www.ijramr.com

ISSN : 2350-0743

International Journal of Recent Advances in Multidisciplinary Research

Vol. 08, Issue 06, pp. 6975-6982, June, 2021

RESEARCH ARTICLE

A REVIEW ON TOXICOLOGICAL STUDY OF MONTELUKAST

Lawanya Pandey, *Gayatri Sawale and Amisha Punmiya

NCRD's Sterling Institute of Pharmacy, Plot No. 93, Sector 19, Near Sea-Woods Railway Station, Nerul (E), Navi Mumbai - 400706. Maharashtra, India

ARTICLE INFO

Article History:

Received 25th March, 2021
Received in revised form
25th April, 2021
Accepted 29th May, 2021
Published online 30th June, 2021

Keywords:

Adverse effects, CYP2C8 Inhibitor, Neuropsychiatric events, RP-HPLC analysis, Sulfoxide impurity, Toxicology.

ABSTRACT

Montelukast is a specific cysteinyl leukotriene receptor antagonist, belonging to the quinoline series and therapeutic agent used for the treatment of bronchial asthma and allergic rhinitis. This review described the impurities, toxicity studies, adverse effects of drug montelukast. The presence of impurities affect the efficacy and safety of pharmaceutical products. Sulfoxide impurity was found to be having a major effect on efficacy. The common adverse effects found were headache, upper respiratory infection and Neuropsychiatric Events, which were not much different compared to placebo. Toxicities of montelukast impurities have to be carefully improved because it is chronically used in patients, particularly children. These studies implied its effectiveness and tolerance in children. It also has been associated with Churg-Strauss syndrome in a small number of adults. We have studied comparative action and side effects of Montelukast with other drugs along with some drug-drug interaction studies. The relation between neuropsychiatric events and montelukast's use is clarified in this review. Major concerns of montelukast-associated adverse drug reactions included the Churg-Strauss syndrome. This drug has some inhibitory effect on Cytochrome enzymes required in drug metabolism. In drug-interaction studies, the recommended dose of montelukast with effect on pharmacokinetics of various drugs are discussed. Our findings suggested that the toxicity of drug impurities can be monitored by measuring its level, safety profile and under good supervision.

INTRODUCTION

Montelukast, marketed under the brand name SINGULAIR or others, is a medication used in the treatment of asthma. It is less preferred than inhaled corticosteroids[(1)]. It is not used for acute asthma attacks. It is used for allergic rhinitis and hives of long duration. It is a second line treatment for allergic rhinitis which should be used in combination with an antihistamine. Montelukast or Montelukast Sodium is a specific cysteinyl leukotriene receptor antagonist. It belongs to the quinoline series. It is a therapeutic agent for the treatment of bronchial asthma and second line treatment of allergic rhinitis(AR). Leukotrienes are critical inflammatory mediators in disease of the lower airway, where they are used in producing inflammation, hyper-responsiveness and bronchoconstriction. An alternative to inhaled corticosteroid (ICS) therapy, the addition of a second method of use of drug (montelukast) results in improved control of symptoms. Montelukast was the first antileukotriene to be licensed for use in children aged ≥6 years. It has been launched worldwide since October 1997(Finland). The regulatory bodies were satisfied with the overall tolerability profile of the medication.[(3)]

Corresponding author:** ***Gayatri Sawale,
NCRD's Sterling Institute of Pharmacy, Plot No. 93, Sector 19, Near Sea-Woods Railway Station, Nerul (E), Navi Mumbai - 400706. Maharashtra, India.

An Impurity is a component of a drug substance which is not a chemical entity or not a form of excipient of a drug product. The presence of such impurities may influence the efficacy and safety of pharmaceutical products, even if it is in a small proportion. The efforts focus on eliminating impurities from drug products, technically it is not possible to remove it all percentage and further elimination increases the cost. Therefore, in order to control impurities, an acceptable risk level concept or Threshold of toxicological concern (TTC) approach is useful. Hence, to meet the requirement of impurities present in the drug, their comprehensive studies are done to identify and characterize impurities of montelukast sodium. Although this drug is well tolerated, several case reports regarding ADRs after use of montelukast have been published. For this reason, it appears desirable to explore, compile and summarize the literature to be a helpful perspective to clinicians, pharmacists and physicians. [(5)]

Analysis of Impurities in drug product using RP-HPLC: An in-house LC gradient method was developed for the separation of impurities of montelukast sodium. This LC method was able to separate all the process-related substances with good resolution.[(3)] Each sample was analysed in triplicate [(Figure 1)]. Quantification of 6 impurities in USP is already conducted using RP-HPLC analysis. Impurities indicated were sulfoxide, cis isomer, Michael adducts I & II, methylketone, methylstyrene impurities [(Figure 2)].

