1 NAME OF THE MEDICINAL PRODUCT

montelukast cinfa 4 mg chewable tablets EFG
montelukast cinfa 5 mg chewable tablets EFG

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 mg montelukast cinfa tablet contains 4 mg of montelukast (as 4.16 mg of montelukast sodium).
Excipient: Each tablet contains 1.2 mg of aspartame (E951).

Each 5 mg montelukast cinfa tablet contains 5 mg of montelukast (as 5.20 mg of montelukast sodium).
Excipient: Each tablet contains 1.5 mg of aspartame (E951).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
montelukast cinfa 4 mg chewable tablets EFG
Reddish, cylindrical, biconvex tablets with MO3 on one side.

montelukast cinfa 5 mg chewable tablets EFG
Reddish, cylindrical, biconvex tablets with MO2 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Montelukast is indicated for the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma not adequately controlled with inhaled corticosteroids and in whom "as needed" short-acting β-agonists do not give adequate clinical control of asthma.

montelukast can also be used as an alternative to low-dose inhaled corticosteroids in patients with mild persistent asthma, in the absence of a recent history of severe asthma attacks requiring oral corticosteroids, who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.2).

montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

montelukast cinfa 4 mg chewable tablets EFG
This medicine must be administered to children under adult supervision. For children who have problems taking a chewable tablet, an oral granule formulation is available (see the Summary of Product Characteristics of montelukast 4 mg granules).
The dose for children between 2 and 5 years of age is one 4 mg chewable tablet daily to be taken in the evening. As regards food intake, montelukast should be taken 1 hour before or 2 hours after meals. No dose adjustment is required in this age group.
montelukast cinfa 5 mg chewable tablets EFG

The dose for children between 6 and 14 years of age is one 5 mg chewable tablet daily to be taken in the evening. As regards food intake, montelukast 5 mg should be taken 1 hour before or 2 hours after meals. No dose adjustment is required in this age group.

The montelukast 4 mg chewable tablet formulation is not recommended in children under 2 years of age.

General recommendations. The therapeutic effect of montelukast on parameters of asthma control occurs within one day. Patients should be instructed to continue taking montelukast even if their asthma is under control, as well as during periods when their asthma is getting worse.

No dosage adjustment is necessary in patients with renal insufficiency or mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment. The dosage is the same for men and women.

montelukast *as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma:*
Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative to low-dose inhaled corticosteroids in patients with mild persistent asthma should only be considered for patients who do not have a recent history of severe asthma attacks that required the use of oral corticosteroids and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week and normal lung function between episodes. If adequate control of asthma is not achieved within about one month, the need for a different or additional anti-inflammatory treatment should be evaluated as recommended by the step system for asthma therapy. Patients should be periodically evaluated to assess whether their asthma in under control.

montelukast as prophylaxis of asthma in patients between 2 and 5 years of age when the predominant component is exercise-induced bronchoconstriction:
In patients between 2 and 5 years of age, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If a satisfactory response is not achieved, an additional or different treatment should be considered.

Treatment with montelukast in relation to other asthma treatments:
When montelukast is used as add-on therapy to inhaled corticosteroids, montelukast should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

For adults aged 15 years and over, a 10-mg film-coated tablet formulation is available.
For children aged 6 to 14 years, a 5-mg chewable tablet formulation is available.
For children aged 6 months to 5 years, a 4-mg oral granule formulation is available.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Patients should be instructed never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication accessible. In the event of an acute attack, a short-acting inhaled β-agonist should be used. Patients should seek medical advice as soon as possible if they need more inhalations than usual of a short-acting β-agonist.

Inhaled or oral corticosteroids should not be replaced suddenly by montelukast.

There are no data to show that oral corticosteroids can be reduced with concomitant administration of montelukast.

On rare occasions, patients treated with anti-asthmatic agents, including montelukast, may present with systemic eosinophilia, which sometimes presents clinical features of vasculitis, consistent with Churg-Strauss syndrome, a condition often treated with systemic corticosteroids. These cases generally, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with the onset of Churg-Strauss disease can be neither excluded nor confirmed. Doctors should be alert to whether their patients present with eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and/or neuropathy. Patients who develop these symptoms should be re-examined and their treatment regimens should be assessed.

