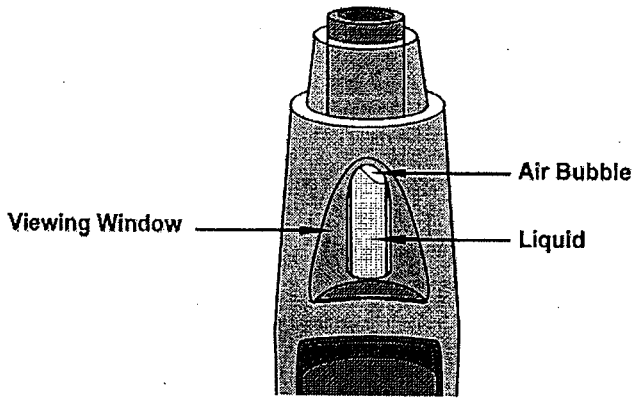


Do not warm the SmartJect autoinjector in any other way (For example, **do not** warm it in a microwave or in hot water).
Do not remove the SmartJect autoinjector cap while allowing it to reach room temperature.

1.4 Check the Liquid in the SmartJect autoinjector

- Look through the viewing window of the SmartJect autoinjector. See Figure 3. Make sure that the liquid in the prefilled syringe is clear and colorless to slightly yellow in color. You may see a small amount of tiny particles that are white, or that you can see through. Do not inject the liquid if it is cloudy or discolored, or has large particles in it.
- You may also notice an air bubble. This is normal. See Figure 3.

Figure 3

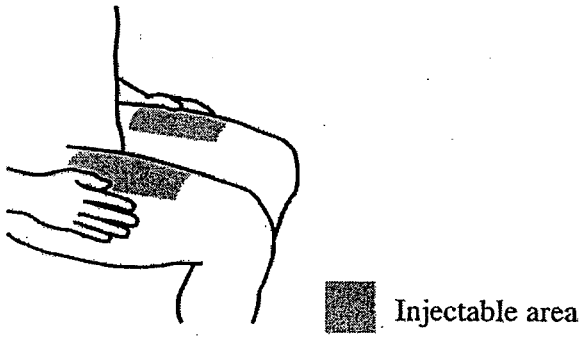


Step 2: Choose and prepare the injection site

2.1 Choose the Injection Site

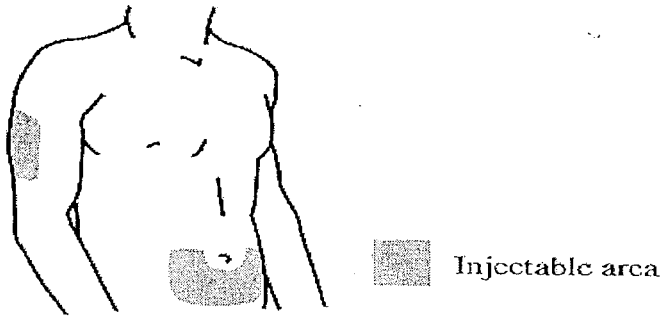
- The recommended injection site is the front of your middle thighs. See Figure 4.

Figure 4



- You can also use the lower part of the abdomen below the navel (belly button), except for the two-inch area directly around the navel. See Figure 5.
- If a caregiver is giving you the injection, the outer area of the upper arms may also be used. See Figure 5.

Figure 5



- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks.

2.2 Prepare the Injection Site

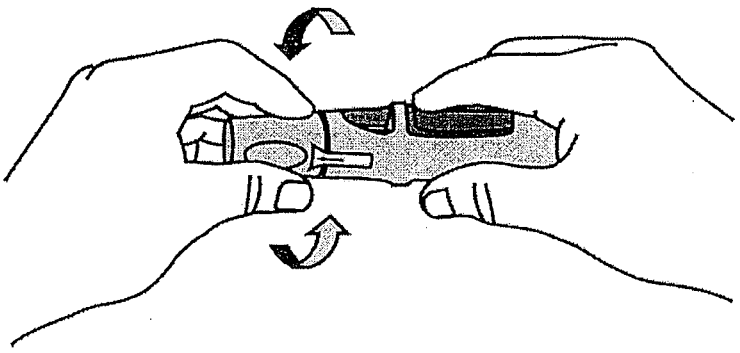
- Wash your hands well with soap and warm water.
- Wipe the injection site with an alcohol swab.
- **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting.
- **Do not** fan or blow on the clean area.

