Singolast®

Montelukast Sodium

FORMS AND PRESENTATION

Singolast® 4: Chewable tablets; Box of 30.
Singolast® 5: Chewable tablets; Box of 30.
Singolast® 10: Film Coated tablets; Box of 30.

COMPOSITION

• Singolast® 4: Each chewable tablet contains Montelukast sodium eq. to Montelukast 4mg.
Excipients: Mannitol, Croscarmellose sodium, Hydroxy propyl cellulose, Ferric oxide, microcrystalline cellulose, Aspartame, ART cherry flavor, Magnesium Stearate.
• Singolast® 5: Each chewable tablet contains Montelukast sodium eq. to Montelukast 5mg.
Excipients: Mannitol, Croscarmellose sodium, Hydroxyl propyl cellulose, Ferric oxide, microcrystalline cellulose, Aspartame, ART Cherry Flavor, Magnesium Stearate.
• Singolast® 10: Each film coated tablet contains Montelukast Sodium eq. to Montelukast 10mg.
Excipients: Lactose, Mannitol, Croscarmellose sodium, Hydroxy propyl cellulose, Microcrystalline cellulose, Magnesium stearate, Red iron oxide, Yellow iron oxide, Carnauba wax, hydroxypropyl methylcellulose, Titanium dioxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Leukotriene receptor antagonist.
ATC Code: R03D C03

Mechanism of action

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 receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Pharmacodynamic effects

Singolast® is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. In clinical studies, Singolast® inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by Singolast®. Treatment with Singolast® inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Singolast®, compared with placebo, decreased peripheral blood eosinophils in adult and pediatric patients. In a separate study, treatment with Singolast® significantly decreased eosinophils in the airways (as measured in sputum).
In adult and pediatric patients 2 to 14-year-old of age, Singolast®, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

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, Singolast® 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. Singolast® 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 Singolast® 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).
Singolast® 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).
Singolast® was neither mutagenic in in vitro and in vivo tests nor tumorigenic in rodent species.

Pharmacokinetic properties

Absorption

Singolast® is rapidly absorbed following oral administration.
• For the 4 mg chewable tablet to pediatric patients 2 to 5-year-old of age in the fasted state, Cmax is achieved 2 hours after administration. The mean Cmax is 66% higher while mean Cmin is lower than in adults receiving a 10 mg tablet.
• For the 5 mg chewable tablet, the Cmax is achieved in two hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.
• For the 10 mg film coated tablet, the mean peak plasma concentration (Cmax) is achieved three 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.

Distribution

Singolast® is more than 99% bound to plasma proteins. The steady-state volume of distribution of Singolast® averages 8-11 litres. Studies in rats with radiolabeled Singolast® 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

Singolast® is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of Singolast® are undetectable at steady state in adults and children.
Cytochrome P450 2C8 is the major enzyme in the metabolism of Singolast®. Additionally, CYP3A4 and 2C9 may have a minor contribution, although it Raconazole, an inhibition of CYP3A4, was shown not to change pharmacokinetic variables of Singolast® in healthy subjects that received 10mg Singolast® daily. Based on in vitro results in human liver microsomes, therapeutic plasma concentrations of Singolast® do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of Singolast® is minimal.

Elimination

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

INDICATIONS

• Singolast® 4: For pediatric patients 2 to 5-year-old of age.
Indicated in the treatment of asthma as add-on therapy in those 2 to 5-year-old patients with 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.
Singolast® 4 may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5-year-old 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. Singolast® 4 is also indicated in the prophylaxis of asthma from 2-year-old of age and older in which the predominant component is exercise-induced bronchoconstriction.
• Singolast® 5: For pediatric patients 6 to 14 -year-old of age.
Indicated in the treatment of asthma for pediatric patients from 6 to 14 -year-old 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 β-agonists provide inadequate clinical control of asthma.
Singolast® 5 may also be an alternative treatment option to low-dose inhaled corticosteroids for 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. Singolast® 5 is also indicated in the prophylaxis of asthma from in which the predominant component is exercise-induced bronchoconstriction.
• Singolast® 10: For adults and adolescents patients.
Singolast® is indicated in the treatment of asthma in adults and adolescents 15 -year-old of age and older 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 β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Singolast® is indicated in asthma. Singolast® can also provide symptomatic relief of seasonal allergic rhinitis. Singolast® is also indicated in the prophylaxis of asthma in adults and adolescents 15 -year-old of age and older in which the predominant component is exercise-induced bronchoconstriction.

CONTRAINDICATIONS

Patients who are hypersensitive to the active substance or to any ingredient in the formulation.

PRECAUTIONS

- The diagnosis of persistent asthma in very young children (6 months – 2 -year-old) should be established by a pediatrician or pulmonologist.
- Patients should be advised never to use oral Singolast® 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.
- Singolast® should not be abruptly substituted for inhaled or oral corticosteroids.
- There are no data demonstrating that oral corticosteroids can be reduced when Singolast® is given concomitantly.
- In rare cases, patients on therapy with anti-asthma agents including Singolast® 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, vasculitis 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.
• Singolast® 4: contains aspartame, a source of phenylalanine. May be harmful for people with phenylketonuria.
Singolast® 4mg contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
• Singolast® 5: contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 5 mg chewable tablet contains phenylalanine in an amount equivalent to 0.842 mg phenylalanine per dose.
Neuropsychiatric events have been reported in adults, adolescents, and children taking Singolast® 5mg Chewable Tablets. 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 Singolast® 5mg Chewable Tablets if such events occur.
• Singolast® 10: contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PREGNANCY AND LACTATION

Pregnancy

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

PIL201/1

Breast-feeding

Studies in rats have shown that Singolast® is excreted in milk. It is unknown if Singolast® is excreted in human milk.