Table 1. Montelukast Data

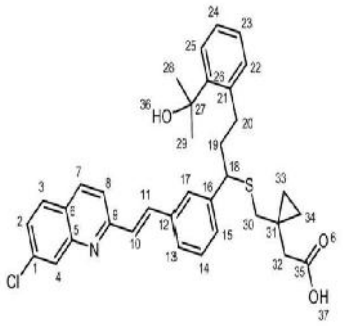
MONTELUKAST DATA[2]		STRUCTURE
Formula	$C_{35}H_{36}ClNO_3S$	
Molar mass	586.19g/mol	
Melting point	145-148^{0}C (293 to 298 °F)	
Route of administration	Oral	
Bioavailability	63-73%	
Protein binding	99%	
Metabolism	Liver (CYP2C8- major, CYP3A4 and CYP2C9- minor)	
Elimination half life	2.7-5.5 hours	
excretion	Biliary	

Table 2. Ingredients of Montelukast dosage form[4]

Active ingredient	Montelukast sodium
Inactive ingredients	
formulation	ingredients
4 mg oral granules	mannitol, hydroxypropyl cellulose, magnesium stearate.
4 mg, 5 mg chewable tablets	mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavour, aspartame, magnesium stearate.
People with phenylketonuria SINGULAIR4-mg chewable tablets SINGULAIR 5-mg chewable tablets	0.674 mg of phenylalanine 0.842 mg of phenylalanine
10 mg tablet	MCC, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate
Film coating	hydroxypropyl methylcellulose, hydroxypropyl cellulose, red ferric oxide, yellow ferric oxide, titanium dioxide, carnauba wax.

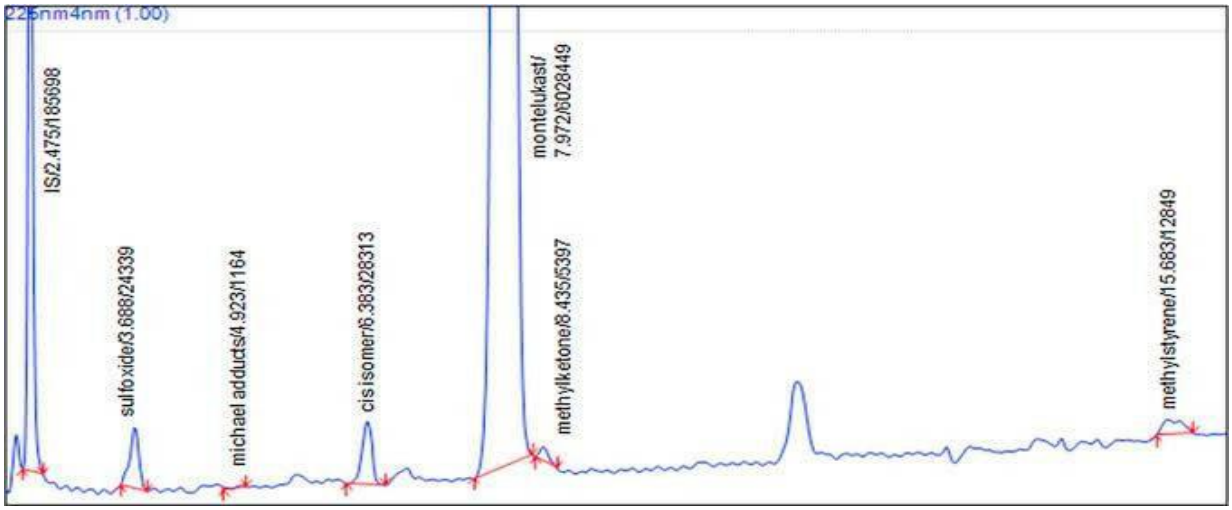


Figure 1. Analysis Result of Impurities

These investigated impurities were chosen by considering the clinical importance of the drug, including its target population and usage duration. Many toxicological study models are conducted in order to study its cytotoxicity, like the Bacterial Reverse Mutation Test and Genetic Toxicity model. But the overall result showed that impurities like sulfoxide were not mutagenic and non-genotoxic. Long-term control medication montelukast is used daily and regularly to achieve and maintain control of asthma. Toxicities of montelukast impurities should be carefully evaluated as it is chronically used in patients, particularly in children sometimes for lifetime courses. From a toxicological perspective, it is important to note that children are more vulnerable than adults to xenobiotics and that they might respond with different health effects. Also cancer risks are higher in early-life exposure than the similar exposure later in life.[5]

Impurities present are, (Figure 3)

Impurity-1: During the basic hydrolysis stage, the cyano group elaborated into a carboxylic group and leads to acid via the transformation of amide intermediate, i.e. impurity-1. If amide intermediate could not be completely hydrolyzed into acid, impurity-1 will be resulted.

Impurity-2: To isolate the montelukast, acetic acid was used in the work up stage. Due to acidic pH, tertiary hydroxyl moiety protonates. Since protonated hydroxyl is a good leaving group, it takes away the adjacent methyl group proton and leads to the formation of impurity-2.

Impurity-3 and -4: Starting material 2 contains saturated and des chloro analogue of 2, these compounds undergo sequential reactions and lead to formation of impurity-3 and impurity-4, respectively.

