SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxofylline (Sustained Release) 400 mg and Montelukast 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated bilayered tablet contains:

Doxofylline ……..…..…… 400 mg

(As sustained release form)

Montelukast Sodium BP

Eq.to. Montelukast……..…… 10 mg

Excipients…….…. Q.S.

Color ……Quinoline Yellow

3. PHARMACEUTICAL FORMS

A white colored, caplet shaped, biconvex, uncoated tablet, plain on both sides.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Bronchial asthma.
Pulmonary disease associated with bronchospasm.

4.2. Posology and method of administration

400 mg tablets – adults: 1 tablet two/three times daily

100 mg ampoules – adults: 2 ampoules by slow intravenous injection to patients in supine position (15-20 minutes), preferably diluted, during the acute phase.
Administration can be repeated at 12 hour intervals, at the physician's discretion.

200 mg sachets - children aged 6-12 years
1-3 sachets per day (12-18 mg/kg) dissolved in plenty of water.

2% syrup: - adults: one 20 ml measures two/three times a day (one 20 ml measure corresponds to 400 mg of doxofylline)

At the recommended posology, the plasma levels of Doxofylline do not generally exceed 20 µg/ml, so it is not essential to check these levels periodically.
If the dosage is increased, the blood levels of the drug must be measured (the therapeutic value is about 10 µg/ml, the value bordering on toxicity is 20 µg/ml).

4.3. Contraindications

DONET 400SR is contraindicated in individuals with known hypersensitivity to the drug or other xanthenes' derivatives. It is also contraindicated in patients with acute myocardial infarction, hypotension and during lactation.

4.4. Special warnings and precautions for use

Numerous factors may reduce the hepatic clearance of xanthine derivatives with increased plasma levels of the drug. These factors include age, congestive cardiac decompensation, chronic obstructive pulmonary disease, severe liver disease, concomitant infections, the concurrent administration of several drugs such as: erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine and propranolol. In these cases, it may prove necessary to reduce the dosage of the drug.

Phenytoin, other anticonvulsants and cigarette smoking may increase the clearance of xanthine derivatives with a reduction of plasmatic half-life. In these cases, it may prove necessary to increase the dosage of the drug.

In case of factors that may influence the clearance of xanthine derivatives, monitoring of the concentration of the blood levels of the drug is recommended for the control of the therapeutic range.

Caution should be observed in administering the product to patients with cardiac disease, hypertension, in the elderly, in patients with severe hypoxemia, hyperthyroidism, chronic cor pulmonale, congestive heart failure, liver disease, peptic ulcer and in those with renal impairment. In particular, it is to be used with caution in patients with congestive heart failure, since the clearance of the drug is considerably slower in these patients in which high blood levels may persist for long periods even after discontinuation of the treatment.

There is no risk of addiction or any other form of dependence.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

4.5. Interaction with other medicinal products and other forms of interaction

DONET 400SR should not be administered with other xanthine preparations. It is recommended to limit consumption of beverages and food containing caffeine.

Caution should be exercised in administering DONET 400SR together with ephedrine or other sympathomimetic drugs.

The concurrent administration of many drugs such as erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine and propranolol may reduce the hepatic clearance of xanthine derivatives with an increase in the plasmatic levels of the drug.

Phenytoin, other anticonvulsants and cigarette smoking may increase the clearance of xanthine derivatives with a reduction of plasmatic half-life. In these cases, it may prove necessary to increase the dosage of the drug.

4.6. Pregnancy and lactation

Animal tests have shown that the active ingredient of DONET 400SR does not interfere with pre- and postnatal growth.

However, as there is not sufficient clinical evidence about the effects of the drug during pregnancy, use of the drug during pregnancy should be evaluated carefully case by case on the basis of the risk- benefit ratio. The drug is contraindicated during lactation.

4.7. Effects on ability to drive and use machines

The product does not affect the patient’s alertness and therefore does not interfere with his/her ability to drive and use machines.