Warnings on excipients:
This medicine may be harmful for people with phenylketonuria since it contains aspartame (E951), which is a source of phenylalanine. Each 4-mg chewable tablet contains phenylalanine in an amount equivalent to 0.67 mg of phenylalanine per dose.
Each 5-mg chewable tablet contains phenylalanine in an amount equivalent to 0.84 mg of phenylalanine per dose.

4.5 Interaction with other medicinal products and other forms of interaction

montelukast can be given with other treatments used systematically in the prophylaxis and chronic treatment of asthma. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinylestradiol/norethisterone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast decreased by about 40% in patients receiving phenobarbital at the same time. Since montelukast is metabolized by CYP 3A4, care should be taken, especially in children, when administering montelukast together with CYP 3A4 inducers, such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent CYP 2C8 inhibitor. However, data from a clinical drug-interaction study including montelukast and rosiglitazone (a test substrate representative of medicinal products primarily metabolized by CYP 2C8), showed that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore it is not anticipated that montelukast will noticeably alter the metabolism of medicinal products metabolized by this enzyme (e.g. paclitaxel, rosiglitazone and repaglinide).

4.6 Fertility, pregnancy and lactation

Use during pregnancy

Animal studies do not indicate harmful effects regarding the impact on pregnancy or the development of the embryo/foetus.

Limited information from available pregnancy databases does not suggest a causal relationship between montelukast administration and malformations (e.g. limb defects), which have been rarely reported in post-marketing experience worldwide.

montelukast may be used during pregnancy only if it is considered to be clearly essential.

Use during lactation

Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is not known whether montelukast is excreted in human milk.

montelukast may be used by breast-feeding mothers only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machines

montelukast is not expected to affect the patient's ability to drive a car or use machines. However, in very rare cases, individuals have reported cases of drowsiness or dizziness.

4.8 Undesirable effects

montelukast has been evaluated in clinical trials as specified below:
• 10-mg film-coated tablets in approximately 4,000 adult patients 15 years or over
• 5-mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age and
• 4-mg chewable tablets in 851 paediatric patients 2 to 5 years of age.

In clinical trials, the following treatment-related undesirable effects were commonly reported ($\geq$1/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

System organ class	**Adult patients 15 years and over (two 12-week trials; n=795)**	**Paediatric patients 6 to 14 years of age (one 8-week trial; n=201) (two 56-week trials; n=615)**	**Paediatric patients 2 to 5 years of age (one 12-week trial; n=461) (one 48-week trial; n=278)**
Nervous system disorders	headache	headache	
Gastrointestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

In clinical trials including a limited number of patients, the safety profile was evaluated with prolonged treatment of up to 2 years in adults and up to 12 months in paediatric patients between 6 and 14 years of age and no changes were observed.
Accumulatively, 502 paediatric patients between 2 and 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

The following undesirable effects have been reported post-marketing:
Infections and infestations: upper respiratory infection.
Blood and lymphatic system disorders: greater possibility of bleeding.
Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.
Psychiatric disorders: sleep disorders including nightmares, hallucinations, insomnia, sleepwalking, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, tremor, depression, suicidal thinking and behaviour (ideas of suicide) in very rare cases.
Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoaesthesia, seizures.
Cardiac disorders: palpitations.
Respiratory, thoracic and mediastinal disorders: epistaxis.
Gastrointestinal disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.
Hepatobiliary disorders: elevated levels of serum transaminases (ALT, AST), hepatitis (including cholestatic hepatitis, hepatocellular hepatitis and mixed-pattern liver injury).
Skin and subcutaneous tissue disorders: angioedema, bruising, urticaria, pruritus, rash, erythema nodosum.
Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.
General disorders and administration site conditions: asthenia/fatigue, malaise, oedema, pyrexia.
Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during treatment with montelukast in asthmatic patients (see section 4.4).

