

Public Assessment Report
Decentralised Procedure

MONTELUKAST 10MG FILM-COATED TABLETS

UK/H/2199/001/DC
UK licence no: PL 04416/0946

Sandoz Limited

MONTELUKAST 10MG FILM-COATED TABLETS

LAY SUMMARY

On 30th November 2009, the UK granted a licence for the medicinal product Montelukast 10mg Film-Coated Tablets (PL 04416/0946). This licence was granted via the decentralised procedure (UK/H/2199/001/DC), with the UK as reference member state (RMS) and Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain and Sweden as concerned member state (CMS).

Montelukast 10mg Film-Coated Tablets is used for the treatment of asthma, preventing asthma symptoms during the day and night.

The active ingredient montelukast sodium belongs to a group of medicines called leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs and also cause allergy symptoms. By blocking leukotrienes, Montelukast 10 mg improves asthma symptoms, helps control asthma and improves seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Montelukast 10mg Film-Coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Montelukast 10mg Film-Coated Tablets
Type of Application	Generic application, Article 10.1
Active Substance	Montelukast sodium
Form	10mg film-coated tablets
Strength	10mg
MA Holder	Sandoz Limited, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE, UK
RMS	UK
CMS	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain and Sweden
Procedure Number	UK/H/2199/001/DC
Timetable	Day 210 – 4 th November 2009

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Montelukast 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 84.7 mg per tablet

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Beige, squared, biconvex, film-coated tablet, encoded 10 on one side

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 beta-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 and adolescents from the age of 15 years.

4.2 Posology and method of administration

The dosage 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.

Method of administration

For oral use.

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 beta-agonists provide inadequate clinical control. Montelukast should not be substituted for inhaled corticosteroids (see section 4.4).

Montelukast should not be used in children below 15 years of age due to the high content of active substance.

Other dosage forms with appropriate strengths are available for younger children.

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 beta-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting beta-agonists than usual.

Montelukast should not be substituted 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**

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 coadministered 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 drugs 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 drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

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 drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin.

4.6 **Pregnancy and lactation**

Use During Pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/fetal 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 is excreted in human milk.

Montelukast may be used in nursing 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 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 ($\geq 1/100$ 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 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 6 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

The following adverse reactions have been reported in post-marketing use:

Blood and lymphatic system disorders

Increased bleeding tendency

Immune system disorders

Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration

Psychiatric disorders

Dream abnormalities including nightmares, hallucinations, psychomotor hyperactivity (including irritability, restlessness, agitation including aggressive behavior, and tremor), depression, insomnia

Nervous system disorders

Dizziness drowsiness, paraesthesia/hypoesthesia, seizure

Cardiac disorders

Palpitations

Gastrointestinal disorders

Diarrhoea, dry mouth, dyspepsia, nausea, vomiting

Hepatobiliary disorders

Elevated levels of serum transaminases (ALT, AST), cholestatic hepatitis

Skin and subcutaneous tissue disorders

Angioedema, bruising, urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia including muscle cramps

General disorders and administration site conditions

Asthenia/fatigue, malaise, oedema

Very rare cases (<1/10,000) of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients (see section 4.4).

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 overdosage 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 dialyzable by peritoneal- or hemo-dialysis.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

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

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 beta-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 FEV₁ (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 beta-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and night-time 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 beclomethasone plus montelukast vs beclomethasone, respectively for FEV₁: 5.43% vs 1.04%; beta-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV₁: 7.49% vs 13.3%; beta-agonist use: -28.28% vs -43.89%). However, compared

with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclomethasone achieved an improvement in FEV₁ 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 Night-time Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and night-time 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 (FEV₁ 8.71% vs 4.16% change from baseline; AM PEF 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed" beta-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 FEV₁ 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV₁ 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 FEV₁ 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV₁ 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 (FEV₁ 8.55% vs -1.74% change from baseline and decrease in total beta-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 (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} 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 C_{max} 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 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Biotransformation

Montelukast is extensively metabolized. 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 radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal 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, gastrointestinal 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/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose monohydrate
Hydroxypropylcellulose type EF
Celulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Coating