Step 3: Injecting SIMPONI using the single dose SmartJect autoinjector

3.1 Remove the Cap

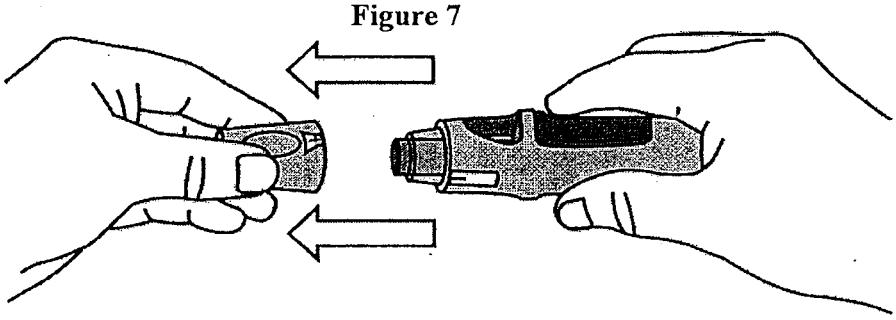
- Do not remove the cap until you are ready to inject SIMPONI. Inject SIMPONI within 5 minutes after the cap has been removed.
- When you are ready to inject, twist the cap slightly to break the security seal. See Figure 6.

Figure 6



- Pull the cap off and throw it in the trash right away. See Figure 7.

Figure 7

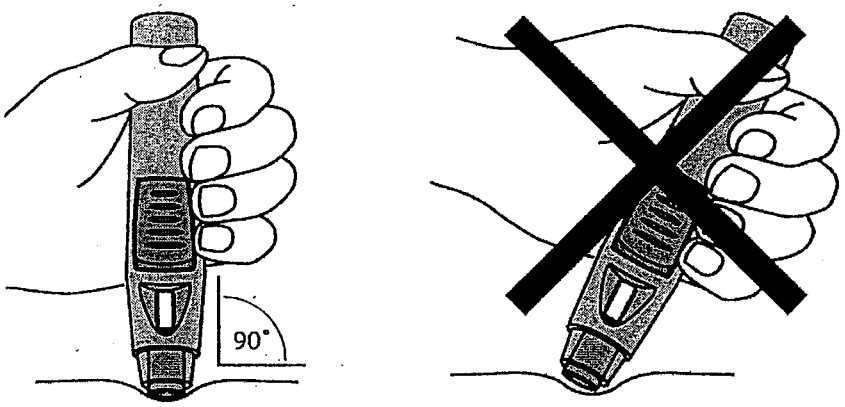


- **Do not** put the cap back on because it may damage the needle inside the SmartJect autoinjector.
- **Do not** use your SmartJect autoinjector if it is dropped without the cap in place.

3.2 Push the SmartJect autoinjector against the skin

- Hold the SmartJect autoinjector comfortably in your hand.
- Do not press the button. Push the open end of the SmartJect autoinjector firmly against the skin at **90-degree angle.** See Figure 8.

Figure 8



- **Use your** free hand to pinch and hold the skin at the injection site. This may make injecting easier.

3.3 Press button to inject

- Continue to hold the SmartJect autoinjector firmly against the skin, and press the button with your fingers (see Figure 9) or thumb (see Figure 10). You will not be able to push in the button unless the SmartJect autoinjector is pushed firmly against your skin.

Figure 9

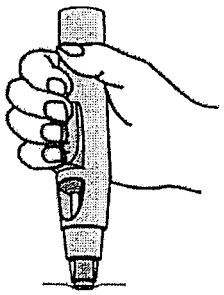
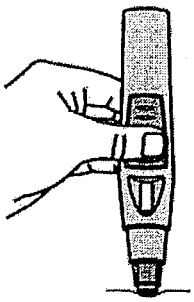
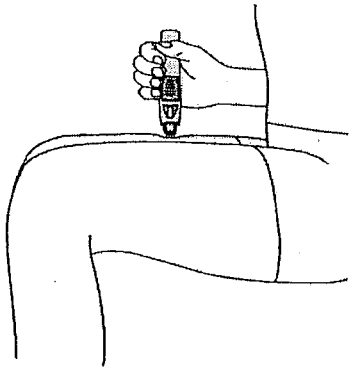


Figure 10



- After the button is pressed, it will stay pressed in so you do not need to keep pressure on it. See Figure 11.