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

Effects on ability to drive and use machines

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

DRUG INTERACTIONS

- Singolast® 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 Singolast® did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl oestradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.
- The area under the plasma concentration curve (AUC) for Singolast® was decreased approximately 40% in subjects with co-administration of phenobarbital. Since Singolast® is metabolised by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when Singolast® is co-administered with inducers of CYP 3A4, 2C8, and 2C9, such as phenytoin, phenobarbital and rifampicin.
- In vitro studies have shown that Singolast® is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving Singolast® and Rosiglitazone (a probe substrate representative of medicinal products primarily metabolised by CYP 2C8) demonstrated that Singolast® does not inhibit CYP 2C8 in vivo. Therefore, Singolast® 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 Singolast® is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving Singolast® and Gemfibrozil (an inhibitor of both CYP 2C8 and 2C9). Gemfibrozil increased the systemic exposure of Singolast® by 4.4-fold. No routine dosage adjustment of Singolast® 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 Singolast® with Itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of Singolast®.
- β-agonist therapy: Singolast® can be added to the treatment regimen of patients who are not adequately controlled on 'as-needed' short-acting beta-agonist. When a clinical response is evident (usually after the first dose), the patient may be able to decrease the use of 'as-needed' short-acting beta-agonist.
- Inhaled corticosteroids: Treatment with Singolast® can be used as add-on therapy in patients when other agents, such as inhaled corticosteroids, provide inadequate clinical control. Singolast® should not be substituted for inhaled corticosteroids

ADVERSE EFFECTS

Undesirable effects that may occur during treatment with Singolast® are classified into the following groups in order of frequency:

Very common (≥1/10)
- Upper respiratory infection

Common (≥1/100 to <1/10)
- Diarrhea
- Nausea
- Vomiting
- Elevated levels of serum transaminases (ALT, AST)
- Rash
- Pyrexia

Uncommon (≥1/1,000 to <1/100)
- Hypersensitivity reactions including anaphylaxis
- Dream abnormalities including nightmares
- Insomnia
- Somnambulism
- Irritability
- Anxiety
- Restlessness
- Agitation including aggressive behavior or hostility
- Depression
- Dizziness
- Drowsiness
- Paraesthesia/hypoesthesia
- Seizure
- Epitaxis
- Bruises
- Urticaria
- Pruritus
- Arthralgia
- Myalgia including Muscular cramp
- Enuresis in children
- Asthenia/fatigue
- Malaise
- Oedema
- Dry mouth
- Dyspepsia

Rare (≥1/10,000 to <1/1,000)
- Increased bleeding tendency
- Disturbance in attention
- Memory impairment
- Tic
- Palpitations
- Angioedema

Very rare (<1/10,000)
- Thrombocytopenia
- Hepatic eosinophilic infiltration
- Hallucinations
- Disorientation
- Suicidal thinking and behavior (suicidality)
- Churg-Strauss Syndrome (CSS)
- Pulmonary eosinophilia
- Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury)
- Erythrema nodosum
- Erythema multiform

DOSAGE AND ADMINISTRATION

• Singolast® 4: This medicinal product is to be given to a child under adult supervision. The dosage for pediatric patients 2-5-year-old of age is one 4 mg chewable tablet daily to be taken in the evening. If taken in connection with food, Singolast® 4mg chewable Tablets should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary. The Singolast® 4 mg chewable Tablet formulation is not recommended below 2 -year-old of age.

• Singolast® 5: The recommended dose for pediatric patients 6-14-year-old of age is one 5 mg chewable tablet daily to be taken in the evening. If taken in connection with food, Singolast® should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary.

• Singolast® 10: The dosage for adults and adolescents 15 -year-old 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 Singolast® on parameters of asthma control occurs within one day.
- Singolast® may be taken with or without food.
- Patients should be advised to continue taking Singolast® even if their asthma is under control, as well as during periods of worsening asthma.
- Singolast® should not be used concomitantly with other products containing the same active ingredient, Singolast®.
- No dosage adjustment is necessary 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.

Singolast® as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma

Singolast® is not recommended as monotherapy in patients with moderate persistent asthma. The use of Singolast® as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients 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. 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, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

Singolast® 4mg chewable Tablets as prophylaxis of asthma for 2 to 5-year-old patients in whom the predominant component is exercise-induced bronchoconstriction

In 2 to 5-year-old patients, 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 Singolast®. If satisfactory response is not achieved, an additional or different therapy should be considered.

Method of administration

Oral use.

Singolast® 4 & 5: The tablet should be chewed.

OVERDOSAGE

No specific information is available on the treatment of overdose with Singolast®. In chronic asthma studies, Singolast® 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 Singolast®. 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 pediatric 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 Singolast® and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

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

STORAGE CONDITIONS

Protect from light. Store below 30°C

Date of revision: December 2019.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh - Lebanon