Hypromellose 6 cps
Titanium dioxide (E 171)
Macrogol 400
Ferric oxide, yellow (E 172)
Ferric oxide, red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Packaged in

OPA/Al/PVC/Al blisters:

7, 10, 14, 20, 21, 28, 30, 49, 50, 56, 84, 90, 98, 100, 140, 200 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd

Woolmer Way,

Bordon,

Hants GU35 9QE,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0946

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2009

10 DATE OF REVISION OF THE TEXT

30/11/2009

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

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Montelukast 10 mg film-coated tablets

Montelukast

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 Montelukast 10 mg is and what it is used for
2. Before you take Montelukast 10 mg
3. How to take Montelukast 10 mg
4. Possible side effects
5. How to store Montelukast 10 mg
6. Further information



1 What Montelukast 10 mg is and what it is used for

Montelukast 10 mg is a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs and also cause allergy symptoms. By blocking leukotrienes, Montelukast 10 mg improves asthma symptoms, helps control asthma and improves seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

Your doctor has prescribed Montelukast 10 mg to treat asthma, preventing your asthma symptoms during the day and night.

- Montelukast 10 mg is used for the treatment of patients who are not adequately controlled on their medication and need additional therapy.
- Montelukast 10 mg also helps prevent the narrowing of airways triggered by exercise.
- In those asthmatic patients in whom Montelukast 10 mg is indicated in asthma, Montelukast 10 mg can also provide symptomatic relief of seasonal allergic rhinitis.

Your doctor will determine how Montelukast 10 mg should be used depending on the symptoms and severity of your asthma.

What is asthma?

Asthma is a long-term disease. Asthma includes:

- difficulty breathing because of narrowed airways. This narrowing of airways worsens and improves in response to various conditions.
- sensitive airways that react to many things, such as cigarette smoke, pollen, cold air, or exercise.
- swelling (inflammation) in the lining of the airways.

Symptoms of asthma include: Coughing, wheezing, and chest tightness.

What are seasonal allergies?

Seasonal allergies (also known as hay fever or seasonal allergic rhinitis) are an allergic response often caused by airborne pollens from trees, grasses and weeds. The symptoms of seasonal allergies typically may include: stuffy, runny, itchy nose; sneezing; watery, swollen, red, itchy eyes.

2 Before you take Montelukast 10 mg

Do not take Montelukast 10 mg

- if you are allergic (hypersensitive) to montelukast or any of the other ingredients of Montelukast 10 mg.

Take special care with Montelukast 10 mg

- If your asthma or breathing gets worse, tell your doctor immediately.
- Oral Montelukast 10 mg is not meant to treat acute asthma attacks. If an attack occurs, follow the instructions your doctor has given you. Always have your inhaled rescue medicine for asthma attacks with you.

- It is important that you take all asthma medications prescribed by your doctor. Montelukast 10 mg should not be substituted for other asthma medications your doctor has prescribed for you.
- Any patient on anti-asthma medicines should be aware that if you develop a combination of symptoms such as a flu-like illness, pins and needles or numbness of arms or legs, worsening of lung (pulmonary) problems, and/or rash, you should consult your doctor.
- You should not take aspirin or anti-inflammatory medicines (also known as non-steroidal antiinflammatory drugs or NSAIDs) if they make your asthma worse.

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.

Some medicines may affect how Montelukast 10 mg works, or Montelukast 10 mg may affect how other medicines work.

Tell your doctor if you are taking the following medicines before starting Montelukast 10 mg:

- phenobarbital (used for treatment of epilepsy)
- phenytoin (used for treatment of epilepsy)
- rifampicin (used to treat tuberculosis and some other infections)

Taking Montelukast 10 mg with food and drink

Montelukast 10 mg may be taken with or without food.

Pregnancy and breast-feeding

Use in pregnancy

Women who are pregnant or intend to become pregnant should consult their doctor before taking Montelukast 10 mg. Your doctor will assess whether you can take Montelukast 10 mg during this time.