Figure 11

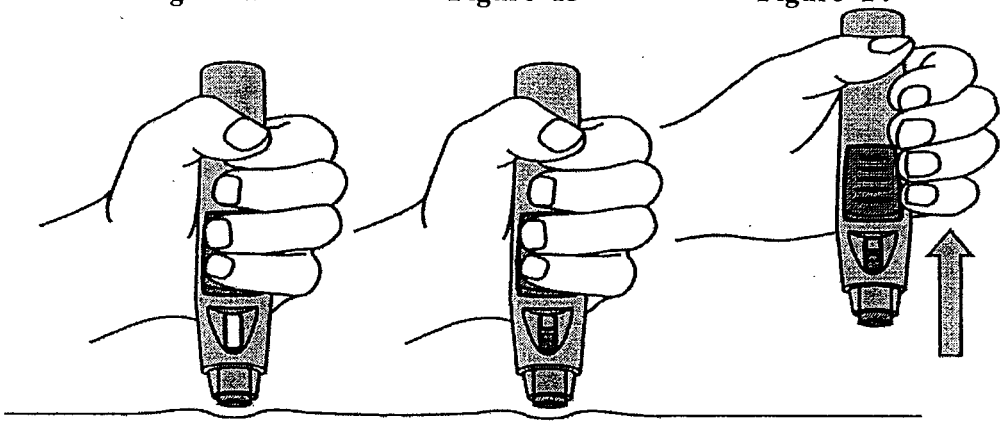


- You will hear a loud 'click' sound. This means that the injection has started. Do not pull the SmartJect autoinjector away from your skin. If you pull the SmartJect autoinjector away from the skin, you may not get your full dose of medicine. See Figure 12.
- **Do not** lift the SmartJect autoinjector yet.

3.4 Wait for Second "Click"

- Keep holding the SmartJect autoinjector against your skin until you hear the second 'click' sound. It usually takes about 3 to 6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound. See Figure 13.
- The second 'click' sound means that the injection is finished and the needle has pulled back (retracted) into the SmartJect autoinjector.
- Lift the SmartJect autoinjector from the injection site. See Figure 14.
- If you have hearing problems, count for 15 seconds from the time you pressed the button and then lift the SmartJect autoinjector from the injection site.

Figure 12 Figure 13 Figure 14

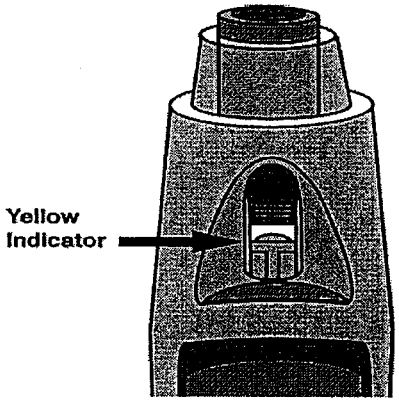


Step 4: After the injection

4.1 Check the Viewing Window

- After you finish injecting, check the viewing window to see the yellow indicator. See Figure 15. This means the SmartJect autoinjector has worked the right way.

Figure 15

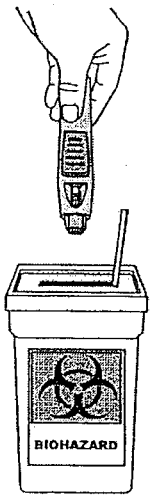


- If you do not see the yellow indicator in the viewing window, call 1-800-457-6399 for help.

4.2 Dispose of the used SmartJect autoinjector

- Place the used SmartJect autoinjector into a closable 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). See Figure 16.

Figure 16



- Ask your doctor for instructions on the right way to throw away (dispose of) the container. There may be local or state laws about how you should throw away used needles and syringes.
- Do not throw away your used SmartJect autoinjector in household trash. Do not recycle.

4.3 Use Cotton Ball or Gauze

- There may be a small amount of blood or liquid at the injection site, which is normal.
- You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site.
- You may cover the injection site with a small adhesive bandage, if needed.

Patient Instructions for Use
SIMPONI™
Prefilled Syringe

If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI. **Do not** try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.