4.9 Overdose

No specific information is available on treatment of montelukast overdose. In chronic asthma trials, montelukast has been administered at doses of up to 200 mg/day to adults for 22 weeks, while short-term trials have administered doses of up to 900 mg/day to patients for about one week, with no clinically relevant undesirable effects.

Cases of acute overdose have been reported in the context of post-marketing experience and in clinical trials with montelukast. These include reports in adults and children with doses of up to 1000 mg (approximately 61 mg/kg in a 42-week-old child). The laboratory and clinical findings observed were consistent with the safety profile seen in adults and paediatric patients. In most cases of overdose, no undesirable effects were noted. The most frequent undesirable effects were consistent with the safety profile of montelukast and included abdominal pain, drowsiness, thirst, headache, vomiting and psychomotor hyperactivity.

It is not known whether montelukast can be eliminated by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist
ATC code: R03D C03

Cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released by various cells, including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airways and cause various effects on the airways, including bronchoconstriction, mucous secretion, vascular permeability and eosinophil recruitment.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical trials, montelukast inhibited LTD_4-induced bronchoconstriction when inhaled at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect of a β-agonist was additive to the effect caused by montelukast. Treatment with montelukast inhibited early- and late-phase bronchoconstriction due to contact with antigens. In comparison to placebo, montelukast reduced peripheral blood eosinophils in adult and paediatric patients. In a different trial, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In paediatric patients between 2 and 14 years of age and adults, montelukast, compared to placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

In trials in adults, compared with placebo, 10 mg of montelukast administered once daily showed significant improvements in early morning FEV_1 (10.4 and 2.7% change from baseline, respectively) and morning peak expiratory flow rate (PEFR) (24.5 and 3.3 l/min. change from baseline, respectively), as well as a significant reduction in total β-agonist use -26.1 and -4.6% change from baseline, respectively). The improvement observed in daytime and night-time asthma symptom scores reported by patients was significantly better than that observed with placebo.

Studies in adults showed the ability of montelukast to add to the clinical effect of inhaled corticosteroids (% change from baseline for FEV_1 with inhaled beclometasone plus montelukast and beclometasone alone, respectively: 5.43 and 1.04%; β-agonist use: -8.70% compared to 2.64%). Compared to inhaled beclometasone (200 μg twice daily with a spacer device), montelukast showed a faster initial response, but during the 12-week trial beclometasone provided a greater average treatment effect (% change from baseline for FEV_1 with montelukast and beclometasone, respectively: 7.49 and 13.3%; β-agonist use: -28.28% and -43.89%). However, compared to beclometasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50% of patients treated with beclometasone achieved an improvement of around 11% or more in FEV_1 compared to baseline, while approximately 42% of those treated with montelukast achieved the same response).

In a 12-week, placebo-controlled trial in paediatric patients between 2 and 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared to placebo irrespective of concomitant control treatment (nebulised/inhaled corticosteroids or nebulised/inhaled sodium cromoglycate). 60% of patients received no other control treatment. Montelukast improved daytime symptoms (including coughing, wheezing, respiratory problems and activity limitation) and night-time symptoms compared with placebo. Montelukast also significantly decreased "as-needed" β-agonist and corticosteroid rescue used for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. The therapeutic effect was achieved after the first dose.

In a 12-month, placebo-controlled trial in paediatric patients between 2 and 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg administered once daily significantly reduced ($p \leq 0.001$) the annual rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥3 consecutive days with daytime symptoms requiring β-agonist use or corticosteroids (oral or inhaled) or hospitalization for asthma]. The percentage reduction in annual EE rate was 31.9%, with a 95% CI of 16.9, 44.1.

In an 8-week trial in paediatric patients between 6 and 14 years of age, the administration of 5 mg of montelukast once daily, compared to placebo, significantly improved respiratory function (8.71 and 4.16% FEV_1 change from baseline; 27.9 and 17.8 l/min morning PEFR change from baseline) and decreased "as needed" β-agonist use — 11.7% and +8.2% change from baseline).

In a 12-month trial comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients between 6 and 14 years of age with mild persistent asthma, montelukast was not inferior to fluticasone in relation to the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between-group difference in least squares mean increase in the percentage of asthma RFDs was statistically significant —2.8 with a 95% CI of -4.7, &#x1e;0.9), but within the limit pre-defined to be clinically not inferior.
Both montelukast and fluticasone also improved asthma control on secondary variables evaluated over the 12-month treatment period:
FEV_1 increased from 1.83 l to 2.09 l in the montelukast group and from 1.85 l to 2.14 l in the fluticasone group. The between-group difference in least squares mean increase in FEV_1 was — 0.02 l with a 95% CI of —0.06, 0.02. The mean increase from baseline in the percentage of predicted FEV_1 was 0.6% in the montelukast treatment group and 2.7% in the fluticasone treatment group. The difference in least squares means for the change from baseline in the percentage of predicted FEV_1 was significant: —2.2% with a 95% CI of —3.6, —0.7.
The percentage of days with β-agonist use decreased from 38.0 to 15.4 in the montelukast group and from 38.5 to 12.8 in the fluticasone group. The between-group difference in least squares means for the percentage of days with β-agonist use was significant: 2.7 with a 95 % CI of 0.9, 4.5.
The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that requires treatment with oral steroids, an unscheduled visit to the doctor's, a trip to the emergency department or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) was significant: equal to 1.38 (1.04, 1.84).
The percentage of patients with systemic (mainly oral) corticosteroid use during the trial period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between-group difference in least squares means was significant: 7.3% with a 95 % CI of 2.9, 11.7.

A 12-week trial in adults showed a significant reduction in exercise-induced bronchoconstriction (EIB) (maximal fall in FEV_1 22.33% with montelukast and 32.40% with placebo; time to recovery to within 5% of baseline FEV_1 44.22 and 60.64 min, respectively). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short-term trial in paediatric patients between 6 and 14 years of age (maximal fall in FEV_1 18.27 and 26.11%; time to recovery to within 5 % of baseline FEV_1 17.76 and 27.98 min). The effect in both trials was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients who were taking concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared to placebo, resulted in a significant

improvement in asthma control (FEV_1 8.55% and —1.74% change from baseline and decrease in total β-agonist use —27.78% versus 2.09% change from baseline).

5.2 Pharmacokinetic properties

Absorption. montelukast is rapidly absorbed after oral administration. With the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration to adults under fasting conditions. The mean oral bioavailability is 64%. Oral bioavailability and C_{max} are not affected by a standard meal. Safety and efficacy were demonstrated in clinical trials in which a 10 mg film-coated tablet was administered, regardless of when food intake occurred.

With the 5 mg chewable tablet, the C_{max} was achieved 2 hours after administration to adults under fasting conditions. Mean oral bioavailability is 73% and decreases to 63% with a standard meal.

Following administration of the 4 mg chewable tablet to paediatric patients between 2 and 5 years of age under fasting conditions, C_{max} was achieved 2 hours after administration. Mean C_{max} is 66% higher than in adults administered a 10 mg tablet, while C_{min} is lower.

Distribution. montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8— 11 litres. Studies in rats using radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, the concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.

Biotransformation. montelukast is extensively metabolized. In studies using therapeutic doses, plasma concentrations of montelukast metabolites are undetectable at steady state in adults and children.

In vitro studies with human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. Based on other *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19 or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination. The plasma clearance of montelukast averages 45 ml/min in healthy adults. After an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. This fact, along with estimates of the oral bioavailability of montelukast, indicates that montelukast and its metabolites are excreted almost exclusively in bile.

Characteristics in patients. It is not necessary to adjust the dosage in patients who are elderly or have mild to moderate liver failure. No studies have been conducted in patients with renal insufficiency. Since montelukast and its metabolites are eliminated by the biliary route, there is no anticipated need to adjust the dose in patients with renal insufficiency. There are no data on the pharmacokinetics of montelukast in patients with severe liver insufficiency (Child-Pugh score > 9).

With high doses of montelukast (20 and 60 times the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

5.3 Preclinical safety data

In animal toxicity studies, minor changes were seen in the serum biochemistry of ALT, glucose, phosphorus and triglycerides, which were transient in nature. The signs of toxicity observed in animals were an increase in the excretion of saliva, gastrointestinal symptoms, loose stools and an ion imbalance. These occurred with doses which provided >17 times the systemic exposure observed with the therapeutic dose. In monkeys, undesirable effects began to appear at doses from 150 mg/kg/day (>232 times the systemic exposure observed with the clinical dose). In animal studies, montelukast did not affect fertility or reproductive capacity with a systemic exposure that exceeded 24 times the systemic clinical exposure. In the fertility study in female rats with 200 mg/kg/day (> 69 times the systemic clinical exposure), a slight decrease was observed in the body weight of offspring. In studies in rabbits, a higher incidence of incomplete ossification was observed compared to control animals with a systemic exposure >24 times higher than the systemic clinical exposure observed with the therapeutic dose. No anomalies were seen in rats. It has been observed that montelukast crosses the placental barrier and is excreted in the maternal milk of animals.

No deaths occurred after a single oral administration of montelukast sodium at doses of up to 5000 mg/kg in mice and rats (15,000 mg/m^2 and 30,000 mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily dose in adult humans (based on an adult patient weighing 50 kg).

It was determined that montelukast was not phototoxic in mice for UVA, UVB or visible light spectra at doses of up to 500 mg/kg/day (approximately >200 times based on systemic exposure).

montelukast was not mutagenic in *in vitro* and *in vivo* tests and was not tumourigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose (E460), mannitol, sodium starch glycollate (potato), aspartame (E951), magnesium stearate (E572), cherry flavour and red iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30 ºC.

6.5 Nature and contents of container

Aluminium/aluminium blister.
Packs containing 28 or 200 tablets (EC).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS CINFA, S.A.
C/ Olaz-Chipi, 10. Polígono Industrial Areta.
31620 Huarte-Pamplona (Navarra) Spain.

8. MARKETING AUTHORIZATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

June 2011

10. DATE OF REVISION OF THE TEXT

May 2011

Summary of Product Characteristics
montelukast cinfa 10 mg film coated tablets

1. NAME OF THE MEDICINAL PRODUCT
montelukast cinfa 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains montelukast sodium, which is equivalent to 10 mg montelukast.

Excipient: Lactose monohydrate 63 mg per tablet
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Cream-colored rounded biconvex and engraved film-coated tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
montelukast is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting ß-agonists provide inadequate clinical control of asthma.

In those asthmatic patients in whom montelukast is indicated in asthma, montelukast can also provide symptomatic relief of seasonal allergic rhinitis.
montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

Montelukast is indicated in adults from 15 years of age.

4.2 Posology and method of administration
The dosage for adults 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis is one 10 mg tablet daily to be taken in the evening.

General recommendations:
The therapeutic effect of montelukast on parameters of asthma control occurs within one day. montelukast may be taken with or without food.

Patients should be advised to continue taking montelukast even if their asthma is under control, as well as during periods of worsening asthma. montelukast should not be used concomitantly with other products containing the same active ingredient, montelukast.

No dosage adjustment is necessary for the elderly, or for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

Therapy with montelukast in relation to other treatments for asthma:
montelukast can be added to a patient's existing treatment regimen.

Inhaled corticosteroids: Treatment with montelukast can be used as add-on therapy in patients when inhaled corticosteroids plus "as needed" short acting ß-agonists provide inadequate clinical control. montelukast should not be abruptly substituted for inhaled corticosteroids (see section 4.4).
5-mg chewable tablets are available for paediatric patients 6 to 14 years of age.
4-mg chewable tablets are available for paediatric patients 2 to 5 years of age.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled ß-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting ß-agonists than usual.