Use in breast-feeding

It is not known if Montelukast 10 mg appears in breast milk. You should consult your doctor before taking Montelukast 10 mg if you are breast-feeding or intend to breast-feed.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Montelukast 10 mg is not expected to affect your ability to drive a car or operate machinery. However, individual responses to medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with Montelukast 10 mg may affect some patients' ability to drive or operate machinery.

Important information about some of the ingredients of Montelukast 10 mg

Montelukast 10 mg film-coated tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Continued on the next page >>

3 How to take Montelukast 10 mg

Always take Montelukast 10 mg as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- You should take only one tablet of Montelukast 10 mg once a day as prescribed by your doctor.
- It should be taken even when you have no symptoms or have an acute asthma attack.
- To be taken by mouth.

The usual dose is
For adults and adolescents 15 years of age and older:

One 10 mg tablet to be taken daily in the evening. Montelukast 10 mg may be taken with or without food.

If you are taking Montelukast 10 mg, be sure that you do not take any other products that contain the same active ingredient, montelukast.

Montelukast 10 mg should not be used in children below 15 years of age due to the high content of active substance.

Other dosage forms with appropriate strengths are available for younger children.

If you take more Montelukast 10 mg than you should
Contact your doctor immediately for advice.

There were no side effects reported in the majority of overdose reports. The most frequently occurring symptoms reported with overdose in adults and children included abdominal pain, sleepiness, thirst, headache, vomiting, and hyperactivity.

If you forget to take Montelukast 10 mg
Try to take Montelukast 10 mg as prescribed. However, if you miss a dose, just resume the usual schedule of one tablet once daily.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Montelukast 10 mg
Montelukast 10 mg can treat your asthma only if you continue to take it. It is important to continue taking Montelukast 10 mg for as long as your doctor prescribes. It will help control your asthma.

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

4 Possible side effects

Like all medicines, Montelukast 10 mg can cause side effects, although not everybody gets them.

In clinical studies with Montelukast 10 mg film-coated tablets, the most commonly (affects 1 to 10 users in 100) reported side effects thought to be related to Montelukast 10 mg were:

- abdominal pain
- headache

Additionally, while the drug has been on the market, the following have been reported:

- allergic reactions including rash, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, itching, and hives
- tiredness, restlessness, agitation including aggressive behavior, irritability, tremor, depression, dizziness, drowsiness, hallucinations, dream abnormalities, including nightmares and trouble sleeping, pins and needles/numbness, seizure
- feeling unwell, joint or muscle pain, muscle cramps, dry mouth, nausea, vomiting, indigestion, diarrhoea, hepatitis
- increased bleeding tendency, bruising, palpitations
- swelling

In asthmatic patients treated with montelukast, very rare cases (affects less than 1 user in 10,000) of a combination of symptoms such as flulike illness, pins and needles or numbness of arms and legs, worsening of lung (pulmonary) problems and/or rash (Churg-Strauss syndrome) have been reported. You must tell your doctor right away if you get one or more of these symptoms.

Ask your doctor or pharmacist for more information about side effects. 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.

5 How to store Montelukast 10 mg

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

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

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 Montelukast 10 mg contains
The active substance is montelukast.

One tablet contains 10.4 mg montelukast sodium which corresponds to 10 mg of montelukast.

The other ingredients are:
Core: Lactose monohydrate, hydroxypropylcellulose type EF, cellulose, microcrystalline, croscarmellose sodium, magnesium stearate

Coating: Hypromellose 6 cps, titanium dioxide (E171), macrogol 400, ferric oxide, yellow (E172), ferric oxide, red (E172)

What Montelukast 10 mg looks like and contents of the pack
Beige, squared, biconvex, film-coated tablet, encoded 10 on one side

Packaged in
OPA/Al/PVC/Al blisters:
7, 10, 14, 20, 21, 28, 30, 49, 50, 56, 84, 90, 98, 100, 140, 200 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Sandoz Ltd,
Woolmer Way, Bordon,
Hants GU35 9QE,
United Kingdom.