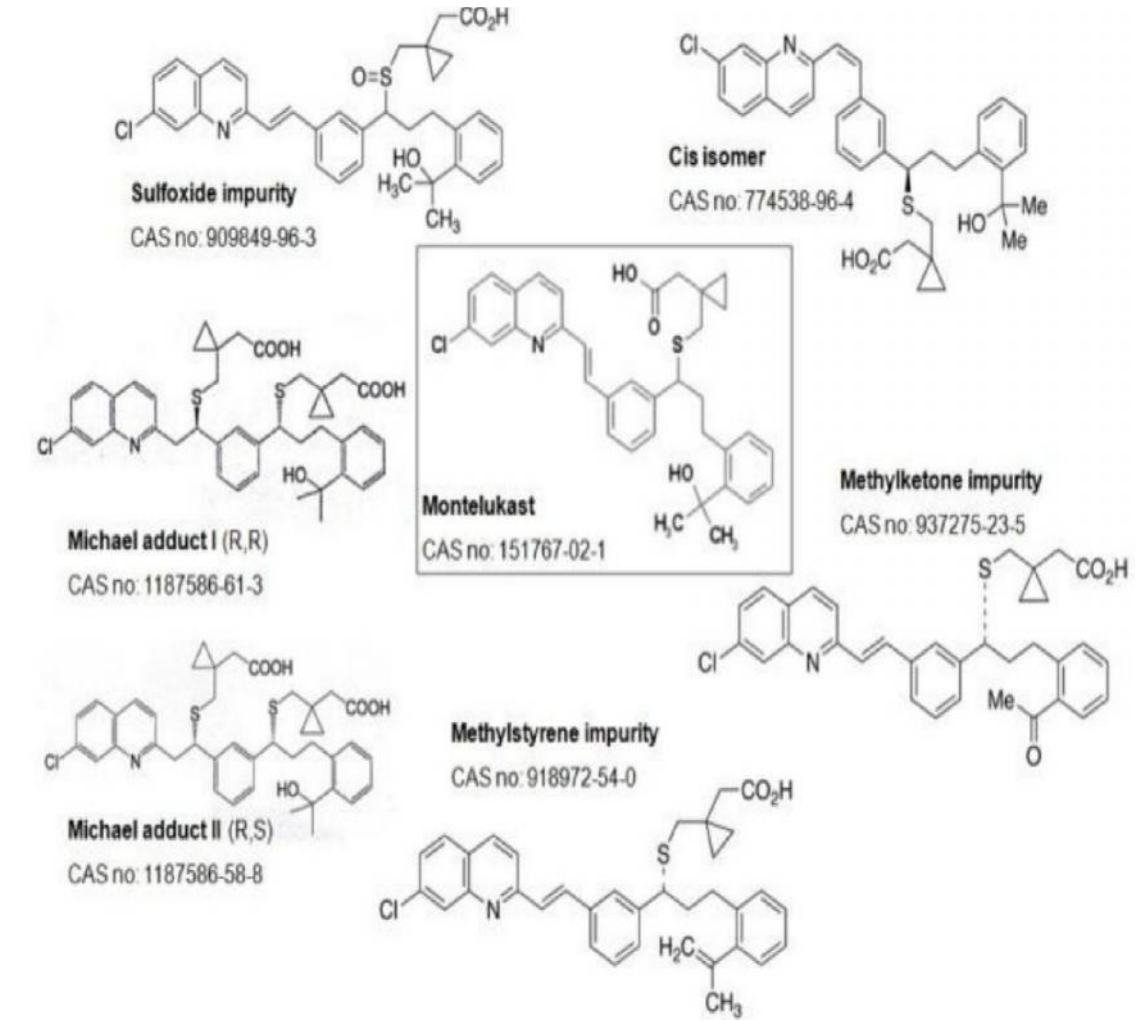


Figure 2. Structures of Impurities

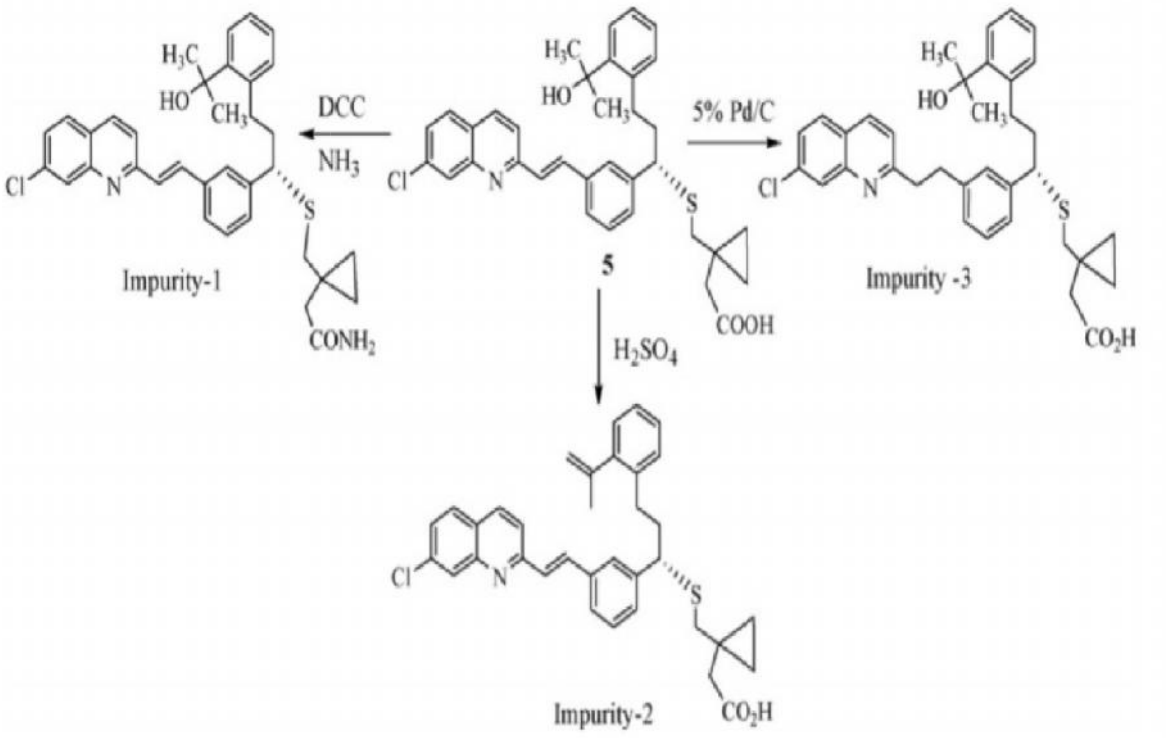


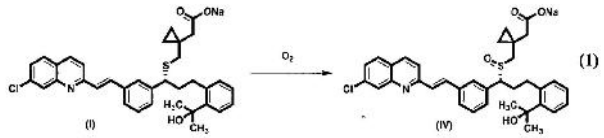
Figure 3. Reactions for Impurities

These 4 impurities in montelukast sodium bulk drug were identified, synthesized, isolated and characterised by HPLC techniques. [3]