4.8. Undesirable effects

Patients treated with xanthine derivatives may suffer nausea, vomiting, epigastric pain, headache, irritability, insomnia, tachycardia, extrasystoles, tachypnea, and in rare cases, hyperglycemia or albuminuria. In case of overdose severe cardiac arrhythmias and tonic-clonic seizure may occur. These effects may represent the first signs of intoxication.

The appearance of side effects may require discontinuation of the treatment which, if necessary, at the physician's discretion, may be resumed at lower doses after all signs and symptoms of toxicity have subsided.

4.9. Overdose
As there is no specific antidote, in case of overdose a symptomatic treatment of cardiovascular collapse should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Doxofylline directly relaxes the smooth muscles of the bronchi and pulmonary vessels. In this way, it acts mainly as a bronchodilator, pulmonary vasodilator and as a relaxant of the bronchial muscle. The action of Doxofylline may be mediated, at least in part, by inhibition of the phosphodiesterase leading to an increase in intracellular cyclic AMP which results in smooth-muscle relaxation.
At higher concentrations, Doxofylline may inhibit the release of histamine by the cells. Prolonged use of the drug does not lead to addiction.

5.2. Pharmacokinetic properties
Doxofylline half-life is more than 6 hours, so constant effective plasma levels may be maintained with three administrations a day.
The kinetics after a single i.v. and oral administration have been studied in man to define the distribution and absorption of the drug.
After intravenous administration of 100 mg of Doxofylline to 5 volunteers, the distribution of the unchanged substance in the serum follows a bi-compartmental model.
The area under the curve of the concentration of the drug in the serum during the distribution phase represents a small fraction of the total area.

Plasmatic clearance is high, with values ranging from 444 to 806 ml/min, whereas distribution volume is about 1 l/kg.

The mean half-life after intravenous administration was calculated to be 65 minutes (from 40 to 96).

After tablet administration, peak plasma levels are reached after 60 minutes, while with the syrup, due to its water and alcohol vehicle, the drug is absorbed more quickly, peak plasma concentration occurring within 30 minutes.

Absolute oral bioavailability is about 62.6%; at pH 7.4 the percentage of product bonded to the plasma proteins is about 48%.
Less than 4% of the oral dose is eliminated unchanged in the urine.

6) PHARMACEUTICAL PARTICULARS

6.1. List of excipients

800 mg tablets
Microcrystalline

Cellulose

Hydroxypropyi

Methylcellulose

Polyiniyl pyrrolidone

K30 Purified water

PEG 6000

PurifiedTalc

Magnesium Stearate

6.2. Incompatibilities

No incompatibility with other substances has been reported for any of the available pharmaceutical forms.

Montelukast 10 mg film coated tablets

Summary of Product Characteristics Updated 24-Nov-2020 | Accord Healthcare Limited

6. Name of the medicinal product

Montelukast 10 mg film-coated tablets

7. Qualitative and quantitative composition

Each film-coated tablet contains montelukast sodium 10.4 mg equivalent to 10 mg montelukast.

Excipient(s) with known effect:

Contain 130.95 mg of Lactose monohydrate per tablet

For a full list of excipients, see section 6.1.

8. Pharmaceutical form

Film-coated tablet

7.9 x 7.9 mm beige coloured, rounded square, biconvex, film coated tablet debossed “M10” on one side and plain on other side.

9. Clinical particulars

9.1.Therapeutic indications

Montelukast 10 mg film-coated tablets is indicated in the treatment of asthma as add-on therapy in those patientswith mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast 10 mg film-coated tablets is indicated in asthma, Montelukast 10 mg film-coated tablets can also provide symptomatic relief of seasonal allergic rhinitis.