Manufacturers:
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1,
39179 Barleben, Germany *or*

Lek Pharmaceuticals d.d., Verovškova 57,
1526 Ljubljana, Slovenia *or*

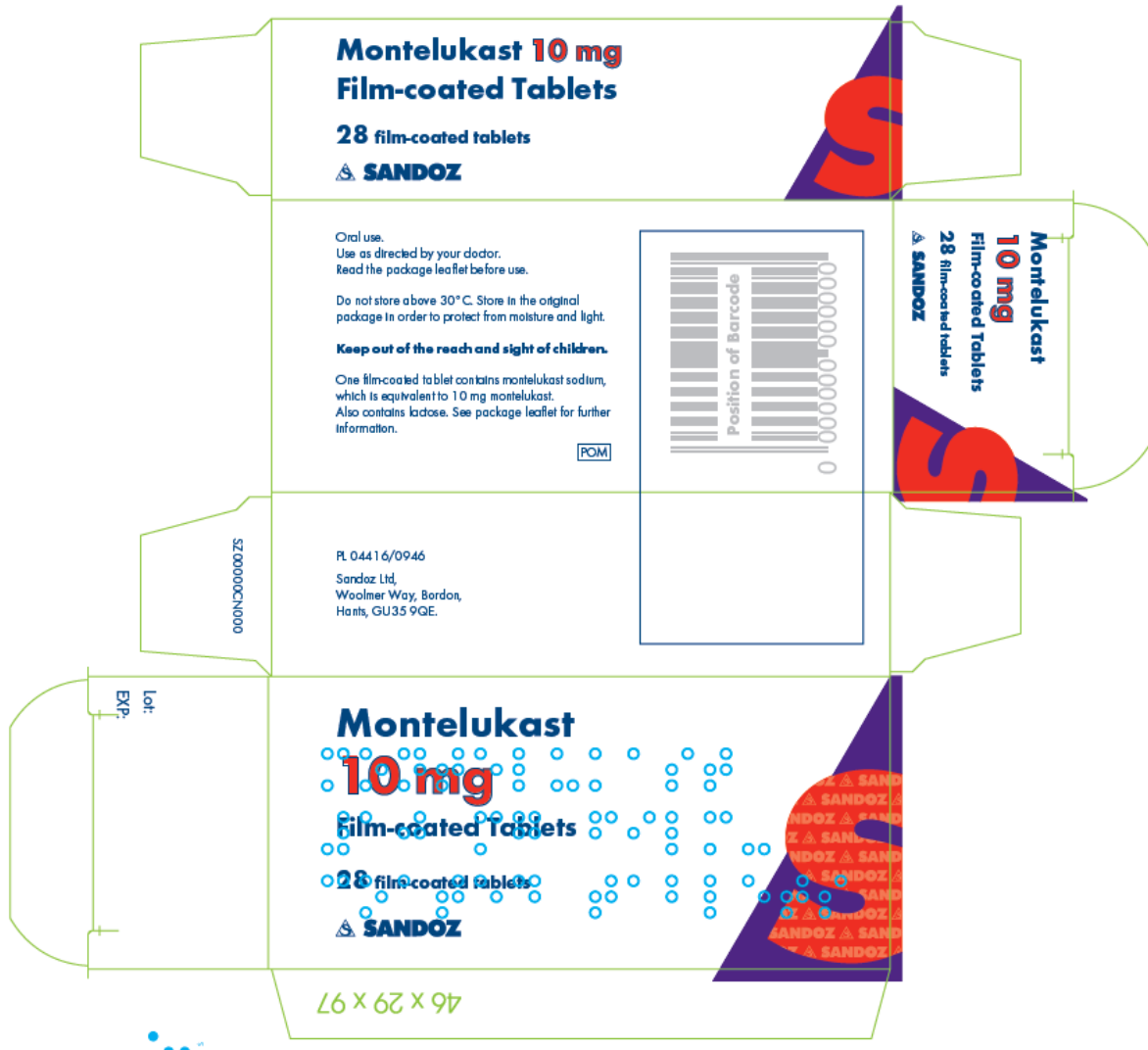
LEK S.A., ul. Domaniewska 50 C, 02-672 Warszawa,
Poland *or*

S.C. Sandoz S.R.L., Str. Livezeni nr7A, 540472
Targu-Mures, Romania.

