T.C.
YEDİTEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

DEPARTMENT OF PHARMACEUTICAL TOXICOLOGY

DISPROPORTIONALITY ANALYSIS OF DATA FROM VIGIBASE AND OTHER GLOBAL PRODUCT SAFETY DATABASES ON TOXICITY OF IRON CHELATING AGENTS

DOCTOR OF PHILOSOPHY THESIS

Burcu Eda Arda, Pharm.

İstanbul-2022

T.C.
YEDİTEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

DEPARTMENT OF PHARMACEUTICAL TOXICOLOGY

DISPROPORTIONALITY ANALYSIS OF DATA FROM VIGIBASE AND OTHER GLOBAL PRODUCT SAFETY DATABASES ON TOXICITY OF IRON CHELATING AGENTS

DOCTOR OF PHILOSOPHY THESIS

Burcu Eda ARDA, Pharm.

Advisor: Prof. Dr. Hande SİPAHİ

THESIS APPROVAL FORM

Institute : Yeditepe University Institute of Health Sciences

Programme : Pharmaceutical Toxicology

Title of the Thesis : Disproportionality analysis of data from VigiBase and other Global Product Safety Databases on toxicity of iron chelating agents

Owner of the Thesis : Burcu Eda Arda

Examination Date : 18/11/2022

This study have approved as a Doctorate Thesis in regard to content and quality by the Jury.

	Title, Name-Surname (Institution)
Chair of the Jury:	Prof. Dr. Ahmet Aydın Yeditepe University
Supervisor:	Prof. Dr. Hande Sipahi Yeditepe University
Member:	Prof. Dr. Terken Baydar Hacettepe University
Member:	Prof. Dr. Gül Özhan İstanbul University
Member:	Assoc. Prof. Dr. Şaziye Sezin Yücelik Atatürk Üniversitesi

APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ..... and numbered .....

Prof. Dr. Bayram YILMAZ

Director of Institute of Health Sciences

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

Burcu Eda ARDA

DEDICATION

It is with genuine gratitude and warm regard that

I dedicate this thesis to my beloved family.

ACKNOWLEDGEMENTS

First of all, I would like to express my appreciation for my advisor, Prof. Dr. Hande Sipahi, for her endless guidance, encouragement, and support, without whom this thesis would be impossible. It was a pleasure to learn from her wisdom and to complete this thesis. She inspired me immensely and encouraged me to think outside of the box.

I also would like to offer my thanks to Prof. Dr. Ahmet Aydın for his guidance, positive encouragement, and endless support. I always felt his moral support throughout my academic life.

I also would like to express my sincerest appreciation to Assoc. Prof. Dr. Muhammed Hamitoğlu. His lessons throughout my PhD education were very useful.

I would like to extend my thanks to Yeditepe University for the facilities and the financial support during this thesis.

I had the pleasure of collaborating with World Health Organization's Uppsala Monitoring Center during my thesis. I would like to thank them for their constant support and prompt help regarding the data they provided. They answered my questions very genuinely and the data they provided added tremendous value to my thesis.

Finally, no words would be enough to express my gratitude for my family. I would like to thank my father, Dr. Yusuf Ali Arda, my mother Sevinç Arda, my brother Pharm. Burak Serhat Arda, for always trusting in me and supporting me to achieve my goals and dreams.

TABLE OF CONTENTS

LIST of TABLES

LIST of FIGURES

LIST of SYMBOLS and ABBREVIATIONS

ADR: Adverse drug reaction

AE: Adverse event

AO: Advers olay

CI: Confidence Interval

CIOMS: Council for International Organizations of Medical Sciences

DAEN: Database of Adverse Event Notifications

DMT1: Divalent Metal Transporter 1

DNA: Deoxyribonucleic acid

e-ALAS: erythroid isoform of aminolevulinate synthase

EMA: European Medicine's Agency

EU: European Union

FAERS: FDA Adverse Event Reporting System

Fe: Iron

FDA: Food Drug Administration

GI: Gastrointestinal

HFE: Hemochromatosis gene

ID: Identification

IV: Intravenous

LIC: Liver iron concentration

LLT: Lowest Level Terms

MDS: Myelodysplastic syndrome

MGPS: Multi-Item Gamma Poisson Shrinker

MRI: Magnetic Resonance Imaging

NTBI: Non-transfferin bound iron

OR: Odds Ratio

PIDM: Programme for International Drug Monitoring

PRR: Proportional Reporting Ratio

PT: Preferred Terms

RBC: Red blood cell

ROR: Reporting Odds Ratio

ROS: Reactive oxygen species

SOC: System Organ Class

Tf: Transferrin

TGA: Therapeutic Good Administration

TITCK: Türkiye İlaç ve Tıbbi Cihaz Kurumu

TÜFAM: Türkiye Farmakovijilans Merkezi (Turkish Center of Pharmacovigilance)

UMC: Uppsala Monitoring Center

USA: United States of America

FDA: Food and Drug Administration

WHO: World Health Organization

ZIP14: Zinc transporter induced in response to pro-inflammatory stimuli

ABSTRACT

ARDA BE, (2022), Disproportionality analysis of data from VigiBase and other Global Product Safety Databases on toxicity of iron chelating agents. Yeditepe University, Institute of Health Sciences, Department of Pharmaceutical Toxicology, Ph.D. Thesis, İstanbul.

Iron supplements are commonly prescribed for treatment of iron deficiencies, associated complications, for its immune and cognition improving activities. Due to this common practice, also after blood transfusions and unintentional ingestions; iron toxicities may occur. Iron chelators; deferasirox, deferiprone and deferoxamine, are used to treat toxicities. Unfortunately, iron chelators are also likely to cause serious adverse reactions. The purpose of this retrospective study is to review iron chelators' pharmacovigilance data by analyzing different sources and comparing real life results, to introduce unknown safety information, and potential new signals. Disproportionality analysis was conducted using safety databases including VigiBase, the WHO global database of individual case safety reports, to known safety profile of products and FAERS, the FDA Adverse Event Reporting System, for iron chelator cases between 2010 and 2021, to investigate the AE associations. Unlisted AEs from databases with strong associations (Reporting odds ratio; ROR≥1) were revealed as potential signals. RORs were calculated for iron chelator associations to headache (common), blurred vision (rare) and sepsis (serious), using 24581 cases from FAERS and 383361 cases from VigiBase. Results were within 95% Confidence Interval (CI). Strong association between deferoxamine and blurred vision (ROR: 2.83, 95% CI 2.01, 4.27), deferiprone and sepsis (ROR: 135.20, 95% CI 132.88, 135.12) were identified. However, upon comparing RORs results from different databases, inconsistencies between chelator-AE associations were obtained. Fatal cases had common patient characteristics, which may effect the warnings and contraindications in local labels. findings suggest that it is essential to combine different resources while reviewing safety data, to promote reporting awareness and safety studies to discover unknown parts of safety profiles.

Keywords: Iron chelators, iron toxicity, pharmacovigilance, iron chelator toxicity, disproportionality analysis

ÖZET

ARDA BE, (2022), VigiBase ve diğer global ürün güvenliği veritabanlarından alınan verilerle demir şelatörlerinin toksisitesine ilişkin orantısızlık analizi. Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Farmasötik Toksikoloji Departmanı, Doktora Tezi, İstanbul.

Demir takviyeleri; demir eksiklikleri, buna bağlı komplikasyonlar ve bağışıklık ve kognitif fonksiyon güçlendirici aktiviteleri için sıklıkla reçetelenmektedir. Bu yaygın uygulama, kan transfüzyonları ve hatalı kullanımlar, demir toksisitelerini beraberinde getirmektedir. Demir şelatörleri, deferasiroks, deferipron ve deferoksamin, demir fazlalığını tedavi etmek için verilir. Şelatörler de ciddi advers olaylara (AO) sebep olabilmektedir. Bu retrospektif çalışmayla; demir şelatörlerinin farmakovijilans verilerini; farklı kaynakları analiz etmek, gerçek yaşam sonuçlarını karşılaştırmak, bilinmeyen güvenlilik bilgilerini ve potansiyel sinyalleri ortaya koymak amaçlanmıştır. Orantısızlık analizi, Dünya Sağlık Örgütü'nün global güvenlik veritabanı VigiBase ve Amerikan Sağlık Otoritesi'nin veritabanı FAERS'den alınan, 2010-2021 yıllarına ait demir şelatörü vakalarında AO ilişkilerini araştırmak amaçlanmıştır. Veri tabanlarından alınan, listelenmemiş ve ilişkilendirilebilir çıkan AO'lar ise (Raporlanan göreceli risk oranı, Reporting odds ratio; ROR≥1) potansiyel sinyal olarak açığa çıkarılmıştır. ROR, 24581 FAERS ve 383361 Vigibase vakası kullanılarak başağrısı (yaygın), bulanık görme (nadir), sepsis (ciddi) AO'larıyla şelatörlerin ilişkisini değerlendirmek için hesaplanmıştır. Sonuçlar %95 güven aralığındadır (CI: Confidence interval). Deferoksamin ve görme bozukluğu için (ROR: 2,83, 95% CI 2,01, 4,27), deferipron ve sepsis için (ROR: 135,20, 95% CI 132,88, 135,12) güçlü ilişkilendirme ihtimali bulunurken, AO'ların veritabanlarından hesaplanan sonuçlarında uyumsuzluk görülmüştür. Ölüm vakalarında, uyarı ve kontrendikasyonları etkileyebilecek ortak hasta özellikleri saptanmıştır. Sonuçlar, değerlendirmede farklı kaynakları kullanmanın, güvenlilik profillerinin bilinmeyenlerinin ortaya çıkarılması için raporlama bilincinin, güvenlilik çalışmalarının desteklenmesinin önemini doğrulamaktadır.

Anahtar kelimeler: Demir şelatör ajanları, demir toksisitesi, farmakovijilans, demir şelatör toksisitesi

1. INTRODUCTION and PURPOSE

Iron is an essential element for human body for its function in important systems. As iron deficiency can be dangerous to sustain its important function, iron supplements are very widely used. This common practice comes with common iron overdoses as well (1). As expected, since iron plays a vital role in many systems, excess iron can damage many functions of the body. For this reason, it is very important that the iron level does not exceed the maximum concentration level, and when it does, it is intervened and brought to the normal blood/iron concentration range. In such circumstances, some methods are needed to remove excess iron from the body (2). Iron chelator agents are frequently preferred because of their rapid effects and the success of iron in preventing side effects (3).

Pharmacovigilance is a discipline with increasing awareness, especially during the COVID-19 pandemic. During the pandemic, people learned definitions such as phases of clinical trials, side effects, safety profile. While adverse event reporting awareness is still fairly low in most of the countries, the awareness is changing (4). Although this awareness is increasing, there is still a long way to go. For example, currently, commonly reported events are either serious or fatal. Reporting unintentional ingestions, overdoses are very uncommon, although they are also as important to know (5). According to the data from VigiBase (6), the World Health Organization (WHO) global database of individual case safety reports, and Food Drug Administration Adverse Event Reporting System (FAERS), reporting an adverse event of a chelating agent is even less (7,8), as there is already a toxic manifestation from a product and there is an attempt to reverse it. The focus is more so on the primary product and the side effect of the antidote is usually neglected.

With this idea, in this thesis, it was aimed to reveal the unknown aspects of the safety profiles of iron chelators. Many sources have been combined to understand the parallelism of the data in the local product information with real-life data. Our sources included local labels, relevant pharmacovigilance announcement regarding iron chelators, which could include past signals and label updates, and finally, real life data from pharmacovigilance databases as well as from local and international literature. For

this purpose, iron chelators currently on the market; deferasirox, deferiprone and deferoxamine, were examined by using two different pharmacovigilance databases; FAERS and VigiBase. During our review, three adverse events with different frequencies and types were specifically selected, and the results from two different pharmacovigilance databases were also compared. The aim was also to understand the impact of toxicities in children and to contribute to the risk benefit profile of these products.

Since pharmacovigilance reporting must continue as long as the drug is on the market (9), it is not possible to reach sufficient reporting amount. There will always be unexpected adverse events and new information related to a drug's safety profile. That is why, additionally, it was also aimed to increase awareness of pharmacovigilance and encourage reporting, especially by healthcare professionals.

At the time of this thesis, no other similar study where chelating agents and data regarding its toxicity and safety were analyzed using many tools including pharmacovigilance databases. This stands out as our innovative, unique and different side.

1.1. Iron and Iron metabolism

Iron is a metallic element, located at number 26 in the periodic table. It can be found in certain minerals as well as mineral waters and in soils. It is an essential constituent of hemoglobin, cytochrome, and other components of respiratory enzyme systems. It takes part in crucial processes in the human body such as the oxygen transport to tissue via hemoglobin and in cellular oxidation mechanisms. Hemoglobin is responsible for carrying oxygen from lungs throughout the human body. Iron is responsible for muscle storage and oxygen usage (10).

Depletion of iron stores might cause anemia related to iron deficiency, as iron is necessary to build up the blood in anemia. Iron is also part of many other proteins and enzymes (11).

Iron molecule loses 2 electrons in the oxidation process, and Iron(II) oxide is formed. This is also known as ferrous oxide, and it means that it can bond with other atoms that contain an extra 2 electrons to share. Iron(III) oxide, which is also called

ferric oxide, has iron that lost 3 electrons and so can take an extra 3 electrons via bonding with other atoms, by using the same mechanism (10).

There are plenty of different iron supplements on the market, but mostly they contain Fe(II) and Fe(III). Injection supplements differ in this case; as most iron supplements have to go through the intestine (12).

So iron's cellular toxicity can vary according to its valency, solubility and linkage, the intestine conditions and time of response (13).

A lot of different molecules including transferrin, ferritin, hepcidin are involved in body iron metabolism as well as in different functions, such as absorption, erythroid iron uptake, reutilization of red blood cells, storage of hepatic iron, and systemic regulation (14).

Ingested iron can be non-heme iron and heme iron. Non-heme iron is mainly composed of inorganic ferric Fe(III) iron, and is absorbed into enterocytes after reduction of Fe(III) to Fe(II) by duodenal cytochrome b (15,16). On the other hand, heme-iron derived obtained from meat is absorbed through a heme carrier protein into enterocytes. Here, it will be degraded. Iron within enterocytes is then transferred from the luminal to the vascular site of the cell, and released into the circulation via ferroportin in the form of Fe(II) (17).

Excreted Fe(II) is thereafter oxidized to Fe(III) by hephaestin. Hephaestin is a homolog of ceruloplasmin, and the resulting ferric iron is bound to serum Tf (18).

For patients who suffer from genetic anemias and bone marrow failures, to overcome the symptoms, regular transfusion is necessary. Transfused red blood cells are degraded by macrophages, in which the recycled iron is overloaded and the excess iron saturates the binding capacity of transferrin. This excess iron appears in the circulation as a form of non-Tf-bound iron (19,20), and it causes organ dysfunction as ROS is produced. Around 0.5 mg of iron is present in one milliliter of blood, and there is no active mechanism in place for this excess iron's excretion (14).

The average life span of circulating red blood cells is around 120 days, which means that 20 mg of iron derived from 20 ml of RBCs are processed every day. Within macrophages, heme derived from phagocytized RBCs is catabolized by HO-1, and free iron is released (21).

Intra-cellular iron is released into the circulation via a transmembrane protein called ferroportin, and the iron is donated to transferrin and reutilized for the process of bone marrow erythropoiesis (22).

As per *Angelucci*'s calculation, at around 7 mg/g of iron is a critical level for the onset of organ dysfunction in liver and [iron accumulation (mg per kg) = liver iron concentration (mg per g weight x 10.6)] (23,24).

Ferritin and hemosiderin are main forms of iron when they are stored in liver. In addition to ferritin and hemosiderin, a fraction of free iron can be found in the form of the labile iron pool (LIP) within cells. This free form may be toxic when in excess. It is active in intracellular metabolism via oxidation–reduction reactions, cell proliferation, and cell signaling (14).

Hepatocytes have two pathways for uptake of iron from the circulation:

1) Tf-bound iron (Fe2-Tf) at physiological iron concentrations,

2) non transferrin bond iron in iron overload conditions (16).

When there is an iron overload, non-transferrin bound iron appears in the blood circulation and is taken up through DMT1 and ZIP14, on hepatocytes (25). Bone marrow erythroblasts need large amounts of iron for hemoglobin synthesis. TfR1 is strongly expressed in erythroblasts and functions as the uptake system of extracellular Fe2-Tf. Iron is transferred to mitochondria within erythroblasts and is then incorporated into the center of the heme ring. Heme ring is synthesized by condensation of daminolevulinic acid, a product made by erythroid d-aminolevulinic acid synthase. The synthesis of eALAS is also regulated by a binding protein called IRP along with TfR1 (26). The phenotype of ringed sideroblastic anemias occur through this pathway, when there is a genetic abnormality (27).

1.2. Iron Deficiency

Iron deficiency anemia is simply due to an insufficient level of iron. As lack of iron directly effects the hemoglobin production, iron and oxygen used by organs and tissues are majorly linked (11).

Hemoglobin synthesis have two main components: heme synthesis and globin production. It starts with globin chain production in the cytosol of erythrocytes and as it

occurs by genetic transcription and translation. Globin gene transcription is induced when heme is present. Heme synthesis, which starts with glycine and succinyl coenzyme A and ends with the protoporphyrin IX ring production, occurs in both the cytosol and the mitochondria of erythrocytes. The binding of the protoporphyrin to a Fe2+ ion forms the final heme molecule (28).

Hemoglobin is a two-way respiratory carrier and takes part in distributing oxygen from the lungs to the tissues. This way, it facilitates the return transport of carbon dioxide. In the arterial circulation, hemoglobin has low affinity for carbon dioxide and a high affinity for oxygen. Hence the lack of hemoglobin may become crucial (29).

Iron deficiency can be corrected with different methods, however; it is initially necessary to treat the reason behind it. Iron supplements are one of the most common ways. Other treatment options may differ according to the underlying cause, such as treating peptic ulcers or removing bleeding tumors (30). Blood hemoglobin levels can be measured by hemoglobin test, if necessary (31).

1.2.1. Anemia

Anemia is a very common blood disorder that effects millions of people in the world. It occurs when a patient does not have enough red blood cells or when the red blood cells do not function properly. Diagnosis can be made when the blood test results in hemoglobin value of less than 13.5 gm/dl for men or less than 12.0 gm/dl for women. Symptoms can also contribute to diagnosis, which may include weakness feeling, shortness of breath, dizziness, fast or irregular heartbeat, cold hands or feet, and so on (32).

Iron deficiency anemia is the most common type, which may be due to blood loss as well as due to poor absorption of iron. Vitamin-deficiency anemia may occur due to low levels of vitamin B12 or folate, which is usually due to being malnourished. On the other hand, there might be some anemia types that are genetic, such as pernicious anemia or aplastic anemia (32). Other reasons may be viral infections, ionizing radiation, and exposure to toxic chemicals or drugs that can cause aplastic anemia. Hemolytic anemia occurs when RBCs are broken up in the bloodstream or in

the spleen. Hemolytic anemia may be due to mechanical causes such as heart valves that are leaking or aneurysms, infections, autoimmune disorders, or abnormalities that occur during childbirth. Inherited abnormalities may also have an impact on the hemoglobin or the RBC cell structure or function. Examples of this type of anemia may be some types of thalassemia and low levels of enzymes (3). Sickle cell anemia is an inherited hemolytic anemia in where hemoglobin protein is aberrant, which causes the RBCs to be rigid and clog the circulation as they are unable to flow through small blood vessels (33). There might be other diseases that are indirectly causing body's RBC producing function. As an example, some patients that have kidney disease may suffer from anemia because of kidneys' inability to make enough erythropoietin to signal the bone marrow to make new or more red blood cells. Cancer treatments such as chemotherapy can also impair the RBC production, and anemia often occurs as a result of that (32).

1.2.2. β-thalassemia

Beta thalassemia, commonly known as Mediterranean thalassemia/anemia, is a blood disorder that reduces the hemoglobin production (34).

Greek words thalassa (sea) and haima (blood) form the word thalassemia. It is a hereditary blood disorder characterized by anomalies in the synthesis process of the beta chains of hemoglobin; and it results in different phenotypes, some people may experience severe anemia while some are clinically asymptomatic. It is seen in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the coasts of Africa and in South America, hence the origin of the word makes sense (35).

Mutations in the hemoglobin subunit beta gene, which is a gene that guides for beta-globin production, cause beta thalassemia. These mutations hence lead to ineffective erythropoiesis, anemia, and hepcidin deficiency (12).

Patients suffering from beta thalassemia having low levels of hemoglobin lead to many tissues and organs not having enough oxygen. It also manifests as a shortage of RBCs, that causes pale skin, weakness, fatigue, and so on. There is also a high risk of occurrence of abnormal blood clots (36). According to the severity, sign and symptoms,

beta thalassemia can be classified into three types, which are summarized in table 1 (35–37):

Table 1. Thalassemia types according to the severity and signs and symptoms

Thalassemia types	Signs and symptoms
Thalassemia major	Signs and symptoms appear within the first 2 years of life. Children might be diagnosed when they do not gain weight and grow at the expected rate, jaundice may be developed. An enlarged spleen, liver, and heart may be seen, their bones may be misshapen. Some patients experience delayed puberty.
Thalassemia intermedia	It is milder than thalassemia major. Signs and symptoms appear in early childhood or later in life. Patients have mild to moderate anemia. Patients may have slow growth and bone abnormalities.
Thalassemia minor	Patients are mostly asymptomatic.

Thalassemia can be managed by different ways including but not limited to blood transfusions, lifestyle and diet change. Side effects such as iron overload must be monitored carefully (35,38). *Olivieri* and *Brittenham* recommend that children with thalassemia major go through determination of liver iron concentration after 1 year of blood transfusions (24).

1.2.3. Myelodysplastic Syndrome

Myelodysplastic syndromes are a group of disorders caused by blood cells that are do not function properly or that are poorly formed. Management of this disease usually aims to slow the disease, ease symptoms and prevent further complications. Common practices to do so may include blood transfusions and medications to boost production of blood cell (39).

Low RBC counts can cause severe fatigue as well as some other symptoms. Patients suffering from myelodysplastic syndrome and anemia might benefit from getting injections of a manmade version of the growth factor erythropoietin, which can

sometimes help the bone marrow make new red blood cells. If that is not helpful or enough, based on the patient's condition, RBC transfusions might be necessary. Although this practice comes with some risks of infections such as infections like hepatitis or, the benefits of the transfused cells are majorly more than its risks (40).

1.2.4. Hemochromatosis

Hereditary hemochromatosis is a common inborn error of iron metabolism characterized by excessive dietary iron absorption and iron deposition in several tissues. Despite the responsible mutation being known in most cases, considerable uncertainty exists in the mechanism by which the normal gene product, HFE, regulates iron homeostasis. Studies in cultured cells have not yet clarified the mechanism by which mutations lead to excess dietary iron absorption (41). It has 4 types, according to mutations, which is summarized in in Table 2 (42);

Table 2. Hereditary hemochromatosis types and their mutations

Type 1	Classical HFE gene mutations resulting in a cysteine-to-tyrosine substitution at amino acid 282 (C282Y) or an aspartate-to-histidine substitution at amino acid 63 (H63D)
Type 2	Nonclassical (also known as juvenile hemochromatosis) resulting from mutations in iron regulatory protein, hemojuvelin (HJV gene)
Type 3	Nonclassical resulting from mutations in the transferrin receptor protein 2 (TFR2 gene)
Type 4	Nonclassical resulting from mutations in the iron exporter, ferroportin (SLC40A1 gene)

At first, most of the patients are asymptomatic. Later, pain in knuckles is often one of the first signs of the disease. Further symptoms may include abdominal pain, loss of body hair and sex drive, heart flutters, lack of energy, memory or brain fog, weight loss and gray or bronze coloring of the skin (43). Hepatic failure, hepatocellular

carcinoma, diabetes mellitus, cardiac failure, impotence in men and arthritis can be some of the clinical symptoms (41).

Hemochromatosis may also be seen when iron builds up due to other medical conditions or medical treatments, which would be called secondary hemochromatosis. These conditions may include anemia, kidney dialysis, chronic liver disease, blood transfusions, iron supplements or injections (44).

There are several ways to diagnose and differentiate the type of hemochromatosis. Blood testing is performed to identify the amount of iron-bound proteins in the bloodstream, and to confirm the presence of mutated genes, a DNA testing can be performed. Serum transferrin saturation test can be helpful to measure the amount of iron bound to transferrin. Transferrin saturation values that are identified to be greater than 45% are considered too high. Serum ferritin test measures the amount of iron stored in the liver. If the serum transferrin saturation test results are higher compared to normal, serum ferritin shall be checked (45).

As many other condition or underlying disease can also cause elevated ferritin, both blood tests are typically abnormal among people with hemochromatosis. For more accurate results, some additional tests may be required, such as liver function tests, MRI, and liver biopsy. Liver biopsies are essential especially if a liver damage is suspected (45).

Treatment options may be variant according to patient's condition, but most preferred options are phlebotomy and chelation therapies. Although phlebotomy is a very effective option, it may be avoided if requested by the patient, due to the procedure's nature. Changes in the diet are also recommended (46,47).

1.3. Iron Deficiency Treatment Protocol in Turkey

In Turkey, in general, treatment protocols from WHO are followed. According to this, oral iron treatment including iron sulphate, iron fumarate, iron gluconate is prescribed. Dose for adults is approximately 180 mg per day and it may differ between 100 to 200 mg according to patients' symptom severity, age, ferritin levels and potential gastrointestinal side effects (48).

In iron deficiency anemia, with oral iron treatment, hemoglobin (Hgb) levels may elevate by 1-2 g/dl in 2 to 4 weeks. Because of this reason, hemoglobin levels may be checked in 2 to 4 weeks. If the underlying condition is treated, with appropriate dosing, patient may recover from anemia in 2 to 4 months. After normal hemoglobin levels, iron treatment may continue for 3 more months for iron storage, especially in cases of menorrhagia or child growth period (3,49).

If the treatment is not enough, blood transfusion may be required. However oral iron treatment is preferred as it is safer and cheaper, compared to intravenous iron (48).

Parenteral iron treatment may be needed if;

- Patient cannot appropriately follow the oral iron treatment
- Patient cannot tolerate the iron treatment
- The anemia symptoms are getting worse
- There is ongoing blood loss
- Gastrointestinal disease such as ulcerative colitis gets worse
- Patient suffers from iron deficiency disease
- Patient is a hemodialysis patient
- Patient suffers from functional iron deficiency (50).

Parenteral treatment may be given via intramuscular or intravenous (iron sucrose, iron gluconate, iron dextran) route. It must be noted that intramuscular route may be painful and both routes may cause allergic reactions, such as hypotension, muscle cramps, diarrhea, urticaria, fever, nausea, vomiting, hypertension, chest pain and anaphylaxis in the early stages, and lymphadenopathy, myalgia, arthralgia and fever in later stages (51).

Total dose may be calculated according to the body weight. Total dose may be divided or given at once.

Hemoglobin iron deficit (mg) = body weight (kg) x (14 - Hgb) x (2.145) (52)

Erythrocyte transfusion may be necessary for patients who experience active bleeding and unstable hemodynamic state, or patients who show signs of organ ischemia due to iron deficiency (53).

Iron deficiency is more likely in women of reproductive age because of the regular blood loss during menstrual cycle (54). In Europe, from 61 to 97% of women have a dietary iron intake below 15 mg/day. This contributes to a low iron status in many women (55).

Iron supplement needs may be present during pregnancy, postpartum or lactation periods. Total iron loss may be around 1000 mg. Pregnant women without anemia can receive 15-30 mg of elemental iron daily. A lot of prenatal vitamin formulations are available in the market today (56). For pregnant women with iron deficiency anemia, suggested iron supplement intake according to hemoglobin count was summarized in Table 3 (57):

Table 3. Iron deficiency criteria for pregnant women

1st trimester	hemoglobin < 11g/dl
2nd trimester*	hemoglobin < 10.4 g/dl
3rd trimester*	hemoglobin < 11g/dl

*If necessary, IV iron may be given during 2nd or 3rd trimesters.

Anemia is often seen with geriatric patients, and it can be due to various reasons. If tolerated, low dose iron treatment may be (15 mg/dl) efficient (48).

1.4. Iron Supplements

Supplemental iron mainly aims to prevent and treat the iron deficiency anemia (10). Therefore, iron supplements are commonly used to treat patients with simple anemia and/or low blood iron levels. Dosage and posology of iron supplements according to indications were summarized in Table 4 (58,59).

Table 4. Dosage and posology of iron supplements according to indications

Indication	Dosage	Posology
Anemia due to iron deficiency	50-100 mg of iron	3 times daily for 3 months up to 6 months
Iron deficiency in women	30-120 mg of iron	Weekly
Low iron levels in pregnant women	45 mg of iron	Daily
Restless leg syndrome	325 mg of ferrous sulfate	Twice daily for 12 weeks
Low levels of red blood cells in people with chronic anemia	a) Total dose of 2232 mg of iron b) 1020 mg of iron	a) Injection delivered over 6 months b) IV over 1 week
Heart failure	200 mg of ferric carboxymaltose	Weekly, until iron level results are normal (followed by 200 mg by injection every month for 6 months)
Children with anemia	4-6 mg/kg of iron	Daily, divided into three doses for 3 months up to 6 months
Breast-fed infants	1 mg/kg elemental iron	Daily from ages 4-6 months
Cognitive function in adolescents	650 mg of ferrous sulfate	Twice daily

For adults and children (age 14+), the maximum dose is 45 mg a day. For children under the age of 14, maximum daily does is 40 mg (59).

In Turkey, there are many iron supplements that provide easy usage with different routes of administration. Most used ones are oral tablets, oral solutions, droplets, duodenal tablets and combined formulations. Combined formulations are preferred as it makes it easier to remember and take other commonly used supplements, such as Zinc. As mentioned, administration of iron may be required for many reasons, hence it has a widespread use. For this reason, both iron deficiency and possible iron excess must be monitored closely, to avoid any complications (56).

1.5. Iron Toxicity

A peak serum iron concentration of five µg or more per ml is associated with moderate to severe poisoning. For younger patients, 75 mg per kg can be perceived as highly dangerous. While intaking 30 mg per kg can lead to symptoms of toxicity, lethal dosage range from 180 mg per kg and upwards (10). Patients who intake less than 20 mg per kg of iron are often asymptomatic (60).

Most common adverse events of iron are constipation and diarrhea. Nausea and vomiting may occur with higher doses. Iron tablet intake may cause black stools. However, some situations where the stools are tarry-looking or black, if they have red streaks, if the patient is experiencing cramps, sharp pains, or soreness in the stomach, might be signs of toxicity. Liquid forms of iron may stain teeth (61).

1.5.1. Acute Iron overdose

After iron intake, serum iron level peaks at around 2 to 4 hours, but serum concentrations of enteric-coated or sustained-release formulations are erratic and show different levels. Around 10% of ingested iron is absorbed from the intestine and is then bound to Tf. Normal serum iron levels can range from 50 to 150 µg/dL, and total iron-binding capacity may range between 300 and 400 µg/dL. Iron levels will rise upon significant ingestion and Tf will become saturated. Excess iron that will then circulate in the blood as free iron, which can be toxic to target organs (62). Acute iron overdose can be divided into four stages, as summarized in Table 5 (10);

Table 5. Iron overdose stages and their signs and symptoms

Stages	Signs and symptoms
Between 0 to 6 hours	Vomiting and diarrhea, hypotension, tachycardia, CNS depression ranging from lethargy to coma.
Between 6 and 24 hours	Temporary remission.
After remission	GI symptoms with shock, metabolic acidosis, coma, hepatic necrosis and jaundice, hypoglycemia, renal failure and pulmonary edema.
Weeks after ingestion	GI obstruction and liver damage.

The process from iron requirement to iron excess for different patient groups vary, as summarized in Figure 1.

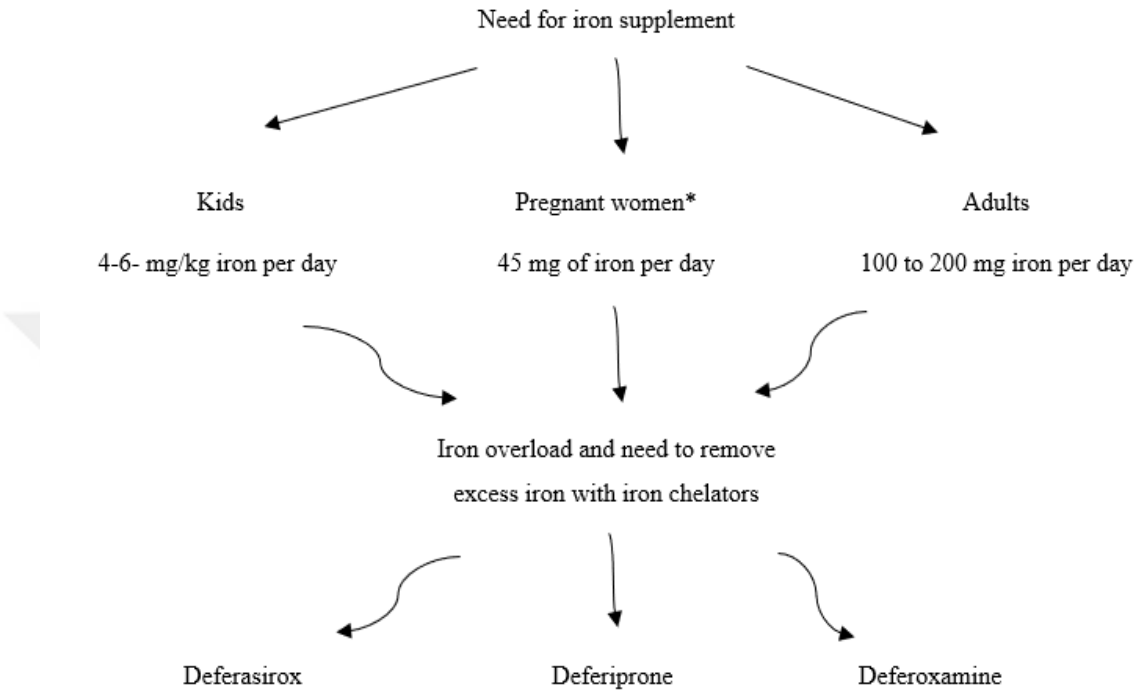

Figure *1*. Iron treatment protocol flowchart

1.5.2. Elimination of Adverse Reactions Related to Iron

To decrease the adverse reactions, starting with low iron doses and increasing it within 4-5 days, dividing the daily dose or intaking with food are highly recommended. Although slow-release iron supplements cause less gastrointestinal side effects, it may be because they are less effective. Iron absorption can be decreased with some other drugs. Thus, there must be at least 2 hours between 2 drug intakes. Absorption increases when the stomach is empty. While acidic juices or vitamin increase the absorption, other multivitamins, calcium and antacids decrease the absorption (48).

Patient history and clinical presentation can help with the iron toxicity diagnosis; serum iron levels and symptoms shall be examined. Serum iron level would reach its peak at around 4 to 6 hours after ingestion, so a laboratory test at this time the most useful method. Sustained-release or enteric-coated preparation may have erratic

absorption, and therefore a second test at around 6 to 8 hours after ingestion shall be checked. As iron is cleared in a fast manner from the serum and deposited in the liver, the iron level drawn after ingestion may appear low if it is measured just after its peak (62).

- Minimal toxicity: peak serum iron levels below 350 µg/dL
- Moderate toxicity: Levels between 350 to 500 µg/dL
- Systemic toxicity: Levels above 500 µg/dL

Other laboratory tests and examination may include electrolytes, kidney function, serum glucose, coagulation studies, complete blood count, and liver function. Plain radiographs may show if there is iron in the GI tract, but many iron preparations are not radiopaque. Normal radiographs do not exclude iron ingestion (62).

1.5.3. Treatment of Iron Toxicity

Under normal circumstances, iron is transported in plasma by Tf. However, when there is an excess amount of iron, it becomes saturated. The hepatocyte can take up both non-transferrin bound iron (NTBI) and transferrin bound iron; and both sources are likely to have an impact on the hepatic iron deposition elevation. As it can generate free radicals, NTBI is extremely toxic. It is also rapidly cleared from plasma by the liver. Hepatocytes take up NTBI by a process that involves iron reduction and transport across the cell membrane by a carrier mediated process. Due to the lack of transferrin and slowed rate of iron release from NTBI accumulated tissues such as liver, pancreas, and heart, these patients may require transferrin infusion for survival (16).

Before there is any damage, it is crucial to remove the unnecessary iron. There are a handful of ways to treat patients with iron toxicity. EDTA (ethylenediaminetetra-acetic acid) could be used as a chelator as it binds to and removes several minerals, including iron, but it is not specific to iron, so it is typically not preferred (63).

As activated charcoal binds iron poorly, administration of activated charcoal is not effective or necessary. Whole-bowel irrigation using polyethylene glycol method can be useful, as this solution may clear the GI tract from iron supplements before they are absorbed. This should be administered at 250 to 500 mL/h in children and 1.5 to 2

L/h in adults via nasogastric tube. Gastric lavage with a large-bore orogastric tube can be considered only if abdominal x-ray demonstrates a large number of pills in the stomach, visibly. Mostly, as the risks of gastric lavage outweigh the benefits, it is not a very common practice (62).

For symptomatic treatment, IV crystalloid infusion can be given to reverse hypovolemia and hypoperfusion. 5 to 10 mg of Vitamin K, subcutaneously, and fresh frozen plasma (10 to 25 mL/kg in adults; 10 mL/kg in children) can correct coagulopathy (62).

Finally, iron chelating agents can be used to remove iron from tissues as well as free iron circulating in plasma. This is a very common way to treat iron toxicities as it is very effectively indicated in patients with systemic toxicity, metabolic acidosis, worsening symptoms, or a serum iron level predictive of moderate or severe toxicity (62). Iron reduction is accomplished with chelation therapy, as chelators are to bind to excess iron so that this excess iron can be removed via urine (63).

1.5.4. Iron Chelators

Iron chelation aims to decrease the body burden of iron, especially iron within labile compartments in plasma as well as in various tissues. By decreasing iron in these sites, it specifically aims to minimize the production of reactive oxygen species, and thus reducing damage to critical organs such as the liver, heart, and endocrine organs, resulting in reduced morbidity and improved survival (2).

Deferoxamine, deferasirox and deferiprone are iron chelators that are commonly used in iron overload. Iron chelators are organic chemicals that form two or more coordination links with an iron. Once this binding is formed, the newly formed complex is called a chelate. An example to that is the iron-binding porphyrin group of hemoglobin (64).

1.5.4.1. Deferasirox

Deferasirox, an iron chelator is indicated in chronic iron overload in patients receiving long term blood transfusions, who are 2 years or older. It is selective for trivalent iron and shows high affinity by forming a 2:1 complex (Figure 2). It has very

low affinity for zinc and copper, but it still shows effective results meaning the serum concentration of these trace metals reduce after administration (65,66).

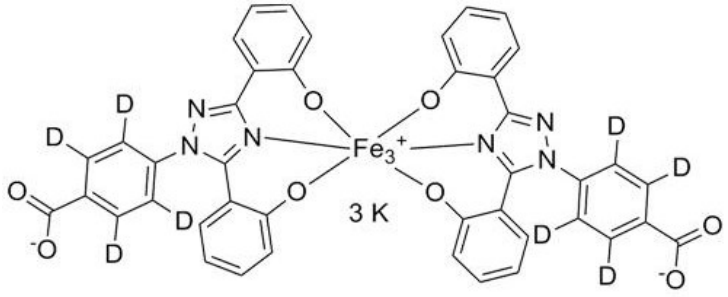

Figure 2. Deferasirox and iron chelation

1.5.4.2. Deferiprone

Deferiprone is also an oral iron chelator to treat thalassemia related syndromes as a second line agent, when iron overload from blood transfusions occurs. As a chelator, it binds to ferric ions (iron III) and forms a 3:1 (deferiprone:iron) stable complex (Figure 3) and is then excreted via urine (67).

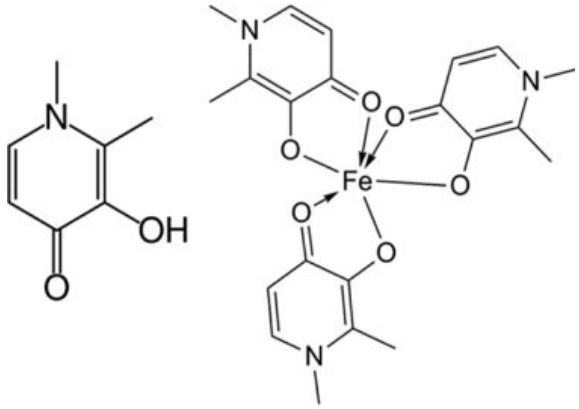

Figure *3*: Deferiprone and iron chelation

1.5.4.3. Deferoxamine

Deferoxamine also known as desferrioxamine or desferal, is produced from *Streptomyces pilosus* and it forms iron complexes to remove excess iron, as well as aluminum from the body. It is indicated in anemia patients who receive blood

transfusions. It binds to free iron and induces its elimination in the urine. By doing so, it reduces the damage to liver and many other organs (68).

Deferoxamine functions in treating iron toxicity by binding trivalent (ferric) iron (Figure 4), forming ferrioxamine, which is then excreted via the kidneys. 100 mg of deferoxamine can bind approximately 8.5 mg of trivalent (ferric) iron (68).

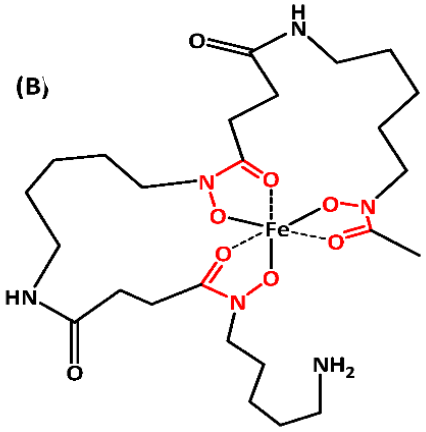

Figure *4.* Deferoxamine and iron chelation

1.5.4.4. Comparison of Available Iron Chelators

In Turkey, at the time of this study, deferiprone (oral, 500 mg film coated tablets and oral, 500 mg/ml syrup), deferoxamine (IM/IV/SC injection ready 500 mg flacon) and deferasirox (oral, water-soluble tablets, 125 mg, 250 mg, 500 mg and oral, film coated tablets, 90 mg, 180 mg, 360 mg) are available to public use. For deferasirox, various generics are available (56).

As discovered during review of national literature in Turkish, deferasirox was highly preferred as a prescribed medication, possibly due to its ease of use. However, as a common practice; in urgent circumstances, and in situations where the patient was hospitalized, IV deferoxamine is being administered (69).

It was also discovered that most of the patients who were prescribed or administered any iron chelator were previously diagnosed with anemia and/or β-thalassemia (2,70–72). Hemochromatosis was also discovered to be one of the reasons to receive iron chelators, as it is a hereditary disease that might require iron administration. Moreover, iron chelation may be needed in many situations where patients receive blood transfusion (73).

As per studies that reviewed thalassemia and its prevalence in the world, approximately there are 270 million carriers with abnormal hemoglobins and thalassemia, of which 80 million are carriers of β-thalassemia. It was also suggested in some surveys that every year, between 300,000 and 400,000 babies are born with a serious hemoglobin disorder, 23,000 of which are with β-thalassemia major (74–79).

In Turkey, there are approximately 1300000 carriers of thalassemia and around 4500 thalassemia patients, as thalassemia is a significant public health issue in Mediterranean countries including Turkey (80).

With chronic anemias, comes the need to support the patients with blood supplements. As an example, patients with beta thalassemia need blood support 3-4 times per week, as long as they live. Blood transfusions are given to correct anemia. In order to prevent iron accumulation, drug chelators are typically given by a subcutaneous infusion lasting (2,38). Chelation therapies are the only solution for severe cases, other than whole bowel irrigation (80).

Chelation therapies can be crucial for children as well. Almost 11,000 iron exposures in children younger than six years of age are reported annually in the United States (81).

For pregnant women, iron chelation treatment is usually not recommended, as the information on fetal development is not fully understood yet (82). FDA's pregnancy category for deferoxamine is C (83), which means that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks (84). For deferasirox and deferiprone, a category is not assigned (85,86).

Prognosis of patients with Thalassemia Major were seen to be improved dramatically after the introduction of deferoxamine, according to *Gabutti* and *Piga* (87). Two clinical trials, both of over 10 years duration, have demonstrated clearly that effective long-term use of deferoxamine in thalassemia major is associated with long-term survival as well as free of the potential complications of iron overload, where the intensity of the body iron burden was recognized as the main determinant of clinical

outcome (88,89). Torcharus and Pankaewthe suggested that quality of life of thalassemic children showed improvement in psychosocial health, and social functioning with iron chelation treatment (90). In Table 6, iron chelators that are in market were compared according to their properties, advantages and disadvantages (56,65,67,68)

Table 6. Comparison of available iron chelators

	Deferasirox	**Deferiprone**	**Deferoxamine**
Chelator: iron binding	2:1	3:1	1:1
Route of administration	Oral	Oral	Subcutaneous or intravenous
Usual dosage	20-30 mg/kg per day	75 mg/kg per day	25-50 mg/kg per day
Schedule	Daily	Three times a day	Administered over 8-24 hours, 5-7 days per week
Advantages	Once daily administration	May be superior in removal of cardiac iron	Long term data available
Disadvantages	Long-term data lacking	Frequent blood count monitoring required	Toxicity compliance
Cost comparison in US	$$$	$$	$
Cost comparison in Turkey	$$ / $$$	$$$	$

Different route of administrations would result in different bioavailabilities, which is an early indication of potentially different adverse events, especially due to deferoxamine's potential to be delivered to the systemic circulation immediately (91).

1.6. Toxicities of Iron Chelating Agents

Product leaflets for deferoxamine, deferiprone and deferasirox list many non-serious adverse reactions including headache, nausea, diarrhea. While these adverse reactions may be non-serious at first, they may become serious in case of a life-threatening situation, death, hospitalization, prolongation of hospitalization, disability or permanent damage, congenital anomaly, any kind of birth defect, requirement for an intervention to prevent permanent impairment or damage (92).

Product leaflets for iron chelators also list serious adverse reaction including hypersensitivity, anaphylactic reactions, vision impairment, tachycardia, diplopia, hypertension, rectal bleeding, gastric ulcer, and many more (56).

1.7. Pharmacovigilance and Its Importance

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. The aims of Pharmacovigilance activities are to improve patient care and safety in relation to the medicine exposure, and to support public health programs by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines (93).

After authorization, medications may be used by a big number of patients, for a long period of time and with other medicines. Certain adverse events may occur in those cases. That is why it is crucial that the safety of all medicines is monitored while they are marketed to be used by patients. Important steps in Pharmacovigilance are shown in Figure 5 (9).

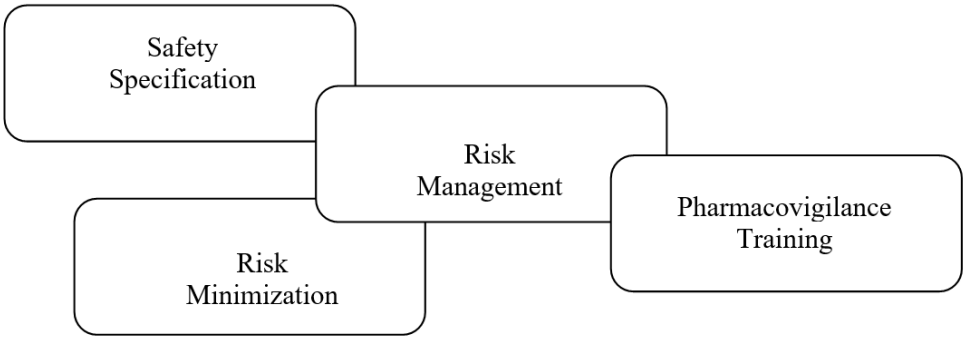

Figure *5*. Important steps for pharmacovigilance

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related or not (93). An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes (92):

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,

- A congenital anomaly/birth defect.

Important medical events do not have to always cause death. However, they might be life-threatening, or require hospitalization. They might also be considered serious when they jeopardize the patient and medical or surgical intervention to prevent one of the outcomes is required. A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the event is associated to drug. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (92,94). Adverse drug reactions are classified into six types, as summarized in table 7 (95,96):

Table 7. Adverse drug reaction classification

Abbreviation	Types	Example
A (Augmented)	Dose related	Anticholinergic effects of tricyclics
B (Bizarre)	Non dose related	Allergic reactions
C (Chronic)	Dose-related and time-related	Adrenal suppression with corticosteroids
D (Delayed)	Time related	Adrenal suppression with corticosteroids
E (End of use)	Withdrawal	Rebound hypertension after stopping clonidine
F (Failure)	Failure of therapy	Increased clearance by dialysis and plasmapheresis.

Adverse reaction reporting databases have always been very important resources for monitoring the safety of drugs: Health authorities such as US FDA (7), Australian Government's Department of Health, TGA (97) and EMA (98) are providing public dashboards that are web-based tools to allow the reporting of consumers and healthcare providers. Main goal of these tools is to expand access of product safety data to public and as well as to promote reporting, hence contribute to the science of pharmacovigilance. These databases are providing safety data on medicinal products, medical devices, vaccines, antidotes etc.