It is important to read, understand, and follow these instructions so that you inject SIMPONI the right way. Call your doctor if you or your caregiver has any questions about the right way to inject SIMPONI.

Important information about your prefilled syringe:

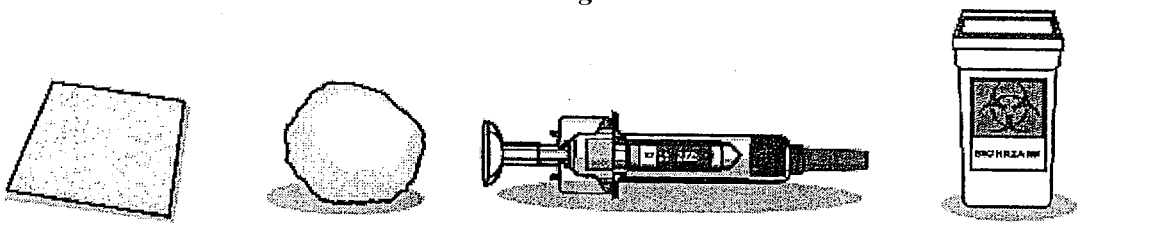
- Always hold the prefilled syringe by the body of the syringe.

Do not:
- pull back on the plunger at any time.
- shake the SIMPONI prefilled syringe. This may damage the medicine.
- remove the needle cover from the prefilled syringe until you get to that step.
- touch the needle guard activation clips to prevent covering the needle with the needle guard too soon (See Figure 2).
- use SIMPONI if it has been frozen or if it has been kept at a room temperature that is too warm. See the Medication Guide section: "How should I store SIMPONI?"
- use your SIMPONI prefilled syringe if it looks damaged.

Step 1: Gather the supplies for your injection

You will need these supplies for an injection of SIMPONI. See Figure 1.
- 1 alcohol swab
- 1 cotton ball or gauze
- 1 SIMPONI prefilled syringe
- sharps container for syringe disposal

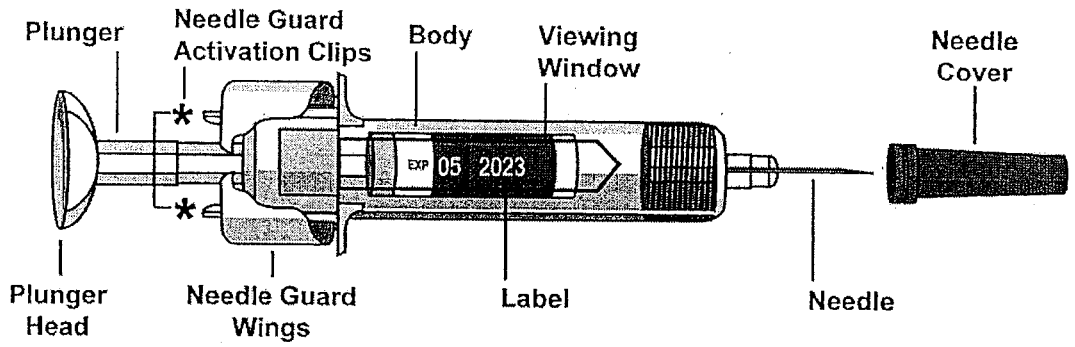
Figure 1



1 alcohol swab | 1 cotton ball or gauze | 1 SIMPONI prefilled syringe | sharps container for syringe disposal

The diagram below shows what the prefilled syringe looks like. See Figure 2.

Figure 2

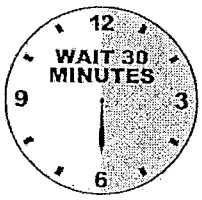


Step 2: Get ready to use your prefilled syringe

2.1 Check the Expiration Date

- Look for the expiration date printed on the back panel of the SIMPONI carton.
- **If the expiration date has passed, do not use the prefilled syringe. Call your doctor** or pharmacist or call 1-800-457-6399 for help.