This leaflet was last approved in 11/2009 (to be amended after approval).

SZ00000LT000

Module 4 Labelling



Montelukast 10 mg Film-coated Tablets SZ00000FL000 PL 04416/0946 SANDOZ Sandoz Ltd		Montelukast 10 mg Film-coated Tablets SZ00000FL000 PL 04416/0946 SANDOZ Sandoz Ltd		Montelukast 10 mg Film-coated Tablets SZ00000FL000 PL 04416/0946 SANDOZ Sandoz Ltd	
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Module 5

Scientific discussion during initial procedure

I INTRODUCTION

On 4th November 2009, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Finland, France, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain, Sweden and the UK agreed to grant a marketing authorisation to Sandoz Limited for the medicinal product Montelukast 10mg Film-Coated Tablets. The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS – UK/H/2199/001/DC). After the national phase, a licence was granted in the UK on 20th November 2009 (PL 04416/0946).

This application was made under Article 10.1 of Directive 2001/83 EC for Montelukast 10mg Film-Coated Tablets, containing the known active substance montelukast sodium. The reference medicinal product for this application is Singulair 10mg Tablets (Merck, Sharp and Dohme), which has been licenced in at least one member state for over 10 years.

Montelukast is an oral cysteinyl leukotriene D₄ receptor antagonist indicated as add-on therapy in asthma patients who are inadequately controlled on inhaled corticosteroids and in whom “as needed” short acting β -agonists provided inadequate control of asthma. Montelukast may also be used as an alternative treatment option to low-dose inhaled corticosteroids in patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids. Montelukast is also indicated in prophylaxis of exercise-induced bronchoconstriction and symptomatic relief of seasonal allergic rhinitis.

The drug product corresponds to the current EU definition for generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance, and the same dosage form.

The bioequivalence study was conducted in accordance with current Good Clinical Practice.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

An acceptable justification for not submitting a European Risk Management Plan has been provided. Other documentation relating to pharmacovigilance system have been provided.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Montelukast 10mg Film-Coated Tablets
Name(s) of the active substance(s) (USAN)	Montelukast sodium
Pharmacotherapeutic classification (ATC code)	Anti-asthmatics for systemic use, leukotriene receptor (R03D C03)
Pharmaceutical form and strength(s)	10mg Film-Coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/2199/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Finland, France, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain and Sweden
Marketing Authorisation Number(s)	PL 04416/0946
Name and address of the authorisation holder	Sandoz Limited, 37 Woolmer Way, Bardon, Hampshire, GU35 9QE, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

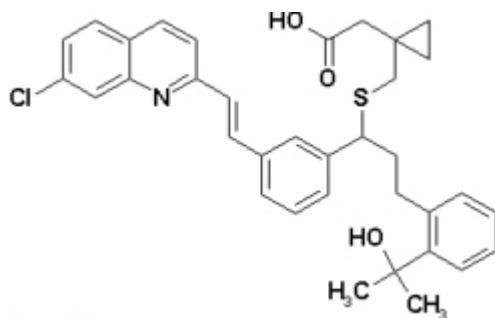
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Montelukast sodium

Chemical Names: Sodium salt of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid

Structure:



Molecular formula: $C_{35}H_{35}ClNO_3SNa$

Molecular weight: 608.18

Physical form: A white to almost white powder, soluble in water, methanol and ethanol, and practically insoluble in acetonitrile.

Montelukast exhibits chirality and polymorphism.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, hydroxypropylcellulose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, purified water and Opadry beige (which consisted of hypromellose, titanium dioxide, macrogol, yellow ferric oxide and red ferric oxide). All excipients are controlled to their respective European Pharmacopoeia monograph, with the exception of red ferric oxide and yellow ferric oxide, which are controlled to suitable French National Formulary specifications. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application. Comparable dissolution and impurity profile are provided for this product versus the originator product.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is supplied in oriented polyamide/aluminium/polyvinylchloride blisters in pack sizes of 7, 10, 14, 20, 21, 28, 30, 49, 50, 56, 84, 90, 98, 100, 140 and 200 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set, with the storage instructions "Do not store above 30°C. Store in the original package in order to protect from moisture and light".