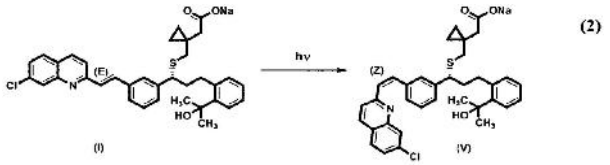
Degradation Study: [6]

In the montelukast molecule there are a number of functional groups that harm the chemical stability of this entity. Montelukast is known to be prone to various types of degradation; it is mainly the case of three kinds of chemical transformation:

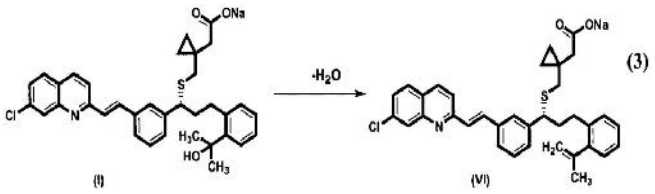
- Oxidation of mercapto group to sulfoxide group according to equation (1),



- Isomerisation at the location of the double bond from (E) to (Z), or from trans to cis by the effect of light according to equation (2),



- Dehydration of tert. alcohol, forming the corresponding olefin according to equation (3).



Sulfoxide Impurity: It is acknowledged that the effective therapy with montelukast taken by a patient is reduced due to generation of sulfoxide as an impurity during manufacturing and storage, as it is considered an inactive compound pharmacologically. The presence of more sulfoxide impurities in drug products for adults may be suggested to occur due to having more ingredients in adult dose formulation compared to pediatric drug products and differences in tablet form, it is impossible to deduce with certainty because many factors play a role in formation of impurities. In a previous thermal stress testing study of montelukast, sulfoxide impurity was observed as a major degradation product. Further in another separate research, it was studied that the presence of microcrystalline cellulose in the formulation may induce peroxide oxidation of montelukast and presence of aspartame as a sweetener might cause higher amounts of sulfoxide impurity. Sulfoxide is one of the metabolites of montelukast. In safety testing of metabolites, if it accounts for plasma levels greater than 10 percent of parent drug systemic exposure. However, sulfoxide metabolite which is identified as a minor metabolite and safety testing is hardly expected to be done. There are many studies on identification, quantification and characterization of impurities in drugs. In such studies of research, sulfoxide impurity exceeded the threshold value in some drug products, hence it was qualified to study as a major impurity.

In cytotoxic study, cytotoxic signs are observed at high doses in some of the strains, but overall results showed that sulfoxide impurity has no mutagenic activity in metabolic activation. In in-vitro human lymphocyte chromosomal aberration test, sulfoxide impurity did not show any clastogenic activity with and without metabolic activation. Some results achieved which showed cytotoxicities at high concentrations, in vivo acute toxicity tests may further be considered to be important for the impurity in the future. In this study, qualification was needed for the sulfoxide impurity above limit. Actually, not only investigated impurities but also all unidentified impurities in drugs may affect organisms as a mixture. However, risks which may occur in organism just in case of interaction between any sorts of impurities are unknown. Furthermore, there are also combinations of montelukast products with desloratadine or levocetirizine in the market. So, interaction with impurities coming from other active substances might also be studied.[5,7]

Comparative Drug studies: Montelukast 4 or 5 mg/day has been analyzed with budesonide inhalation suspension 0.5 mg/day for patients aged 2–8 years, suffering from mild asthma or recurrent wheezing during a 12-month, multicenter, randomized study. The frequencies of adverse effects were comparable, which were of mild to moderate intensity. Those who took montelukast, experienced mostly of headache, lower tract infection, and abnormal behavior, which were drug-related. Few patients stopped taking montelukast due to adverse events, but there have been no deaths. Montelukast (10 mg/day) has been analyzed with levocetirizine 5 mg/day for 2 days. For ragweed-induced rhinitis during a double-blind, parallel-group, randomized, placebo-controlled study. Treatment-related adverse events were common with montelukast, when compared with placebo (8.6%) and levocetirizine (8.3%). Drug related adverse effects were seen mostly with montelukast (5.8%) than levocetirizine (3.8%) or placebo (2.9%). there have been no serious treatment-related adverse events. Headache was the foremost typical adverse event with montelukast (3.2%) and placebo (1.9%) but it had not been reported in those taking levocetirizine. A review of comparisons of montelukast and inhaled glucocorticoids compared to inhaled glucocorticoids alone or montelukast with inhaled glucocorticoids versus active control and inhaled glucocorticoids in adolescents and adults. The addition of montelukast didn't end during a greater overall rate of adverse events or increased withdrawal rates related to adverse events. [8]

Placebo-controlled studies: The efficacy and safety of montelukast are studied in a world , multicenter, randomized study. The patients were assigned for 12 weeks of treatment with placebo or montelukast 4 mg as a chewable tablet and there have been no clinically relevant differences between the groups within the general frequencies of adverse effects, individual adverse effects, or the frequency of laboratory adverse effects, especially raised serum transaminase activities. (Table 3) But Asthma was more frequent within the placebo group. The withdrawal frequency was similar compared to the 2 groups. Accidental administration of montelukast up to 18 times the daily dose of 4 mg was well tolerated. The authors came to the conclusion that montelukast is well tolerated in this specific group of preschool children. The security and tolerability of montelukast in patients is evaluated during a meta-analysis of pooled data from multicenter, randomized studies and long term extension studies.