A Montelukast 10 mg film-coated tablet is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

The recommended dose for adults and adolescents 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 10 mg film-coated tablets on parameters of asthma control occurs within one day. Montelukast 10 mg film-coated tablets may be taken with or without food. Patients should be advised to continue taking Montelukast 10 mg film-coated tablets even if their asthma is under control, as well as during periods of worsening asthma. Montelukast 10 mg film-coated tablets 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 10 mg film-coated tablets in relation to other treatments for asthma

Montelukast 10 mg film-coated tablets can be added to a patient's existing treatment regimen. *Inhaled corticosteroids:*

Treatment with Montelukast 10 mg film-coated tablets can be used as add-on therapy in patients when inhaled corticosteroids plus "as needed" short acting β-agonists provide inadequate clinical control. Montelukast 10 mg film- coated tablets should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

Paediatric population

Do not give Montelukast 10 mg film-coated tablets to children less than 15 years of age. The safety and efficacy of Montelukast 10 mg film-coated tablets in children less than 15 years has not been established.

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.

Method of administration:

Oral use.

9.2. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

9.3. 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 β- agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting β-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 have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been 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 monohydrate.

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

Neuropsychiatric events have been reported in adults, adolescents, and children taking Montelukast 10 mg film-coated tablets (see section 4.8). Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Montelukast 10 mg film-coated tablets if such events occur.

9.4.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, 2C8, and 2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8, and 2C9, 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.)

In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.

Based on in vitro data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

9.5.Fertility, pregnancy and lactation

Pregnancy

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

Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

Montelukast 10 mg film-coated tablets may be used during pregnancy only if it is considered to be clearly essential.

Breastfeeding

It is unknown whether montelukast is excreted in human milk. Studies in rats have shown that montelukast is excreted in milk (see section 5.3).

Montelukast 10 mg film-coated tablets may be used in breast-feeding only if it is considered to be clearly essential

9.6. Effects on ability to drive and use machines

Montelukast has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

9.7.Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4000 adult and adolescent asthmatic patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult and adolescent 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 and Adolescent 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
Gastrointestinal 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.

Tabulated list of Adverse Reactions

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 Reactions**	**Frequency Category***
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very Rare

Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor§)	Uncommon
	disturbance in attention, memory impairment , tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive- compulsive symptoms, dysphemia	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), pulmonary eosinophilia	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, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

*Frequency Category: Defined for each Adverse Reactions 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.

§ Frequency Category: Rare

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

9.8.Overdose

In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult 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.

Symptoms of overdose

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.

Management of overdose

No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

10.Pharmacological properties

10.1. Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene

receptor antagonist ATC code: R03D03

Mechanism of action

The cysteinyl leukotrienes (LTC_4, LTD_4, and 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 ($CysLT_1$) 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.

Pharmacodynamic effects

Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β 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.

Clinical efficacy and safety

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 β-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 FEV_1: 5.43% vs 1.04%; β- 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%; β 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 and adolescent 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" β-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 β-agonist use -27.78% vs 2.09% change from baseline).

10.2. 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.

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *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.

10.3. 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 (>69fold 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/m2 and 30,000 mg/m2 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.

11.Pharmaceutical particulars

11.1. Special precautions for disposal and other handling

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

6.3. Shelf-life

Each uncoated bilayered tablet contains:

Doxofylline ……400 mg
(as sustained release form)

Montelukast Sodium BP
Eq.to., Montelukast……..…… 10 mg

Excipients…….....Q.S.
Color ……Quinoline Yellow
36 months

6.4. – Special precautions for storage

The preparation must be stored “at ordinary environmental conditions" as laid down by. DONET 400SR

6.5. - Nature and contents of container

DONET 400SR mg tablets:
1 X 10 Tablet Alu Alu Blister

6.6. Instructions for use and handling

No particular precautions need be taken in handling the product. See Posology and method of administration.

7. MARKETING AUTHORIZATION HOLDER

4Care life Science (P) Limited SurveyNo.23/3P&24, Opp. Jeans Factory, Daduram Vistar, Village-Bagdol, Tal-Kathlal, Dist- Kheda - 387630, Gujarat, India.

8. MARKETING AUTHORIZATION NUMBER(S)

9. DATE OF FIRST AUTHORIZATION

10. DATE OF REVISION OF THE TEXT