2.2 Wait 30 minutes

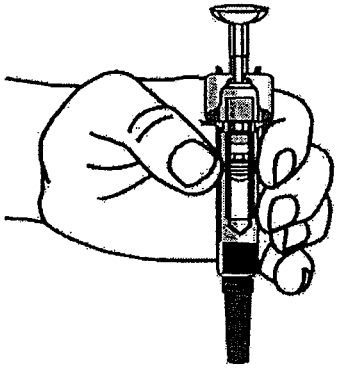


- To ensure proper injection, allow the prefilled syringe to sit at room temperature outside of the carton for 30 minutes and out of the reach of children.
- **Do not** warm the prefilled syringe in any other way (For example, **Do not** warm it in a microwave or in hot water).
- **Do not** remove the prefilled syringe needle cover while allowing it to reach room temperature.

2.3 Check the Liquid in the Prefilled Syringe

- Hold your SIMPONI prefilled syringe by the body with the covered needle pointing down. See Figure 3.

Figure 3



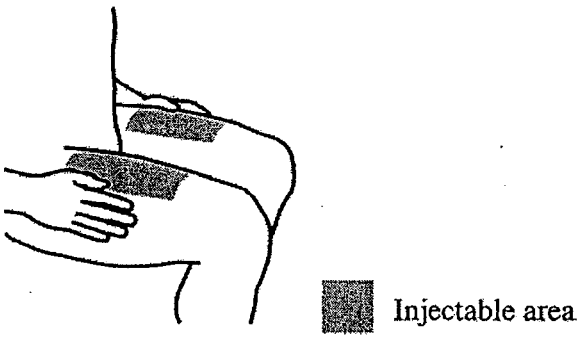
- Look at the liquid through the viewing window of the prefilled syringe. Make sure that the liquid in the prefilled syringe is clear and colorless to slightly yellow in color. You may see a small amount of tiny particles that are white, or that you can see through. Do not inject the liquid if it is cloudy or discolored, or has large particles in it.
- You may also see an air bubble. This is normal.

Step 3: Choose and prepare the injection site

3.1 Choose the Injection Site

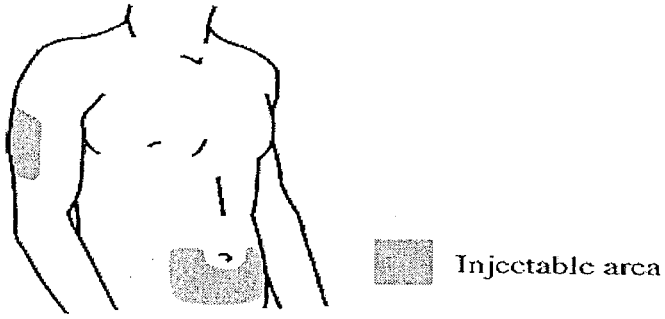
- The recommended injection site is the front of your middle thighs. See Figure 4.

Figure 4



- You can also use the lower part of the abdomen below the navel (belly button), except for the two-inch area directly around the navel. See Figure 5.
- If a caregiver is giving you the injection, the outer area of the upper arms may also be used. See Figure 5.

Figure 5



Do not inject into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks.

3.2 Prepare the Injection Site

- Wash your hands well with soap and warm water.
- Wipe the injection site with an alcohol swab.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

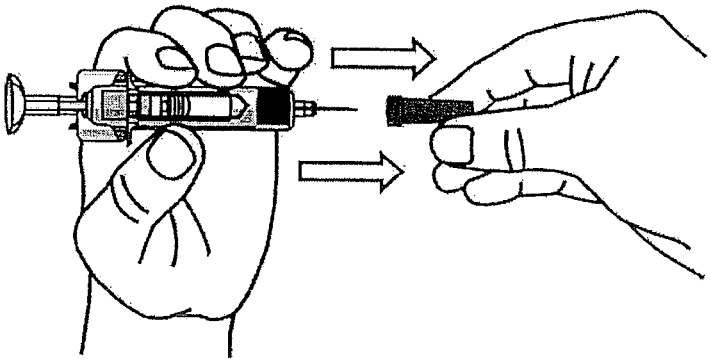
Step 4: Inject SIMPONI

Do not remove the needle cover until you are ready to inject SIMPONI. Inject SIMPONI within 5 minutes after you remove the needle cover.

4.1 Remove the Needle Cover

- **Do not** touch the plunger while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. See Figure 6.