Table 3. Adverse experiences occurring in patients with an incidence greater than that in patients treated with placebo.

	Montelukast 10 mg/day (%) (n = 1955)	Placebo (%) (n = 1180)
Body as a whole		
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive system disorders		
Dyspepsia	2.1	1.1
Gastroentellitis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous system, psychiatric	1.9	1.4
Dizziness	18.4	18.1
Headache		
Respiratory system disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/skin appendages disorder		
Rash	1.6	1.2
Laboratory adverse experience*		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

*Number of patients tested: ALT and AST, n = 1935 and 1170: pyuria, n = 1924 and 1159 (montelukast and placebo, respectively).
ALT: Alanine aminotransferase: AST: Aspartate aminotransferase.

There have been no clinically important differences in individual adverse events between the 2 treatment groups. No dose related adverse effects of montelukast have been found up to 20 times the daily dose of 10 mg. [9,10]

Drug-Drug Interactions: [10-12]

- Theophylline, Prednisone, and Prednisolone - SINGULAIR has been administered with other therapies routinely employed in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of Montelukast don't have clinically important effects on the pharmacokinetics of drugs like theophylline, prednisone, and prednisolone Montelukast dose of 10mg for pharmacokinetic steady state, did not cause clinically significant changes within the kinetics of 1 intravenous dose of theophylline. Montelukast's higher dose daily, didn't cause any major change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or intravenous prednisolone.
- Oral Contraceptives, Terfenadine, Digoxin, and Warfarin - In drug interaction studies, the recommended clinical dose of Montelukast did not have clinically important effects on the pharmacokinetics of the drugs, oral contraceptives (norethindrone, ethinyl oestradiol), terfenadine, digoxin and warfarin. Montelukast's higher dose regularly didn't significantly change the plasma concentrations of either component of a pill containing norethindrone 1 mg/ethinyl oestradiol 35 mcg. Montelukast of a dose of 10 mg once daily dosed to pharmacokinetic steady state do not change the plasma concentration profile of terfenadine or fexofenadine, the carboxylate metabolite; did not change the pharmacokinetic profile or urinary excretion of immunoreactivity digoxin; did not change the pharmacokinetic profile or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the International Normalized Ratio (INR).
- Thyroid Hormones, Sedative Hypnotics, Non-Steroidal Anti-Inflammatory Agents, Benzodiazepines, and Decongestants - Medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants. Cytochrome P450 (CYP) Enzyme Inducers, Phenobarbital, which induces hepatic metabolism, decreased the realm under the plasma concentration curve. No dosage adjustment for SINGULAIR is recommended. It is reasonable to use appropriate clinical monitoring when potent CYP enzyme inducers, like phenobarbital or rifampin, are co-administered with SINGULAIR. Effect of Montelukast on Cytochrome P450 (CYP) Enzymes is that Montelukast is a potent inhibitor of CYP2C8 in vitro.The data from a clinical drug-drug interaction study demonstrated that the pharmacokinetics of rosiglitazone are not altered when the drugs are administered, indicating that Montelukast do not inhibit CYP2C8 in vivo. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by the enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide). Co-administration of Montelukast with itraconazole (CYP3A4 inhibitor), resulted in no significant increase within the systemic exposure of Montelukast. Studied Data from a clinical drug-drug interaction study involving Montelukast and gemfibrozil (an inhibitor of both CYP2C8 and 2C9) demonstrated that gemfibrozil, at a therapeutic dose, increased the systemic exposure of Montelukast by 4.4-fold. Co-administration of itraconazole, gemfibrozil, and Montelukast didn't further increase the systemic exposure of Montelukast. Based on available clinical data, no adjustment in dosage of montelukast is required when given with gemfibrozil.

Other interactions: [4,11-13]

SINGULAIR is not used in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. SINGULAIR should not be substituted for inhaled or oral corticosteroids.

- Aspirin Sensitivity - Patients with diagnosed aspirin sensitivity should continue avoidance of aspirin or NSAIDs while taking SINGULAIR. It is used in improving airway function in asthmatics having aspirin sensitivity; it hasn't been shown to have bronchoconstriction response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin sensitive asthmatic patients.
- Physicians must know the eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy of their patients. An interaction between SINGULAIR and these underlying condition has not been established.
- Nonclinical Toxicology of Carcinogenesis, Mutagenesis, & Impairment of Fertility – No evidence of tumorigenicity was seen in carcinogenicity studies. There

is no further study regarding mutagenic or clastogenic activity within the subsequent assays; the microbial mutagenesis assay, the V-79 mammalian cell assay, the alkaline elution assay in rat hepatocytes, the chromosomal abnormality assay in Chinese hamster ovary cells, and within the in vivo mouse bone marrow chromosomal abnormality assay. Montelukast had no effects on fertility in male rats (oral doses - 800 mg/kg).

- Montelukast (leukotriene receptor antagonist) was investigated for its inhibition of the human drug-metabolizing enzyme cytochrome P4502C8 (CYP2C8). It was demonstrated to be an inhibitor of CYP2C8-catalyzed amodiaquine N-deethylase, rosiglitazone N-demethylase, and paclitaxel 6 α -hydroxylase in human liver microsomes. Inhibition was also detected when the reaction was catalysed by recombinant heterologously expressed CYP2C8.The mechanism was of competitive inhibition, with Ki values ranging from 0.0092 μM to 0.15 μM. Inhibition potency was highly dependent on the microsomal protein concentration. Boosting the microsomal protein concentration by 80-fold yielded a 100-fold reduction in inhibition potency. Preincubation of montelukast with human liver microsomes and NADPH did not alter the inhibition potency, which suggested that montelukast is not a mechanism-based inactivator. It is a selective inhibitor for human CYP2C8; inhibition of other human cytochrome P450 enzymes was less. These in vitro data shows the use of montelukast as a selective CYP2C8 inhibitor that can be used to find the contribution of this enzyme to drug-metabolism reactions. These data also elevates the possibility that montelukast could have an effect on the metabolic clearance of drugs which are having CYP2C8-catalyzed metabolism as a major clearance pathway, thereby eliciting pharmacokinetic drug-drug interactions. so, it is theoretically possible that the combination of montelukast with a CYP2C8 substrate (e.g. amodiaquine (anti-malarial drug)) could elevate the plasma concentrations of the substrate.
- Additionally, it is unknown whether Montelukast is excreted into human breast milk, but there is caution regarding the use of such medication

Adverse Reactions: The clinical trials were conducted under widely varying conditions, where adverse reaction rates were studied in the clinical trials of a drug. The common adverse reactions in controlled clinical trials were found to be upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhoea, influenza, rhino rhea, sinusitis.

Adults, 15 Years aged and Older with Asthma SINGULAIR has been evaluated for safety in clinical trials. In placebo-controlled clinical trials, the next adverse effects reported with SINGULAIR occurred in more than or capable 1% of patients and at an incidence greater than that in patients who were treated with placebo. Neuropsychiatric disorders and sleep disturbances, which affect the paediatric population, show a negative impact on patients' quality of life, although most of them had a clinical resolution after discontinuing Montelukast. Currently, the pharmacological mechanisms causing neuro-psychiatric alterations are not clear. Various preclinical experiments, that explore the function of this pathway in the central nervous system, reveal an over-expression in the reparative process that occur during pathological conditions. Even though studies on children are lacking, it might be hypothesized that, in susceptible paediatric patients, blocking CysLT1 by its specific antagonists can lead to neuropsychiatric adverse reactions. Montelukast can cause hepatobiliary and pancreatic dysfunction. It has been described in a case of fatal hepatotoxicity and in this case, it was not possible to describe the mechanism triggering hepatotoxicity. Various experimental models of drug-induced hepatotoxicity have shown a protective effect of Montelukast in rats[2,11].

Neuropsychiatric Events - Serious neuropsychiatric events have been reported with use of Montelukast Sodium (SINGULAIR). The post marketing study reports showed that aggressive behaviour, anxiousness, depression, disorientation, disturbance in attention, stuttering, hallucinations, insomnia, irritability, memory loss, obsessive-compulsive symptoms, restlessness, suicidal thoughts-behaviour and tremor as side effects. NP events have been seen in adult, adolescent and paediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during SINGULAIR treatment for asthma, but some were reported after SINGULAIR discontinuation. Due to the chance of NP events, the advantages of SINGULAIR not outweighs the risks in some patients, mostly when the symptoms of disease could also be mild and adequately treated with alternative therapies. We can reserve the use of SINGULAIR for patients suffering from allergic rhinitis who have an inadequate response or intolerance to alternative therapies. Pharmacists must discuss the benefits and side effects of SINGULAIR use with patients and caregivers when prescribing SINGULAIR and advise patients or caregivers to be alert for changes in behaviour or for new NP symptoms when taking SINGULAIR. If new NP symptoms are seen, then it's an advice to a patient to discontinue SINGULAIR and should get in touch with a healthcare provider immediately. In some cases, symptoms went after stopping SINGULAIR therapy, but in some cases symptoms persisted even after discontinuation of SINGULAIR. So, it should continue to monitor and give supportive care until symptoms resolve and re-evaluate the benefits and risks of restarting treatment with SINGULAIR if such events occur. Many studies that have analysed published case reports or data-bases of adverse drug response reporting systems gave suggestions that Montelukast use is related to the neuropsychiatric events such as anxiety, sleep disturbance, depression, and suicidality. Montelukast may affect nerve remyelination when it is given with Pexidartinib and this may lead to clinical benefits or side effects[4,14,15]

Cardiovascular events – Cysteinyl leukotriene namely LTC4, LTD4 and LTE4 are pro-inflammatory mediators of the 5-lipoxygenase pathway, which has a role in asthma as well as genetic and preclinical evidence of a contribution to cardiovascular (CV) diseases. From the study, it was reported that 4.6% of asthmatic patients had suffered a major CV event during the observatory period. The result showed a potential role of LTRAs, montelukast in targeting inflammation and reducing ischemic events in asthmatic patients[16,17].

Parasomnia - Parasomnias in the form of sleep talking or sleepwalking were not formerly reported as adverse effects of Montelukast. Sleep talking is an event of utterances to coherent chat during sleep, and it is of slight medical concern. Sleepwalking events are partial arousals which occur during the first half of sleep. Sleepwalking can be minor or complicated behaviours including even driving. Although

Montelukast decreases AHI in patients with OSA by managing upper airway ARS, its use may result in the outcome of parasomnias. In such an event, the discontinuation of Montelukast is usually adequate to lessen this adverse effect. Alternative Medicine modalities to treat ARS in patients developing parasomnias while receiving Montelukast should be investigated. Those possible alternatives may include a higher dose of inhaled corticosteroids in asthma, topical nasal corticosteroids or nasal antihistamine drugs for rhinitis, or the use of omalizumab [(18,19)].

Simplicity of the treatment regimen, as well as efficacy and the frequency of adverse effects contribute to the tolerability of a drug. In general, Montelukast is well tolerated in paediatric patients, although it remains important to continue to monitor patients for adverse effects. Montelukast is a well-tolerated drug in adult and paediatric patients. In the present research, it appears clear that Montelukast administration has several ADRs, of which physicians should be aware in their clinical practice, considering that the administration of Montelukast, along with related other therapies, could increase the risk of drug-drug interaction. A better comprehension of the mechanisms leading to ADRs related to this anti-leukotriene could help researchers and clinicians to define a therapeutic strategy aimed to reduce Montelukast toxicity. Further, it is necessary to conduct more accurate epidemiological studies on a large scale to discover risk factors favouring Montelukast.

Safety profile : [(8,20-21)] The most commonly reported clinical adverse events of montelukast drug treatment were fever, upper respiratory infection, and asthma exacerbation. Although montelukast is considered a safe drug because it's reported incidence of adverse drug reactions (ADRs) was similar to that of the control group. Major concerns related to montelukast-associated ADRs included the occurrence of Churg-Strauss syndrome (CSS) and the possible association between LTRA (Leukotriene Receptor Antagonist) and suicidality. A case-crossover study of some patients with CSS reported that the use of montelukast was associated with a 4.5-fold increased risk of Churg-Strauss syndrome onset within 3 months. Churg-Strauss syndrome , also known as eosinophilic granulomatosis with polyangiitis, which is a rare autoimmune disorder, causing vasculitis in patients with a history of asthma or allergic rhinitis. Treatment for CSS is with glucocorticoids and other immunosuppressive drugs. Hence, montelukast is a confounding factor and the withdrawal of steroid use may be associated with the development of CSS symptoms.

- The United States Food and Drug Administration issued a warning in 2008 on the possible association between montelukast use and suicidality. Moreover, in 2020, it was announced that the drug requires a boxed warning about mental health side effects because many other anti-allergy medicines and many health care professionals and patients or caregivers are unaware of the risk of mental health side effects.
- One of the studies investigated the relation in montelukast and antidepressant use and it was concluded that montelukast initiation was weakly associated with antidepressant prescription. However, the study concluded that antidepressant use may be correlated with asthma severity and not a Montelukast. These findings do not guarantee the safety of montelukast, so clinicians should consider the benefits and risks of montelukast before prescribing it. The efficacy of montelukast for pediatric asthma is inferior to that of ICSs(Inhaled corticosteroids). Nonetheless, montelukast has several advantages.
- First, patients using ICS, have to use the correct inhalation technique, as no special skills are required to administer montelukast.
- Second, both patients and prescribing physicians prefer using a drug that is administered once a day.
- Third, there is no impact on growth, unlike of ICSs use, which can potentially impair a child's growth.
- Montelukast maintenance therapy is mainly recommended for asthmatic children who experience symptoms more than once a month and is recommended as an alternative method for children with step 2 asthma.

Serum EDN (eosinophil-derived neurotoxin) can be used as a biomarker for monitoring the effectiveness of pediatric asthma. It was recommended that starting maintenance therapy with montelukast when the EDN level is ≥53 ng/mL and stopping when the EDN level decreases to <45 ng/mL.
However, additional studies are needed to determine the validity of these recommendations.

Montelukast in COVID-19 Treatment: Although quantity is not quality, effects of Montelukast may constitute as many synergistic and potentiating therapeutic possibilities in COVID-19. Montelukast is a commonly used drug that does not require any prior cardiological or biological examination; it can be prescribed for pregnant women and frail older adults, and it shows a "comfortable" therapeutic range. Moreover, it could be all the more effective for patients with comorbidities such as diabetes, sleep apnea, smoking, obesity, or symptomatic atherosclerotic lesions. We support the conduct of clinical trials testing the effect of Montelukast in COVID-19 patients from a variety of populations, while keeping in mind its adverse effects. Finally, it should also be emphasized that a potential massive use of MK in COVID-19 would risk depriving asthma patients of their treatment, which should also be anticipated. [(22)]

CONCLUSION

- Impurity levels of generic and innovator drugs were not observed to be significantly different. All these impurities were isolated by liquid chromatography and specific spectroscopic techniques.
- The sulfoxide impurity was concluded to be an ordinary non mutagenic impurity in studies conducted by reviewed research for hazard identification. Investigated impurities as well as all unidentified impurities in drugs may affect organisms as a mixture.
- Drugs possessing CYP2C8-catalyzed metabolism elicites pharmacokinetic drug-drug interactions with Montelukast.
- Studies have analyzed case reports of adverse drug response, that montelukast use is associated with neuropsychiatric events. Montelukast is a confounding factor and the withdrawal of steroid use, associated with the development of CSS symptoms.
- This result is positive for regular consumers, children and adults. Compliance is further built by the level of support and supervision provided by parents and caregivers.
- Simplicity of treatment, efficacy, and tolerability of drugs contribute to monitoring patients for adverse effects and

effects due to toxicity of drug impurity. These findings help to characterize the parameters affecting the stability of drugs and provide useful insight into ways of analysis.

- Using Montelukast in COVID-19 can risk depriving asthma patients of their treatment.

LITERATURE CITED

1.Montelukast Sodium Monograph for Professionals" Drugs.com. AHFS. Retrieved 23 December 2018. https://www.drugs.com/monograph/montelukast.html

2. Internet - Wikipedia https://en.m.wikipedia.org/wiki/ Montelukast #cite_ref-AHFS2018_4-0
3. M. Saravanan, K. Siva kumari, P. Pratap Reddy, M.N. Naidu, J. Moses Babu, Alok Kumar Srivastava, T. Lakshmi Kumar, B.V.V.N. Chandra Sekhar,Bollikonda Satyanarayana. Identification, synthesis, isolation and spectral characterization of potential impurities of montelukast sodium. Journal of Pharmaceutical and Biomedical Analysis 48 (2008) 708–715. doi:10.1016/j.jpba.2008.07.007
4. Merk Sharp & Dohme Corp., a subsidiary of Merk & Co., Inc. (SINGULAIR) https://www.merck.com/research-and-products/singulair/
5. Emerce E, Cok I, Degim IT. Determination of the impurities in drug products containing montelukast and in silico/in vitro genotoxicological assessments of sulfoxide impurity. Toxicol Lett. 2015 Oct 14;238(2):90-9. doi:

10.1016/j.toxlet.2015.07.003. Epub 2015 Jul 20. PMID: 26205398.

6. Internet - NDA Organization https://newdrugapprovals.org/tag/montelukast-sodium/
7. Internet - PubChem, Compound Summary https://pubchem.ncbi.nlm.nih.gov/compound/Montelukast-sulfoxide
8. Internet – Science Direct https://www.sciencedirect.com/ topics/pharmacology-toxicology-and-pharmace utical-science/montelukast
9. Montelukast, Editor(s): J.K. Aronson, Meyler's Side Effects of Drugs (Sixteenth Edition), Elsevier,2016, Pages 1105-1107, ISBN 9780444537164, https://doi.org/10.1016/B978-0-444-53717-1.01106-9. https://www.sciencedirect.com/science/article/pii/B9780444537171011069

10.Anjuli Nayak. A review of montelukast in the treatment of asthma and allergic rhinitis. 2004 Mar;5(3):679-86. PMID: 15013935, doi: 10.1517/14656566.5.3.679 https://pubmed.ncbi.nlm.nih.gov/15013935/

11.Price,D.TolerabilityofMontelukast. Drugs59,35–42(2000). https://doi.org/10.2165/00003495-200059001-00006 https://link.springer.com/article/10.2165/00003495-200059001-00006#citeas

12.Robert L Walsky, R Scott Obach, Emily A Gaman, Jean-Paul R Gleeson, William R Proctor. Selective inhibition of human cytochrome P4502C8 by montelukast, Drug metabolism and disposition 33 (3), 413-418, 2005 DOI: https://doi.org/10.1124/dmd.104.002766

13.Artesunate Amodiaquine Winthrop (artesunate, amodiaquine) (summary of product characteristics). Gentilly, France: Sanofi-aventis; August 2010. http://www.wipo.int/export/sites/www/research/en/data/sanofi/marketed_produ cts/Artesunate_and_Amodiquine.pdf

14.Aldea Perona, A., García-Sáiz, M. & Sanz Álvarez, E. Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase® . Drug Saf 39, 69–78 (2016). https://doi.org/10.1007/s40264-015-0360-2

15."New Strategies for Restoring Myelin on Damaged Nerve Cells") Check |url= value (help). Neuroscience News. https:/neurosciencenews.com/remyelination-optic-nerve-17255

16.Internethttps://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-war ning-about-serious-mental-health-side-effects-asthma-and-allergy-drug#:~:text=Common%20side%20effects%20of%20montelukast,runny%20nose%2C%2 0and%20sinus%20infection.

17.Marschallinger J, Schäffner I, Klein B, Gelfert R, Rivera FJ, Illes S, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat Commun 2015;6:8466.

18.B. V. Vaughn and O. F. D'Crus, “Cardinal manifestations of sleep disorders,” in Principles and Practice of Sleep Medicine, pp. 647–657, Elsevier, St. Louise, Mo, USA, 5th edition, 2011.

19.SamerAlkhuja,NatalyaGazizov, Mary Ellen Alexander, "Sleeptalking! Sleepwalking! Side Effects of Montelukast", Case Reports in Pulmonology, vol.2013,ArticleID813786,3 pages,2013. https://doi.org/10.1155/2013/813786 https://www.hindawi.com/journals/cripu/2013/813786/

20.Storms W, et al. Clin Exp Allergy. 2001. Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged > or = 6 years. PMID: 11167954 https://pubmed.ncbi.nlm.nih.gov/11167954/#:~:text=No%20dose-related%20a dverse%20effects,safety%20experience%20seen%20to%20date.

21.P. Guilpain, J.-F. Viallard, P. Lagarde, P. Cohen, M. Kambouchner, J.-L. Pellegrin, L. Guillevin, Churg–Strauss syndrome in two patients receiving montelukast, Rheumatology, Volume 41, Issue 5, May 2002, Pages 535–539, https://doi.org/10.1093/rheumatology/41.5.535

22.JeJean Barré, Jean-Marc Sabatier and Cédric Annwei l.Front. Pharmacol., 04 September 2020 | Montelukast Drug May Improve COVID-19 Prognosis: A Review of Evidence. https://doi.org/10.3389/fphar.2020.01344,

****