Montelukast should not be substituted abruptly for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These cases usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

This medicinal product 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
Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo.* Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

4.6 Pregnancy and lactation

Use during pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between montelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience. montelukast may be used during pregnancy only if it is considered to be clearly essential.

Use during lactation

Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is not known if montelukast isexcreted in human milk.

montelukast may be used in breast-feeding only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machines

montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

• 10 mg film-coated tablets in approximately 4000 adult asthmatic patients 15 years of age and older.

• 10 mg film-coated tablets in approximately 400 adult asthmatic patients with seasonal allergic rhinitis 15 years of age and older.

• 5 mg chewable tablets in approximately 1750 paediatric asthmatic patients 6 to 14 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly (1/100 to <1/10) in asthmatic patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class Adult Patients	**Adults patients 15 years and older (two 12-week studies; n=795)**	**Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)**
Nervous system disorders	headache	headache
Gastro-intestinal disorders	abdominal pain	

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

Post-marketing Experience

Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Experience Term, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	**Adverse Experience Term**	**Frequency Category***
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, depression	Uncommon
	tremor	Rare
	hallucinations, suicidal thinking and behaviour (suicidality)	Very Rare
Nervous system disorder	dizziness, drowsiness paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
Gastrointestinal disorders	diarrhoea‡, nausea‡, vomiting‡	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash‡	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum	Very Rare
Musculoskeletal, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise,	Uncommon

	oedema,	

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (1/10), Common (1/100 to < 1/10), Uncommon (1/1000 to < 1/100), Rare (1/10,000 to < 1/1000), Very Rare (< 1/10,000).

†This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.

‡This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.

4.9 Overdose

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast.

These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ***Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonist***

ATC-code: R03D C03

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a ß-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric

patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV_1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total ß-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclometasone plus montelukast vs beclometasone, respectively for FEV1: 5.43% vs 1.04%; ß-agonist use: -8.70% vs 2.64%). Compared with inhaled beclometasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclometasone provided a greater average treatment effect (% change from baseline for montelukast vs beclometasone, respectively for FEV_1: 7.49% vs 13.3%; ß-agonist use: -28.28% vs -43.89%). However, compared with beclometasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclometasone achieved an improvement in FEV_1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study,montelukast 10 mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Nighttime Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacy was not a primary objective in this study.

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV_1 8.71% vs 4.16% change from baseline; AM PEFR 27.9
L/min vs 17.8 L/min change from baseline) and decreased "as-needed" ß-agonist use (-11.7% vs +8.2% change from baseline).

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period.
Reduction in EIB was also demonstrated in a short term study in paediatric patients (maximal fall in FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV_1 8.55% vs -1.74% change from baseline and decrease in total ß-agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

Absorption.

Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved 3 hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the Cmax is achieved in 2 hours after administration in adults in the fasted state.
The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

Distribution.

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 litres. Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.

Biotransformation.

Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination.

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

Characteristics in patients.

No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score>9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastro-intestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided>17-fold the systemic exposure seen at the clinical dosage. In

monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/ kg/day (>69 fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure>24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg in mice and rats (15,000 mg/m^2 and 30,000 mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately>200-fold based on systemic exposure).

Montelukast was neither mutagenic in *in vitro* and *in vivo* tests nor tumorigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate
Low-substituted Hydroxypropyl-cellulose (E-463)
Hydroxypropylcellulose
Magnesium stearate

Film coating:
Hypromellose
Macrogol 6000
Titanium dioxide (E 171)
Talc
Red and yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30ºC.
Store in original package in order to protect from light and moisture.

6.5 Nature and contents of container

Packaged in aluminium-polyamide-PVC/aluminium blister.
Blisters in packages of 1, 14, 20,28, 30, 50, 84 and 100 tablets.
Not all pack sizes will be marketed

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AHORISATION HOLDER
LABORATORIOS CINFA, S.A.
Ctra. Olaz-Chipi, 10.
31620 Huarte-Pamplona (Navarra) Spain.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL

10. DATE OF REVISION OF THE TEXT