Figure 6

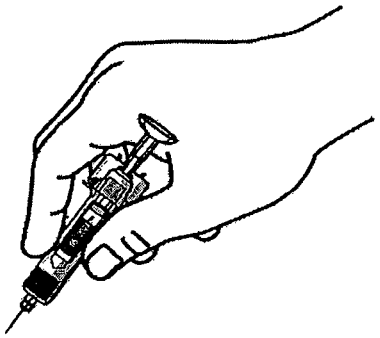


- Put the needle cover in the trash.
- You may see an air bubble in the prefilled syringe. This is normal.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch any surface.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place.

4.2 Position the prefilled syringe and inject SIMPONI

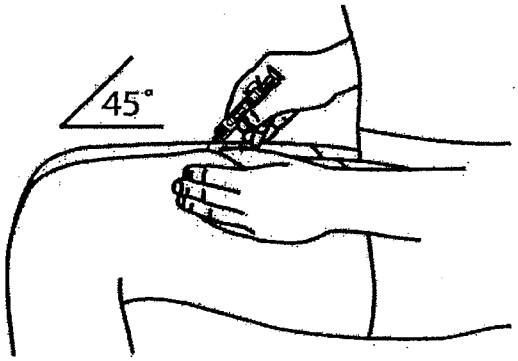
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. See Figure 7.

Figure 7



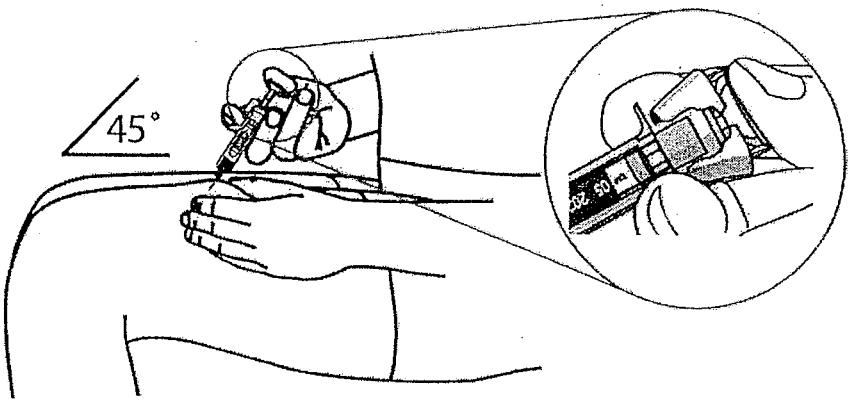
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the area of skin that you previously cleaned. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a **45-degree angle.** See Figure 8.

Figure 8



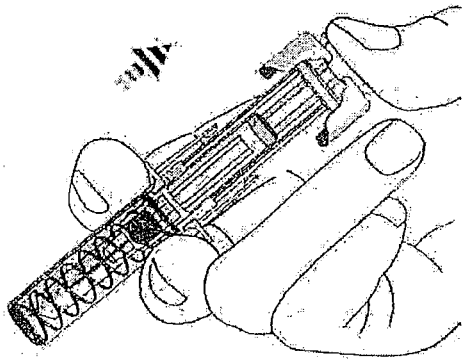
- Inject all of the medicine by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. See Figure 9.

Figure 9



- When the plunger is pushed as far as it will go, keep pressure on the plunger head. Take the needle out of the skin and let go of the skin.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard. See Figure 10.

Figure 10

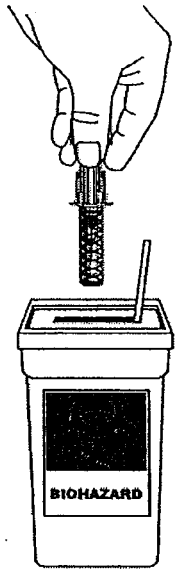


Step 5: After the injection

5.1 Dispose of the used prefilled syringe

- Place the used prefilled syringe in a closable 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). For the safety and health of you and others, needles and used syringes **must never** be re-used. See Figure 11.

Figure 11



- Ask your doctor for instructions on the right way to throw away (dispose of) the container. There may be local or state laws about how you should throw away used needles and syringes.
- Do not throw away your used prefilled syringe in household trash. Do not recycle.

5.2 Use Cotton Ball or Gauze

- There may be a small amount of blood or liquid at the injection site, which is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds. Do not rub the injection site.
- You may cover the injection site with a small adhesive bandage, if needed.

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US License No. 1821

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