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling

The SPC, PIL and labelling are pharmaceutically satisfactory. The marketing authorisation holder has committed to submitting mock-ups of the patient information leaflet and labels to the relevant regulatory authorities before marketing the product in any member state.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

The MAA form is pharmaceutically satisfactory.

Expert Report

The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

III.2 NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of montelukast are well-known. As montelukast is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

ENVIRONMENTAL RISK ASSESSMENT

There is no environmental risk assessment statement included in the application. This is acceptable for a generic product.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory from a preclinical viewpoint.

NON-CLINICAL EXPERT REPORT

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

OVERALL CONCLUSION ON THE NON-CLINICAL PART

The applicant has provided an adequate review of the available non-clinical data. The pattern of toxicity seen with irinotecan is consistent with its anti-cancer actions. There were no new non-clinical data identified in the literature review that would change the risk-benefit analysis for irinotecan.

III.3 CLINICAL ASPECTS*Pharmacokinetics*

With the exception of the bioequivalence study, no new data have been submitted and none are required for an application of this type. The bioequivalence study was conducted in line with Good Clinical Practice and the Declaration of Helsinki.

Bioequivalence

A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Montelukast 10mg Film-Coated Tablets (test) versus Singulair 10mg Tablets (reference) in healthy fasted subjects.

A single dose of test or reference study drug was administered with 240ml of water after an overnight fast of at least 10 hours. Blood samples were taken pre- and up to 24 hours post dose. Each treatment arm was separated by a 7-day washout period.

Results

The pharmacokinetic results for active montelukast sodium are presented below:

Pharmacokinetic variables (arithmetic mean \pm SEM)	Test	Reference
C _{max} [ng/ml]	475.79 \pm 31.69	475.32 \pm 31.21
AUC(0-t) [ng/ml * h]	3215.98 \pm 213.78	3121.47 \pm 196.03
AUC(0- ∞) [ng/ml * h]	3339.50 \pm 229.30	3242.58 \pm 210.00
T _{max} [hours, median]	3.25	3.00
T _{1/2} [hours]	5.22 \pm 0.21	5.38 \pm 0.25
Residual Area [%]	3.5 \pm 0.3	3.6 \pm 0.4
F _{rel} (AUC(0-t)) [%]	-	103.8 \pm 3.4*

*: Ratio in % of Test/Reference.

Pharmacokinetic variables - N = 26		Point Estimate (Test/Reference) *	90 % Confidence Interval	Intra-subject CV %	Sequence effect
Primary	AUC(0-t)	102.4	96.6 – 108.5	12.3	No effect
	C _{max}	99.5	89.9 – 110.0	21.5	No effect
Secondary	AUC(0- ∞)	102.3	96.6 – 108.2	12.0	No effect
	T _{max}	-	(-0.47) – 0.38 **	-	-

*: Ratio of geometric means of Test and Reference. **: Non-parametric 90 % CI.

Conclusions

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence*. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

Pharmacodynamics

No new data have been submitted and none are required for an application of this type.

Clinical efficacy

No new data have been submitted and none are required for an application of this type.

Clinical safety

Montelukast sodium has an acceptable adverse events profile. No new safety concerns arise from the bioequivalence study and the safety profiles of this product and the reference product (Singulair 10mg Tablets) are similar.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Clinical Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form

The MAA Form is medically satisfactory.

Clinical Conclusion

The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Montelukast 10mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Montelukast 10mg Film-Coated Tablets beyond those already described.

EFFICACY

No new data have been submitted and none are required for an application of this type.

Montelukast 10mg Film-Coated Tablets is the generic version of Singulair 10mg Tablets (Merck, Sharp and Dohme). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, irinotecan hydrochloride trihydrate.

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence*. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for this generic application. Montelukast sodium has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with montelukast sodium is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome