RID-AR Tablets & RID-AR KID DT/Syrup (Montelukast sodium + Levocetirizine dihydrochloride)

Composition

RID-AR Tablets
Each uncoated bilayered tablet contains:
Montelukast sodium IP equivalent to montelukast.........................10 mg
Levocetirizine dihydrochloride IP....5 mg
Excipients........................................q.s.

RID-AR KID Dispersible Tablets
Each uncoated tablet contains
Montelukast sodium IP equivalent to
Montelukast .........................4 mg
Levocetirizine dihydrochloride IP....2.5 mg
Excipients........................................q.s.

RID-AR KID Syrup
Each 5 ml of syrup contains
Montelukast sodium IP equivalent to
Montelukast .................4 mg
Levocetirizine dihydrochloride IP....2.5 mg
Excipients........................................q.s.

Dosage Form

Oral Tablets, Dispersible Tablets and Syrup

Pharmacology

As RID AR Tablets, RID AR KID Dispersible Tablets and Syrup are a combination of montelukast and levocetirizine, the pharmacological properties of both the molecules are given separately:

Pharmacodynamics

Montelukast
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 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 that binds with high affinity and selectivity to the CysLT<sub>1</sub> receptor. Montelukast inhibits physiologic actions of LTD<sub>4</sub> at the CysLT<sub>1</sub> receptor without any agonist activity. In patients with seasonal allergic rhinitis aged 15 years and older who received montelukast, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of montelukast. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known.

Levocetirizine
Levocetirizine, the R-enantiomer of cetirizine, is a potent and selective antagonist of peripheral H<sub>1</sub>-receptors. Binding studies revealed that levocetirizine has high affinity for human H<sub>1</sub>-receptors (Ki = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l). Levocetirizine dissociates from H<sub>1</sub>-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours. The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo controlled trials in the model of the allergen challenge chamber. In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction compared with placebo in 14 adult patients: Inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment. The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies. Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose levocetirizine has comparable activity to cetirizine, both in the skin and in the nose. Pharmacokinetic/pharmacodynamic relationship 5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations. ECGs did not show relevant effects of levocetirizine on QT interval.

Montelukast

Absorption
After administration of the 10 mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C<sub>max</sub>) is achieved in 3 to 4 hours (T<sub>max</sub>). The mean oral bioavailability is 64%. The oral bioavailability and C<sub>max</sub> are not influenced by a standard meal in the morning. For the 4 mg chewable tablet, the mean C<sub>max</sub> is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state. The safety and efficacy of montelukast in patients with asthma were demonstrated in clinical trials in which the 10 mg film-coated tablets were administered in the evening without regard to the time of food ingestion. The safety of montelukast in patients with asthma was also demonstrated in clinical trials in which the 4 mg chewable tablets were administered in the evening without regard to the time of food ingestion. The safety of montelukast in patients with asthma was also demonstrated in clinical trials in which the 4 mg chewable
tablet and 4 mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of montelukast in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10 mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

**Distribution**
Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 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.

**Metabolism**
Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

*In vitro* studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. 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.

However, *In vitro* studies have shown that montelukast is a potent inhibitor of cytochrome P450 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*, and therefore is not anticipated to alter the metabolism of drugs metabolized by this enzyme.

**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 in several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast is nearly linear for oral doses up to 50 mg. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (14%).

**Levocetirizine**
The pharmacokinetics of levocetirizine is linear with dose and time independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

**Absorption**
Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 g h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270ng/ml and 308ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed. A dose of 5 mg (10 ml) of levocetirizine dihydrochloride oral solution is bioequivalent to a 5mg dose of levocetirizine tablets. Following oral administration of a 5mg dose of levocetirizine oral solution to healthy adult subjects, the mean peak plasma concentrations were achieved approximately 0.5 hours post-dose.

**Distribution**
No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain-barrier. Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

**Biotransformation**
The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting
from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose. Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances or vice-versa, is unlikely.

**Elimination**

The plasma half-life in adults is 7.9 ± 1.9 hours. The mean apparent total body clearance is 0.63 ml/min kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

**Renal Impairment**

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is, therefore, recommended to adjust the dosing intervals of levocetirizine, based on the creatinine clearance in patients with moderate and severe renal impairment. In anuric end-stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour haemodialysis procedure was.

**Indications**

RID AR Tablets, RID AR KID Dispersible Tablets and Syrup are indicated for relief of symptoms of allergic rhinitis (seasonal and perennial).

**Dosage And Administration**

**RID AR Tablets**

Adults (>15 years):
1 tablet once daily

**RID AR KID Dispersible Tablets**

Children (2-5 years):
1 tablet once daily

**RID AR KID Syrup**

Children (2-5 years):
5 ml syrup as measured from the given cup once daily.

**Contraindications**

RID AR Tablets, RID AR KID Dispersible Tablets and Syrup are contraindicated in patients with known hypersensitivity to montelukast, levocetirizine, to other piperazine derivatives or to any of the excipients. Also, contradicted in patients with severe renal impairment at less than 10 ml/min creatinine clearance, and patients undergoing haemodialysis. Children 6 months to 11 years of age with impaired renal function should not be administered. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Warnings And Precautions

General

Montelukast

Eosinophilic Conditions

Patients on therapy with 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast and these underlying conditions has not been established.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast.

Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking montelukast. Post-marketing reports with montelukast use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving montelukast appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

Levocetirizine

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with levocetirizine. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor co-ordination such as operating machinery or driving a motor vehicle after ingestion of levocetirizine. Concurrent use of levocetirizine with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

Urinary retention has been reported post-marketing with levocetirizine. Levocetirizine should be used with caution in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention. Discontinue, if urinary retention occurs.

Drug Interactions

Montelukast

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

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, such as phenytoint, phenobarbital...
and rifampicin. Although additional specific interaction studies were not performed, montelukast was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

*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 metabolised 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.)

Levocetirizine

*In vitro* data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No *in vivo* drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine. Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, glipizide and diazepam, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect. The extent of absorption of levocetirizine is not reduced with food although the rate of absorption is decreased. Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol. Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.

### Renal Impairment

Levocetirizine is known to be substantially excreted by the kidneys and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Dosage adjustment may be required in patients with impaired renal function. Hence this combination is not recommended in patients with impaired renal function.

### Hepatic Impairment

As levocetirizine is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment. But montelukast is mainly excreted through bile; caution is to be exercised while prescribing this combination in patients with impaired hepatic function. The pharmacokinetics of montelukast in patients with more severe hepatic impairment or with hepatitis has not been evaluated.

### Pregnancy

There are no adequate and well controlled studies of either montelukast or levocetirizine in pregnant women. Because animal reproduction studies are not always predictive of human response, this combination should be used during...
pregnancy only if it is considered to be clearly essential.

**Lactation**

It is not known if montelukast is excreted in human milk. Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk this combination is not recommended during lactation.

**Pediatric Use**

The safety and efficacy of montelukast in children with perennial allergic rhinitis below 6 months of age has not been established. The safety and effectiveness of levocetirizine in pediatric patients under 2 years of age have not been established.

**Geriatric Use**

**Montelukast**

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

**Levocetirizine**

Clinical studies of levocetirizine for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

**Undesirable Effects**

There is no data available on undesirable effects of this combination. However, side effects have been reported with individual molecules.

**Montelukast**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions (incidence ≥5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.

Montelukast has been evaluated for safety in approximately 2950 adult and adolescent patients with asthma 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with montelukast occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo: abdominal pain, asthenia/fatigue, fever, trauma, dyspepsia, dental pain, infectious gastroenteritis, headache, dizziness, influenza, cough, nasal congestion, rash, increased ALT and AST and pyuria.

Cumulatively, 569 patients were treated with montelukast for at least 6 months, 480 for one year, and 49 for two years
in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Montelukast has been evaluated for safety in 2199 adult and adolescent patients with seasonal allergic rhinitis 15 years of age and older in clinical trials. Montelukast administered once daily in the morning or in the evening had a safety profile similar to that of placebo. In placebo-controlled clinical trials, the following event was reported with montelukast with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection, 1.9% of patients receiving montelukast vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Montelukast has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received montelukast in two, 6-week, clinical studies. Montelukast administered once daily had a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with montelukast with a frequency ≥1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.

Montelukast has been evaluated for safety in 476 pediatric patients with asthma 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with montelukast for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of montelukast in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving montelukast, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis. The other adverse effect reported frequently in clinical trials with montelukast in this age group was headache. The frequency of less common adverse events was comparable between montelukast and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for montelukast. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 8 years of age receiving montelukast, the following events not previously observed with the use of montelukast in this age group occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, skin infection, and myopia.

Montelukast has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 230 for 6 months or longer, and 63 patients for one year or longer in clinical trials. In pediatric patients 2 to 5 years of age receiving montelukast, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis. Another adverse effect commonly reported in the clinical trials with montelukast in this age-group was thirst.

Montelukast has been evaluated in 280 pediatric patients with seasonal allergic rhinitis 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group safety study. Montelukast administered once daily in the evening had a safety profile similar to that of placebo. In this study, the following events occurred with a frequency ≥2% and at an incidence greater than placebo: headache, otitis media, pharyngitis, and upper respiratory infection. The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.
Montelukast has been evaluated for safety in 175 pediatric patients 6 to 23 months of age with asthma. The safety profile of montelukast in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. In pediatric patients 6 to 23 months of age receiving montelukast, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between montelukast and placebo. The other commonly reported adverse effects in clinical trials of montelukast in this age group included hyperkinesia, asthma, diarrhoea, eczematous dermatitis, rash.

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

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

**Blood and lymphatic system disorders:** Increased bleeding tendency, thrombocytopenia.

**Immune system disorders:** Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

**Psychiatric disorders:** Agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, psychomotor hyperactivity dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor, disturbance in attention.

**Nervous system disorders:** Drowsiness, dizziness, paraesthesia/hypoesthesia, seizures.

**Respiratory, thoracic and mediastinal disorders:** Epistaxis, Churg-Strauss Syndrome, pulmonary eosinophilia

**Cardiac disorders:** Palpitations.

**Gastro-intestinal disorders:** Diarrhoea, dry mouth, dyspepsia, nausea, vomiting, pancreatitis.

**Hepatobiliary disorders:** Elevated levels of serum transaminases (ALT, AST), rare cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with montelukast. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast was administered to patients who had underlying potential for liver disease, such as alcohol use or other forms of hepatitis.

**Skin and subcutaneous tissue disorders:** Angiooedema, bruising, urticaria, pruritus, rash, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis.

**Musculoskeletal and connective tissue disorders:** Pyrexia, Arthralgia, myalgia including muscle cramps

**General disorders and administration site conditions:** Asthenia/fatigue, malaise, oedema.

Patients with asthma on therapy with 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

**Levocetirizine**

Use of levocetirizine has been associated with somnolence/headache, fatigue, nasopharyngitis, dry mouth, and pharyngitis in subjects 12 years of age and older and pyrexia, somnolence, cough, and epistaxis in children 6 to 12 years of age in clinical trials. Further uncommon incidences of adverse reactions like asthenia or abdominal pain, and urinary retention were observed. Additional adverse reactions of medical significance observed at a higher incidence than in placebo in adults and adolescents aged 12 years and older exposed to levocetirizine are syncope (0.2%) and weight increased (0.5%)

Adverse reactions reported in subjects 1 to 5 years of age and in 6 months to 11 months of age were pyrexia, diarrhoea, vomiting, otitis media, constipation, salivary hypersecretion, thirst, hunger, fatigue, anorexia, somnolence, psychomotor hyperactivity, sleep disorder, middle insomnia, epistaxis, pruritus, headache.

In addition to the adverse reactions reported during clinical studies and listed above, very rare cases of the following
adverse drug reactions have been reported in post-marketing experience:

Immune system disorders: Hypersensitivity including anaphylaxis
Psychiatric disorders: Aggression, agitation, hallucinations, depression.
Nervous system disorders: Convulsion, paraesthesia, dizziness.
Eyes disorders: Visual disturbances, blurred vision
Cardiac disorders: Palpitations, tachycardia
Respiratory, thoracic, and mediastinal disorders: Dyspnoea
Gastrointestinal disorders: Nausea, vomiting
Hepatobiliary disorders: Hepatitis
Skin and subcutaneous tissue disorders: Angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
Musculoskeletal, connective tissues, and bone disorders: Myalgia
Investigations: Weight increased, abnormal liver function tests
Renal and urinary disorders: dysuria

Besides these events reported under treatment with levocetirizine, other potentially severe adverse events have been reported from the post-marketing experience with cetirizine. Since levocetirizine is the principal pharmacologically active component of cetirizine, one should take into account the fact that the following adverse events could also potentially occur under treatment with levocetirizine: suicidal ideation, orofacial dyskinesia, severe hypotension, cholestasis, glomerulonephritis, and still birth.

**Overdosage**

There is no data reported on the overdosage of this combination. However, overdosage has been reported with individual molecules.

**Montelukast**

No specific information is available on the treatment of overdosage with montelukast. 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 a week without clinically important adverse experiences.

There have been reports of acute overdosage in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg. 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 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.

In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

**Levocetirizine**

Symptoms of overdose may include drowsiness in adults, and in children, initially agitation and restlessness, followed by drowsiness. There is no known specific antidote to levocetirizine. Should overdose occur consider standard measures to remove any unabsorbed drug. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

**Packaging Information**

RID AR Tablets: Blister pack of 10 tablets
RID AR KID Dispersible Tablets: Blister pack of 10 tablets
RID AR KID Syrup: Bottle pack of 30ml

Last updated: November 2013
Last reviewed: November 2013

RID-AR Tablets & RID-AR KID DT/Syrup

Source URL: https://ciplamed.com/content/rid-ar-tablets-rid-ar-kid-dtsyrup