Some available Adverse Event Reporting Systems are:

- **VigiBase** is the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. It

is the largest pharmacovigilance database, with over 30 million reports of entered adverse effects of medicines, submitted, since 1968, by member countries of the WHO PIDM. As each country receives spontaneous reports of suspected adverse effects nationally, after being reviewed and analysed internally, these are shared to be included in VigiBase, where post-marketing data from a majority of the world's countries is collected in one place. This database offers cases from all around the world, since approximately half of available data is from the USA, and about 20% of it is from the European Union. VigiBase is continuously updated with incoming reports (8). Although this database is publicly available, due to the sensitivity of the data and personal data privacy, some case related details are blinded, unless purchased. UMC offers eligible professionals who have a valid purpose to use the specialized services such as VigiBase Extract Case Level (8,99,100). The information in VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the UMC or the World Health Organization.

- **The FDA Adverse Event Reporting System (FAERS)** is a database that contains adverse event reports and other safety information that were received by FDA. The database also supports post-marketing safety surveillance programs. There are over 20 million cases in FAERS. Before being published, the data from FAERS is evaluated by clinical reviewers (7).
- **EMA's database "Eudravigilance",** which has been active since 2012 (101), holds information on more than 12.45 million safety reports, referring to 7.95 million cases, as well as information on 744,219 medicinal products on the EU market by the end of 2017. EMA uses this platform for signal detection activities, to support other pharmacovigilance procedures for data analysis. Furthermore, all ICSRs from the European Economic Area are submitted to the World Health Organisation UMC directly from EudraVigilance (102).
- **The Therapeutic Goods Administration (TGA) database "DAEN":** which also receives adverse event reports from a wide range of sources, such as consumers, general practitioners, nurses, other health professionals and the

industry. DAEN can provide information regarding adverse events related to medicines and vaccines, as well as information about adverse events related to medical devices used in Australia. The reports in this database start from 1 January 1971 up to 90 days prior to the date of access. During this period, the TGA checks the completion and accuracy of these reports, and performs data analyses to check for patterns of adverse events that may point toward a signal (97).

Other than the mentioned databases, other country or region specific adverse event reporting databases such as Japanese Adverse Drug Event Report Database (103), Canada Vigilance Adverse Reaction Online Database (104), Interactive Adverse Drug Reaction overviews by Danish Health Authority (105) were available.

VigiLyze, which is a system by VigiBase to support the entire signal detection and management process, aims to show the related investigations when searching for a specific product and reactions in the future. This may minimize the duplication of doing the same assessment. This system currently offers line listings, overview graphs and disproportionality calculations for national data. Currently, VigiLyze is only available to National Pharmacovigilance Centres that are members of the WHO Programme for International Drug Monitoring (106).

Turkish Ministry of Health has a very well-established department for the national pharmacovigilance activities since 1985. TUFAM (Turkish Center of Pharmacovigilance) (96) was called Turkish Drug Adverse Effects Monitoring and Evaluation Center (TADMER) when it was first founded and in 1987, it was accepted as the 27th member of World Health Organization Programme for International Drug Monitoring (97).

Legislation regarding the mandatory pharmacovigilance activities to be conducted by Marketing Authorization Holders in Turkey was first published in 2005 (98) and Turkish guidelines for Good Pharmacovigilance Practices was published in 2014 (99).
TUFAM is continuously monitoring and inspecting the Pharmacovigilance activities carried out by the Marketing Auhorization Holders in Turkey to ensure systematic monitoring of adverse reactions and benefit/risk balances in order to maintain the safe use of products in the market (107). Some of the routinely conducted activities are,

including but not limited to, monitoring, recording, evaluating safety data, to follow the safety warnings related to products by monitoring official websites of the health authorities, evaluation of the benefit-risk ratio, taking the necessary precautions for the drugs that are licensed/registered in our country, minimization of the risk accordingly, generating safety related reports such as Risk management plans and Periodic Benefit/Risk Assessment Reports, publication of Dear Healthcare Professional Letters, taking necessary measures to encourage the spontaneous reporting of healthcare professionals in order to carry out the pharmacovigilance system in the best way. TUFAM organizes training programs and meetings regularly on pharmacovigilance to support pharmacovigilance system in Turkey, informs license holders and relevant international organizations about taken measures and works in liaison with Scientific Advisory Boards when necessary. Announcements are also published based on received questions and updates to current guidelines and legislations. TUFAM also ensures cooperation and coordination with other departments within the Ministry (108).

TUFAM also created pharmacovigilance contact points in healthcare centers such as hospitals and toll free call center to raise awareness and to promote spontaneous reporting (109,110).

TUFAM allows anyone to report an adverse event to the official website. There is no obligation to belong to a certain occupational group to report pharmacovigilance data. With the obtained information, TUFAM works together with the license holder to take the necessary action (109).

Standard wording promoting the reporting of adverse events is compulsory to be added in all summaries of product characteristics and patient information leaflets in Turkey. They are required to include a section named “Reporting Adverse Reactions” below the section “Possible Adverse Reactions,” which guides consumers to the electronic system and tollfree phone line to report any adverse event they experience. Reportedly, as per Pharmacovigilance Center in Turkey, the number of adverse reaction reports submitted by consumers increased after the boxes with product information leaflets containing the standard text became available to public via pharmacies (100).

At the time of this article, there is no adverse event database provided by TUFAM, that is available to public, to disclose safety information regarding Turkey.

However, as VigiBase contains cases from all over the world, it also includes Turkey(79). Frequency of product use can be estimated by reviewing published articles and World Health Organization, UMC's database, which is called VigiBase (75).

1.7.1. VigiAccess

VigiAccess is an online tool that was launched by the World Health Organization in order to provide public with a part of the information from VigiBase (8), in 2015. Due to the data privacy laws, individual case safety reports, also known as ICSRs, cannot be viewed by public. For the same reasons, when health care professionals need data for studies like ours, the data provided upon their request is pseudonymized and country names are not included (111).

1.7.2. MedDRA

Medical Dictionary for Regulatory Activities "MedDRA" is providing a dictionary-like data for medical terminology. It is widely used to classify adverse event information associated with the use of medication. Coding data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to readily exchange and analyze data related to product safety. MedDRA ensures to classify safety data from clinical trials; from spontaneous adverse event reports by health care professionals, consumers and other sources. MedDRA was developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), is being continuously updated to support regulators and industry (29).

MedDRA allows us to analyze the data that is coded into a standardized terminology, with its straightforward and sophisticated analyses. It is useful to analyze individual medical events or issues by using its hierarchical structure. This tool is also used for signal detection and monitoring of clinical syndromes whose symptoms encompass numerous systems or organs using its multiaxial hierarchy or through the special feature of Standardized MedDRA Queries (35).

1.7.3. Additional Monitoring Programmes

Additional monitoring was introduced first time in 2010 by the pharmacovigilance legislation in EU, which then became effective in July 2012 (112).

In Turkey, Turkish Guidelines of Good Pharmacovigilance Practices: Module II: Additional Monitoring became effective on 15 July 2014 (113).

Medicines that require additional monitoring must have a black inverted triangle (▼) shown in their package leaflet as well as in the information for healthcare professionals called the summary of product characteristics, together with a short sentence explaining what this triangle means. Additional monitoring is targeted to increase reporting of suspected adverse drug reactions for products for which the clinical evidence base is less known. Mainly, the intention is to collect information as early as possible to further inform the safe and effective use of these medicines and their benefit-risk profile when used in everyday medical practice (9). There may be various reasons for the medicines to be under additional monitoring. As per the legislations in EU, they must be under additional monitoring if (112):

- The product contains a new active substance authorised in the EU after 1 January 2011;
- It is a biological medicine, such as a vaccine or a medicine derived from plasma (blood), authorised in the EU after 1 January 2011;
- It has been approved conditionally: if the marketing authorization holder must provide more data about it, or if it has been approved under exceptional circumstances, which means that there are specific reasons why the marketing authorization holder cannot provide a comprehensive set of data;
- The company is required to carry out additional studies, as to provide more data on long-term use of the medicine or on a rare adverse event observed during clinical trial phases;
- It is authorised with specific obligations on the recording of suspected adverse drug reactions (112).

As per the legislations and guidelines in Turkey, medicinal products must be under additional monitoring if:

- The ingredient is included in the additional monitoring list of other international applications;
- The product is a licensed biosimilar drug or a biosimilar drug pending license approval;

- The product is being monitored with a special monitoring system in Turkey. (i.e.: Systems where drug safety monitoring forms, web-based monitoring systems or restricted distribution programs are required);
- The product has been licensed or is pending license under exceptional circumstances;
- Product is licensed on the condition of performing post-registration safety study;
- Product license application was submitted after 15.04.2014 (for active ingredients that were not licensed as primary or excipient previously);
- Product is a biotechnological medication for which a license application was submitted after 15 April 2014;
- Product is a blood product that was licensed after 01 January 2011;
- Products that the institution deems necessary for additional monitoring (113).

In EU, a medicine can be included in this list when it is approved for the first time, but it can also be included at any time during its life cycle. Medicines remain under additional monitoring for the first five years, however the Pharmacovigilance Risk Assessment Committee may decide to change this at any time point (112).
Similarly, the institution in Turkey may remove a product from the list five years after it is licensed in Turkey or extend this period. The product may be included in the list if concerns regarding its safety arise, during its lifecycle (113).

Boxed warnings (formerly known as Black Box Warnings) are signs on product labels that are intended to bring the patient’s attention to the major risks of the medicine. The warning or restriction must be formatted with a box or border around the text and prominently displayed on the package or any promotional material as well as in the manufacturer's website. A boxed warning can be added, taken away, or updated throughout a medication’s tenure on the market. Currently, there is black box warnings for iron containing products, shown in Figure 6 (114) and ferriprox (deferiprone), shown in Figure 7 (115).

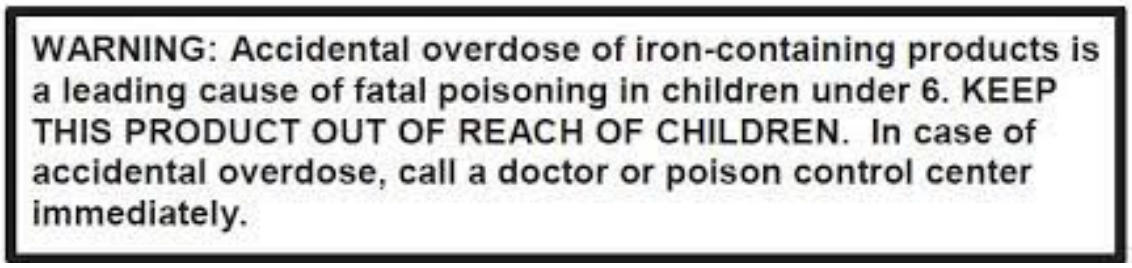

Figure *6.* Black box warning for iron containing products

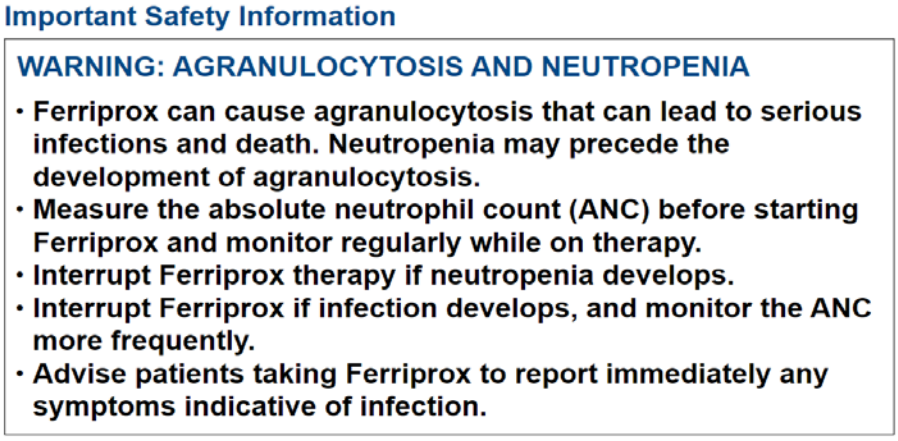

Figure *7.* Black box warning for Ferriprox (deferiprone)

In some situations, some crucial safety information may be distributed to health care professionals in an expedited manner. These letters are called “Dear Health Care Professional Letters” or “Dear Doctor Letters”. They are usually in the form of a mass mailing from the marketing authorization holder and intended to alert doctors and other health care providers about important new or updated information regarding the respective medicinal product (116). In Turkey, as per the guidelines, in case of a safety concern that needs to be distributed immediately, pharmaceutical companies work together with the Ministry of Health to act in a timely manner, in order to minimize the potential risks. In the contact of reporting suspected adverse reactions, health care professionals can include doctors, pharmacists, dentists, nurses and midwives (109).

In Turkey, in the past, there has been one dear doctor letter which was distributed due to adverse reactions related to deferasirox in 2009. These adverse reactions included hepatic and renal insufficiency, renal tubulopathy, gastrointestinal bleeding and ulceration. The letter suggested some precautions, tests and signs to be aware of. Mentioned adverse reactions were also added to product information leaflet.

No other information was distributed in an expedited manner for other iron chelators in Turkey (117).

1.7.4. Risk Management Plans

A medicinal product is authorized on the basis that in the specified indication(s), at the time of license approval, the risk-benefit ratio is considered to be. Usually, a medicinal product will be associated with various adverse reactions that may differ in severity, likelihood of occurrence, effect on individual patients and public health impact, and so on. As not all adverse reactions and risks will have been identified initially and there are always potential effects and risks to be discovered, with Risk Management plans, Pharmacovigilance workers aim to identify, characterise and minimise a medicinal product's important risks. Accordingly, a Risk Management Plans contains (118):

1. The identification or characterization of the safety profile, with prioritizing important identified, important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied;

2. The planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse reactions;

3. The planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (the 'risk minimization plan').

In time, if there are more information and knowledge regarding a product's safety profile, the risk management plan develops as well (118).

An update to the risk management plan shall be considered when data submitted in the procedure results or is expected to alter routine pharmacovigilance activities beyond adverse reaction reporting and signal detection activities. Recommendations regarding specific clinical measures to address these risks may also trigger the update. As an example, an update might be required with a significant change of the plans for annual enhanced safety surveillance, which is a routine pharmacovigilance activity, or when monitoring of an organ function such as kidneys is added as a recommendation in the Special warnings and precautions for use in the summary of product characteristics. Such updates should remind to consider to update the plans to evaluate the effectiveness of risk minimization activities. Emerging safety issues can also trigger an update, in

cases of a signal or significant risk, whether it be identified or potential, that could be an important identified risk. An update will surely be necessary when the emerging safety issue is confirmed and the important identified or potential risk is required to be included in the safety concerns list in the risk management plan (119).

Out of the mentioned iron chelators, Deferasirox has an active risk management plan. Although the risk management plans in Turkey and EU have difference, the main principle and goals are very similar (120,121). The important information that is addressed in Exjade's risk management plan in EU is listed in table 8 (120);

Table 8. Information to be collected as per Exjade's risk management plan

Important identified risks
- Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome]),
- Increased liver transaminases or hepatic failure
- Gastrointestinal hemorrhage and ulcers, esophagitis
- Hearing loss
- Lens opacities, retinal changes and optic neuritis
- Severe cutaneous adverse reactions including Stevens-Johnson syndrome, Toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms
Important potential risks
- Compliance with posology and biological monitoring
- Medication errors
Missing information
- Long term safety in pediatric non-transfusion-dependent thalassemia patients aged 10 to 17 years
- Safety of new formulation (FCT/granules)

According to the information below, identification of an important risk regarding the use of deferasirox, a new significant information regarding its safety or its indicated population, an introduction to a new additional risk management activity could trigger an update to current risk management plan (118).

There is also an active risk management plan for Deferiprone in EU. The aim is similar to other risk management plans, meaning that it aims to identify the following information (122):

- Important identified risks regarding agranulocytosis, neutropenia, use in pregnancy, arthropathy (including arthralgia), increased liver function test values, skin disorders, allergic reactions

- Important potential risks related to carcinogenicity,
- Missing information for lactation toxicity, off-label use, long-term safety data and risk in immunocompromised patients.

In Turkey, there are some implemented risk management materials for deferasirox. These materials are to inform the patient on why this product was prescribed to them, how it works, various forms of deferasirox, how will the treatment with them be, birth control, potential adverse events and how to report adverse events. The same material is provided to patients who are prescribed deferasirox, independent of the dosage or route of administration. There is also a risk management material that provides guidance to physicians, which includes information about indications, contraindications, tests to be performed prior to treatment, how to calculate the dose, treatment principals for different patient groups and different indications, renal and hepatics complications and so on (121,123).

1.7.5. SIDER

SIDER is a public website which contains information on medication available to public and their reported adverse events. The information is extracted from public documents and package inserts. Information in the site provides side effect frequency, drug and side effect classifications as well as links to further information, for example drug–target relations. At the time of our study, SIDER contains information related to 5868 side effects, 1430 drugs with 39.9% pairs with frequency information. The reason why the data received from SIDER differs from other sources is that adverse events from unofficial channels are also included (124).

1.7.6. Signal Detection

According to the WHO and Uppsala Monitoring Center's definition, a safety signal refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It's important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment (125).

To identify the unexpectedly high reporting associations, which are then called "signals", authorities use some techniques to find a causal association between the

particular adverse event and the product. Disproportionality methods are inexpensive and quick methods that are being largely used to identify statistical associations between products and events in their safety databases. These methods compare the observed count for a product-event combination with an “expected” count (126,127).
The evidence in a signal is only an early indication, as in time, more information can be collected, and the theory might change. A signal may provide additional as well as new information about adverse or beneficial effects, or information about an already-known association of a medicine with an adverse drug effect, such as the range of severity of the effect or its outcome. As an example, it might be a dose range which might be more risky or perilous, a pharmaceutical group-effect or a lack of effect by a specific product.

The result of a causality assessment may be described in different ways such as certain, probable/likely, possible, unlikely, conditional/unclassified or unassessable/unclassifiable (125).

FDA publishes reports containing list potential signals of serious risks/new safety information that were identified using the database, four times a year. A product being listed in a report might not necessarily mean that FDA has decided to conclude that the drug has the listed risk, but it means that a potential safety issue is identified by FDA, and the casual relationship between the drug and the listed risk is not certain yet. If after further evaluation, it is decided by the FDA that the drug is indeed associated with the risk, a variety of actions may be taken, which may be updating the labeling of the drug, requiring development of a Risk Evaluation and Mitigation Strategy or gathering additional data to better characterize the risk. Additional information on each potential safety issue, such as an FDA Drug Safety Communication, is also provided (128).

Turkish Ministry of Health is currently not publishing any report related to identified signals, however it is required for all marketing authorization holders to monitor, review and have an overview on local and global safety signals regarding their products and to take necessary actions, if applicable. Turkish Ministry of Health is also closely monitoring global health authorities, such as EMA, FDA and TGA (107).

2. MATERIAL and METHOD

2.1. Materials

Our study was designed as an observational and retrospective pharmacovigilance study that aimed to carry out a review and retrospective analysis of Individual Case Safety Reports recorded from databases. While investigating our options, it was identified that different databases contain different types of cases with different specifications. In Table 9, details related to databases were summarized, which were important in our resource selection.

Table 9. Comparison of databases

Database	Data originated from	Detailed case information availability	Ability to generate line listings	Ability to search both adverse events and product names	Ability to search both product and API names
FAERS	USA				
Eudravigilance	EU			x	
DAEN	Australia				
VigiBase	All over the world	X		X	

As summarized in Table 9, different types of reports from different databases can be generated. All these databases offered the option to generate line listings and to search both product and active pharmaceutical ingredient names.

With DAEN and FAERS, it was possible to generate a more detailed report, that would be more convenient for data mining purposes, as both adverse event and product names can be filtered, and more case related information, including patient demographics, age, sex etc can be examined.

DAEN gives us the option to filter medicines, by adding up to 5 active ingredient or product name, it also filters date and adverse drug reactions' MedDRA system organ classes (97).

FAERS provides more filter options as report type, year, region, sex, age and reporter type can be selected to obtain more accurate results. This option played a big

role in our database choice. Also, FAERS contained the highest amount of reports out of all mentioned databases (except VigiBase) which made it more convenient for our data mining exercise (7). It was realized that more detailed information that allows to mine data can be extracted from FAERS, by generating reports for specific products and active ingredients, year, report type, region etc.

Upon reviewing our database options, World Health Organization's (WHO) database (VigiBase) (8) and US FDA database FAERS were selected (7). Both databases contain adverse events reported by drug manufacturers, health-care professionals, and consumers. While FAERS contained cases from Americas region, VigiBase contained cases from all over the world. UMC offers healthcare professionals services including custom searches results and trainings (129). For that reason, an agreement between Yeditepe University and UMC, dated 3-Aug-2022, was established to purchase right data for our study, which also contained cases from Turkey. Although UMC has provided the data, the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, National Centers, or WHO. While data from FAERS contain case details such as patient age group, gender, indication, reporter detail, adverse event and such, data purchased from VigiBase contained case information details such as patient age group, gender, area of origin, reporter detail, indication, dosage form, dose, adverse event and so much more.

While conducting our research, cases related to deferoxamine, deferiprone and deferasirox reported from 2010 to 2021 were selected. Disproportionality analysis was crucial to detect and quantify the associations between iron chelators and suspected adverse drug reactions. Our aim was to examine the data from different sources, from different perspectives. For this reason, before examining the data on iron chelators, the product information of iron chelators in Turkey were reviewed. Specifically, one common adverse event (headache), one very rare adverse event (blurred vision), one serious adverse event with difference frequencies (sepsis) were selected to see how well these data matched real-life data along with their disproportionality analysis results. UMC's training called "Statistical reasoning and algorithms in pharmacovigilance" (130) was also completed accordingly. To further examine the results, the data from SIDER were also reviewed (124). Afterwards, accepted signals published during the

same time interval were examined (100,128,131,132). Finally, to elicit new data, adverse events from real-life reports that might be related to the drug but were not listed in the product information were examined.

2.1.1. Information for Iron Chelators from Local Labels in Turkey

For this review, original licensed products that are marketed in Turkey were selected. The reason behind this is the fact that these products are fairly old in the market, which would increase the information collected from patients in Turkey. This also makes the information included in the product leaflet accurate and convenient. Adverse reaction frequencies are recommended by CIOMS III Working group (133) and are as per Table 10 and Figure 8.

Table 10. Adverse reaction frequencies

Very common:	≥ 1/10 (≥ 10 %)
Common, Frequent:	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon, Infrequent:	≥ 1/1000 and < 1/100 (≥ 0,1% and < 1%)
Rare:	≥ 1/10000 and < 1/1000 (≥ 0,01% and < 0,1%)
Very rare:	< 1/10000 (< 0,01 %)

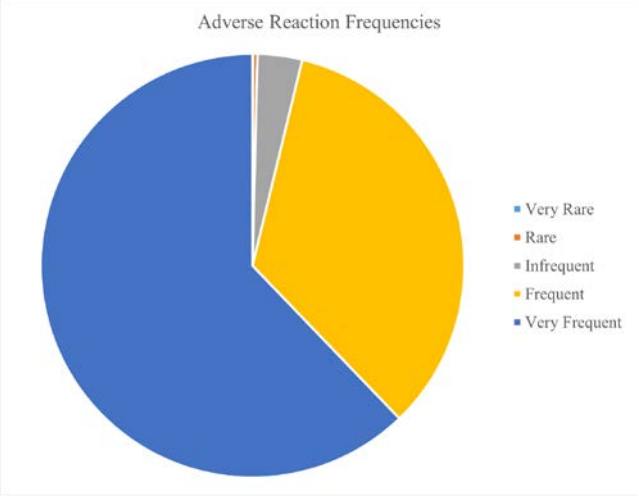

Figure *8.* Adverse reaction frequencies

2.1.2. Findings from FAERS

While reviewing the data from FAERS (7), from the line listing retrieved in May 2021, it was identified that some cases contained more than one product. As an example, it was possible to identify 19699 Deferasirox cases, but in total 21729 cases included Deferasirox and one or more other product. To review the cases with higher

probability of relatedness, cases that included deferasirox, deferiprone and deferoxamine; only and separately, were chosen.

Each ADR report includes patient information including a Case ID, a Suspected Product Name and active ingredient, reason for use, reactions and seriousness criteria, outcome, sex of the patient, event date, received date, Case Priority (expedited or direct), Patient Age and weight, reporter type and source, concomitant products if any, manufacturer information, country of occurrence. MedDRA coding numbers were not included in the line listing, but the events were coded according to Questions and Answers on FDA's Adverse Event Reporting System page (134). However, PT and SOC information not being provided limited our research.

As a screening strategy, one very common adverse event, that is headache, one rare adverse event, that is blurred vision and one serious adverse event with different frequencies, that is sepsis, were chosen. The purpose was to compare the association of adverse events to iron chelators, to understand if the listed data is parallel to real life data and to also see if data from different databases are similar. Accordingly, disproportionality analysis results between databases were compared. Additionally, case details were also reviewed for this purpose, to better understand the patient demographics and case details.

2.1.3. Findings from VigiBase

The results received from VigiBase contained cases from all over the world from 2010 to 2021. In total, 24835 cases that were reported in relation to deferoxamine, deferiprone and deferasirox were received. Each report contained Report ID, Case entry date, region, seriousness information, reporter and report type, age group, gender, product dose and formulation, treatment duration, route of administration, indication, MedDRA coded SOC, PT and LLT names, outcome, reaction duration, dechallange and rechallenge information. As a screening strategy, from VigiBase, same adverse events selected from FAERS were also selected for VigiBase, to understand if the results would be similar.

In order to review the data, cases from VigiBase and the listed adverse events from local labeling were compared for each selected adverse event and iron chelator, to see if they are aligned or not.

In addition to this, adverse events that are listed as “very rare” from local labels were selected. These adverse events were chosen to see if events listed as very rare show a different frequency in real-life data.

For deferiprone and deferasirox, no adverse event was listed as very rare, but for deferoxamine, some very rare adverse events were identified. Despite this, these adverse events can be more frequent in real-life data from VigiBase and were investigated for signal detection.

Adverse events that were listed as unknown for deferiprone, deferasirox and deferoxamine were selected. The fact that no definite judgment has been made regarding the frequency of these adverse events suggested that real-life data from VigiBase may clarify this area. Therefore, adverse events of unknown frequency were compared with real-life data.

When examining the reports from VigiBase, it was realized that a lot of adverse events were not listed in the product information leaflets. These adverse events belong to different system organ classes and the number of reports for each adverse event were different in a non-homogenous way. It is not possible to logically base the reason why these cases were not previously listed in their labels, but adverse event reports from VigiBase that may be considered related based on the results of the disproportionality analysis, can be reviewed. As explained in this thesis, if ROR is greater than 1, this shows a result of exposure associated with higher odds of outcome and if ROR is smaller than 1, this shows a result of exposure associated with lower odds of outcome (135).

Additionally, fatal cases related to iron chelators were also selected from VigiBase data. There were 2210 cases for deferoxamine, 411 cases for deferiprone and 81694 cases for deferasirox that resulted in death. These cases constituted around %20 of total cases.

2.1.4. Data from SIDER

SIDER contains many cases related to deferasirox, deferiprone and deferoxamine. It is also important to note that cases were coded using MedDRA by the system as well. The difference that was observed from other databases was that SIDER was listing adverse events instead of reported cases.

2.1.5. Signals

Health authorities such as FDA and EMA are publishing signals related to marketed products in respected territories. Report lists the names of products and potential safety issues that were collected during specific periods. Identified safety signals are referred to as Disproportionately Reported Combinations (136).

To review the signals retrospectively, archived reports named “Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System” were collected. These reports include potential signals of serious risks or new safety information that were identified using the FAERS database during each quarter from 2008 to 2015. Data was then moved to FAERS for the launch of FAERS on September 10, 2012 (131).

Then, data from September 2012 was reviewed, which was collected from FAERS. FDA staff in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research regularly examine the database to monitor safety of the products. In case of an identification of a potential signal of a serious risk, this is entered as a safety issue into the authority’s system for further evaluation. Potential signals of serious risks are normally based upon a collection of FAERS reports, although a single FAERS report could lead to further evaluation of a potential safety issue. At the time of our thesis, latest report for Potential Signals of Serious Risks/New Safety Information Identified by the FDA were listing data covering the period from January 2022 to March 2022 (128).

To also analyze the data from European Union, “List of safety signals discussed since September 2012” was extracted, which is a list that was published in 2019 and is being updated continuously to inform Health care professionals and marketing authorization holders (132).

2.2. Methods

2.2.1. Disproportionality analysis

In the past, some other pharmacoepidemiological methods were being used to identify and to quantify adverse drug reactions. Some of these methods, such as case–control or cohort studies are still widely used. However, their set up are not so practical as it requires many details like specific organization, which causes delay, requires some

budget and also use of large databases. Previously, the databases that are accessible today were not inclusive of many cases. As the case volume grew in time, the need to mine the data became relevant and obvious (137,138).

Disproportionality Analysis can be performed via multiple techniques, but there are some technics that are mostly preferred by authorities. These methods include Multi-item Gamma Poisson Shrinker (MGPS); which is commonly used by US FDA, Bayesian Confidence Propagation Neural Network; which is commonly used by WHO's UMC, Proportional Reporting Ratio (PRR and aPRR); which is commonly used by UK Medicines Control Agency (MCA), Reporting Odds Ratios and Incidence Rate Ratios; which is commonly used by some other national spontaneous reporting centers and drug safety research units (127,139).

When the result is 1 or more than 1 for any of these methods, it indicates that the probability of this event due to this product's exposure is higher than expected (127,139).

- Multi-item Gamma Poisson Shrinker (MGPS)

MGPS may be needed when there are small observed or expected numbers of reports of the product-event pair of interest.

- Bayesian Confidence Propagation Neural Network

Bayesian logic specifies the relation between the prior and posterior probability before and after linking data fields. This method is currently used by the WHO Monitoring Centre in the Bayesian confidence propagation neural network analysis (BCPNN). BCPNN aims to analyze large data sets, is robust in handling incomplete data, to be used with complex variables. This tool is useful for finding drug and adverse drug reaction combinations with other variables, which are highly associated compared to the generality of the stored data, or a section of the stored data. The method is transparent for easy checking and flexible for different types of research (140).

- Proportional Reporting Ratio (PRR)

PRR is the proportion of spontaneous reports for a product that are linked to a specific adverse outcome, divided by the corresponding proportion for all or several other drugs. PRR method is arguably the easiest method to interpret (141).

- Reporting Odds Ratios and Incidence Rate Ratios

The PRR does not estimate relative risk. If, however, a spontaneous report database is viewed as source data for a case-control study, ROR can be used to estimate relative risk. Treating the data as source data for a case-control study allows for further reduction of bias by the judicious choice of controls (141). ROR being equal to 1 would mean that exposure does not affect the odds of the outcome. Similarly, if ROR is greater than 1, this shows a result of exposure associated with higher odds of outcome and if ROR is smaller than 1, this shows a result of exposure associated with lower odds of outcome (135). Analysis is performed by using a contingency table, summarized in table 11 (127,139).

Table 11. Contingency table example

	Selected adverse event	**All adverse events**
Selected product	a	b
All products	c	d

$$PRR = [a \div (a + b)] / [c \div (c + d)]$$

$$ROR = [a \div b] / [c \div (d)]$$

- The 'PRR' result of X indicates that for the product, the probability of reporting this particular event, rather than any other event, is X times higher compared to the probability for reference drugs. "ROR" questions an increased risk of adverse drug reaction reporting, and not risk of adverse drug reaction occurrence, in absolute terms. So, the odds of reporting of this particular event related to this particular product are X times higher than the odds of reporting of this particular event among all other reports in the database. "ROR" offers an advantage over "PRR" by estimating the relative risk (139).
- A confidence interval gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data (142).

$$\text{Lower 95\% CI} = e^{\ln(OR) - 1.96\sqrt{(1/a + 1/b + 1(c + 1/d)}}$$

$$\text{Upper 95\% CI} = e^{\ln(OR) + 1.96\sqrt{(1/a + 1/b + 1(c + 1/d)}}$$

3. RESULTS

3.1. Information for Iron Chelators from Local Labels in Turkey

Upon reviewing the available products for iron chelation in Turkey, it was identified that some mentioned adverse reactions are similar. Although mechanism of actions (65,67,68) differ, there are similarities in the product effects. These effects include both wanted and unwanted effects (143–146). Table 12 lists the common and very common adverse events for iron chelators from the product characteristics sheets.

Table 12. Common and very common adverse events from local labels

	Deferasirox	Deferiprone	Deferoxamine
Appetite problems	-	✓	-
Arthralgia	-	✓	✓✓
Arthropathy	-	✓	-
Back pain	-	✓	-
Blood creatinine elevation	✓✓	-	-
Bone disease	-	-	✓
Chromaturia	-	✓✓	-
Constipation	✓	-	-
Diarrhea	✓	✓	-
Dyspepsia	-	✓	-
Fatigue	-	✓	-
Growth retardation	-	-	✓
Headache	✓	✓	✓
Indigestion	✓	-	-
Itching	✓	-	-
Liver enzymes (ALT, AST) increased	-	✓	-
Myalgia	-	-	✓✓
Nausea	✓	✓✓	✓
Neutropenia	-	✓	-
Non-flatulent	✓	-	-
Pain in extremities	-	✓	-
Proteinurea	✓	-	-
Rash	✓	-	-
Stomachache	-	✓✓	-
Transaminases increased	✓	-	-
Urticaria	-	-	✓
Vomiting	✓	✓✓	-
Weight increased	-	✓	-

Principally, it was noted only a few adverse events are seen with more than one iron chelator agent. While headache may be observed after exposure to any iron chelator (143–145,147), diarrhea may be seen after deferasirox (143) and deferiprone (144). It is

also noted that nausea may be experienced after exposure to deferasirox or deferoxamine (143,145). Different to deferiprone and deferoxamine, a high risk of blood creatinine level exists for deferasirox (143,147).

3.2. Findings from FAERS

From the data received from FAERS, related to iron chelators, as shown in Figure 9, 24581 case entries were obtained for all 3 molecules. One entry does not mean one patient, as for some reports, for only one patient, more than one event was reported.

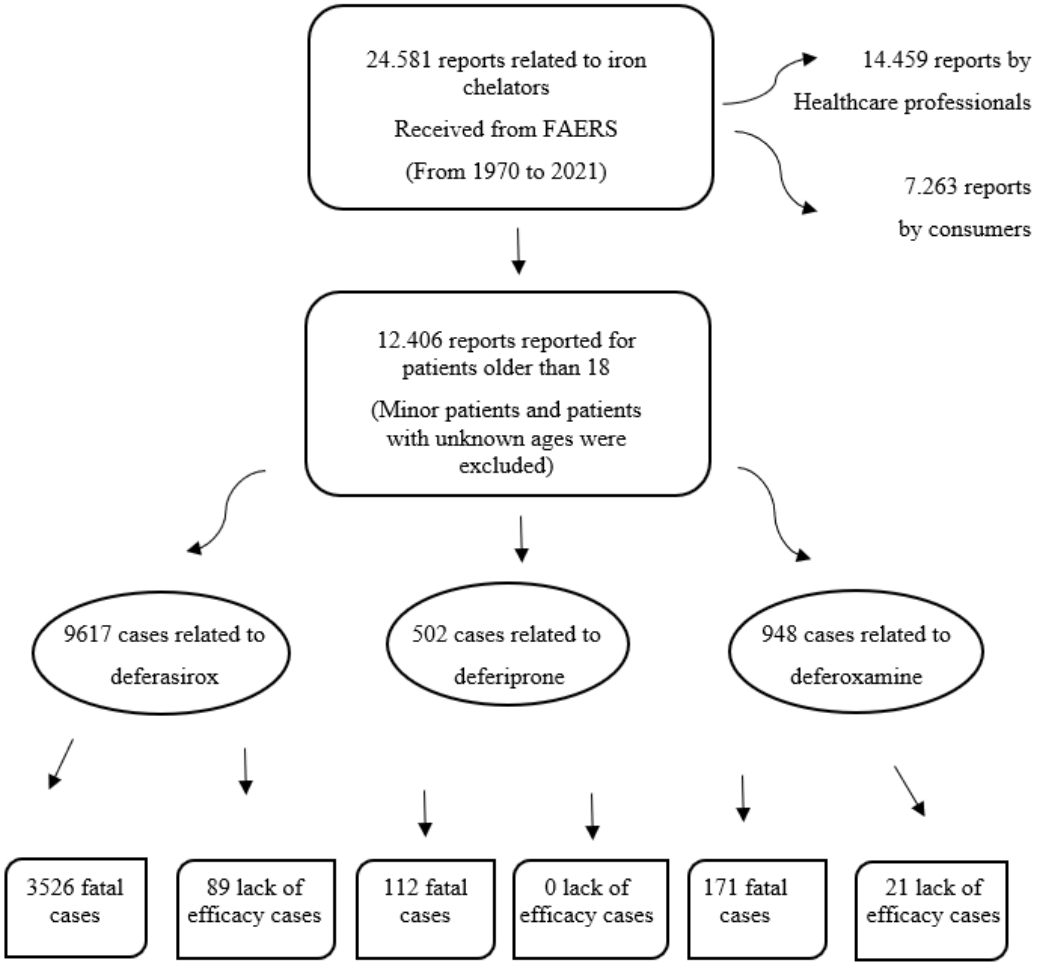

Figure 9. Number of reports included from the data extracted from FAERS

Of 24581 cases, 12406 were reported for patients over 18. 9617 cases were reported related to deferasirox and 3526 of them were marked as fatal. 809 cases were reported for lack of efficacy. 502 cases were reported related to deferiprone and 112 of them were marked as fatal. None of them were reported for lack of efficacy. 948 cases

were reported related to deferoxamine and 171 of them were marked as fatal. 21 cases were reported for lack of efficacy.

Number of reports by healthcare professionals is also added as it affects the medical interpretation of the cases. Number of reports related to each iron chelator and lack of efficacy and fatal cases were listed.

Before exploring the specific adverse reactions, a further examination was necessary to understand the patient characteristics, to better analyze and to mine the data. Accordingly, as per Figure 10, there are differences in the number of reports for iron chelator throughout the years. For all years included, deferasirox has the most reports. While during the first years like 2010, 2011 and 2012, the difference is immense, in time, this difference starts to become more understandable. The number of reports for deferiprone and deferoxamine are still very low, however there is a significance increase for deferiprone related reports during 2021. The reason behind this increase was also studied further during this study.

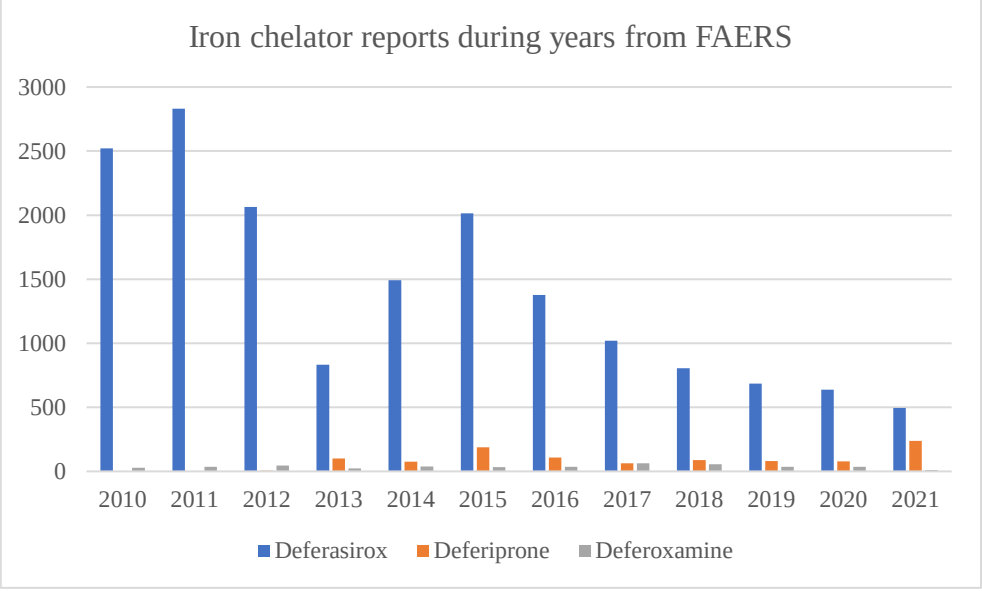

Figure *10.* Number of iron chelator reports during years from FAERS

Table 13 list summarizes the case details for iron chelators from FAERS. According to that, there is almost a homogenous distribution between male and female patients, with slight differences. For deferiprone, female cases are a little more compared to male cases. Age mean of patients that took deferiprone and deferoxamine are exactly the same, which is 41. For deferasirox, this metric is 53. Finally, almost all

of the reported cases were serious. Additionally, some reports were reported for the situation were the product was ineffective.

Table 13. Reported case details for iron chelators according to the data from FAERS

Product	Male (%)	Female (%)	Age Mean	Serious cases (%)	Lack of efficacy
Deferasirox	47%	45%	53	88%	231
Deferiprone	45%	52%	41	87%	3
Deferoxamine	43%	45%	41	84%	44

According to the line listing from FAERS, some commonly reported adverse events for all iron chelators were GI related; (such as diarrhea, abdominal pain, gastric disorder, vomiting), blood iron level abnormalities (increased, overloaded), renal complications (such as impairment, failure, acidosis), hepatic complications (such as cirrhosis, failure, enzyme abnormalities, hemorrhage, jaundice), platelet count abnormalities. Unexpectedly, 388 cases were reported for patients physically falling and injuring a limb.

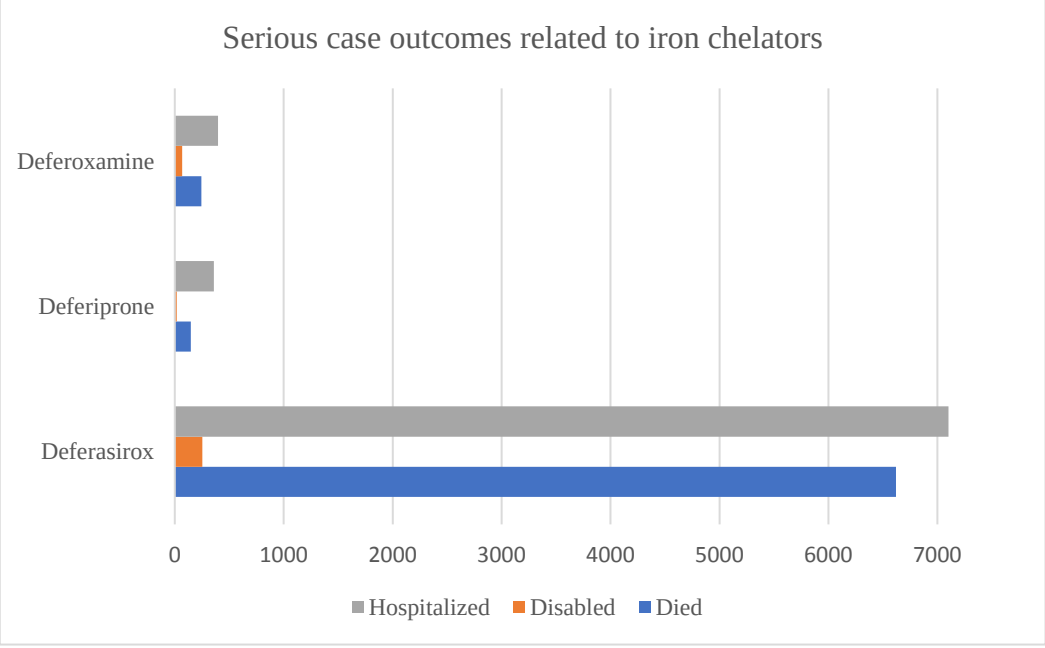

Figure *11.* Number of serious outcomes for iron chelators cases from FAERS

According to Figure 11, logically, as more cases were reported related to deferasirox, more data was reached related to serious cases. For all 3 iron chelators, most of the serious cases resulted in hospitalization. For deferasirox, hospitalization number is close to death. Possible reactions that led to death included spleen disorder,

hepatomegaly, renal disorder, iron overload, drug ineffective, acute biphenotypic leukaemia, decreased platelet count decreased, liver disorder, pneumonia, cytomegalovirus infection reactivation, multiple organ dysfunction, etc.

3.2.1. Findings from VigiBase

UMC provided us with cases related to iron chelators, which in total were 383361 entries for all 3 molecules. One entry does not mean one patient, as for some reports, for only one patient, more than one event was reported.

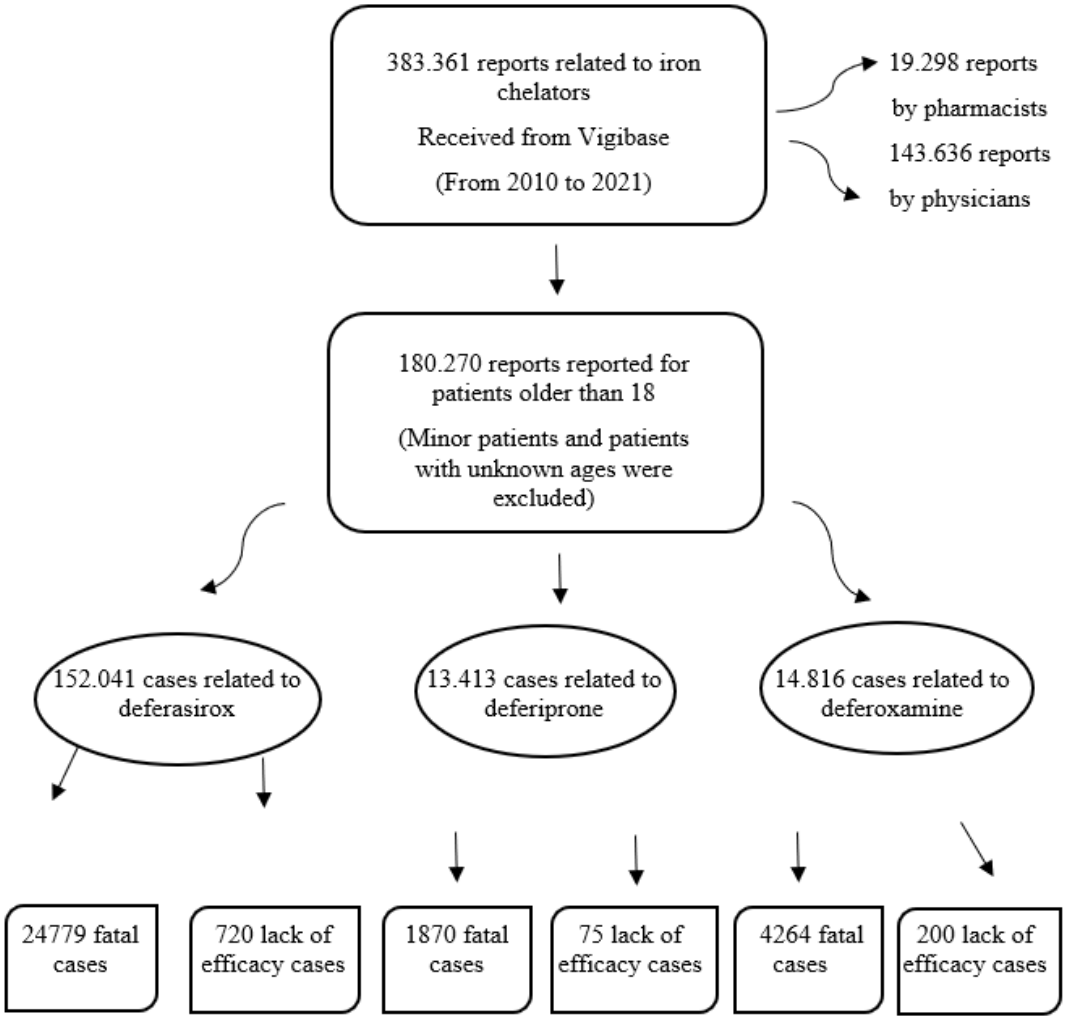

Figure *12*. Number of reports included from the data extracted from VigiBase.

As shown in Figure 12, of 383361 cases, 180270 were reported for patients over 18. 152041 cases were reported related to deferasirox and 24779 of them were marked as fatal. 720 cases were reported for lack of efficacy. 13413 cases were reported related to deferiprone and 1870 of them were marked as fatal. 75 cases were reported for lack

of efficacy. 14816 cases were reported related to deferoxamine and 4264 of them were marked as fatal. 200 cases were reported for lack of efficacy. Number of reports by healthcare professionals is also added as it affects the medical interpretation of the cases. Number of reports related to each iron chelator and lack of efficacy and fatal cases were listed.

As seen in Figure 13, there are differences in the amount of reports for iron chelator throughout the years. For all years included, deferasirox has the most reports. In general, the waves in reported numbers and total reports for each iron chelator was very similar to the numbers from FAERS. The number of reports for deferiprone and deferoxamine are still very low.

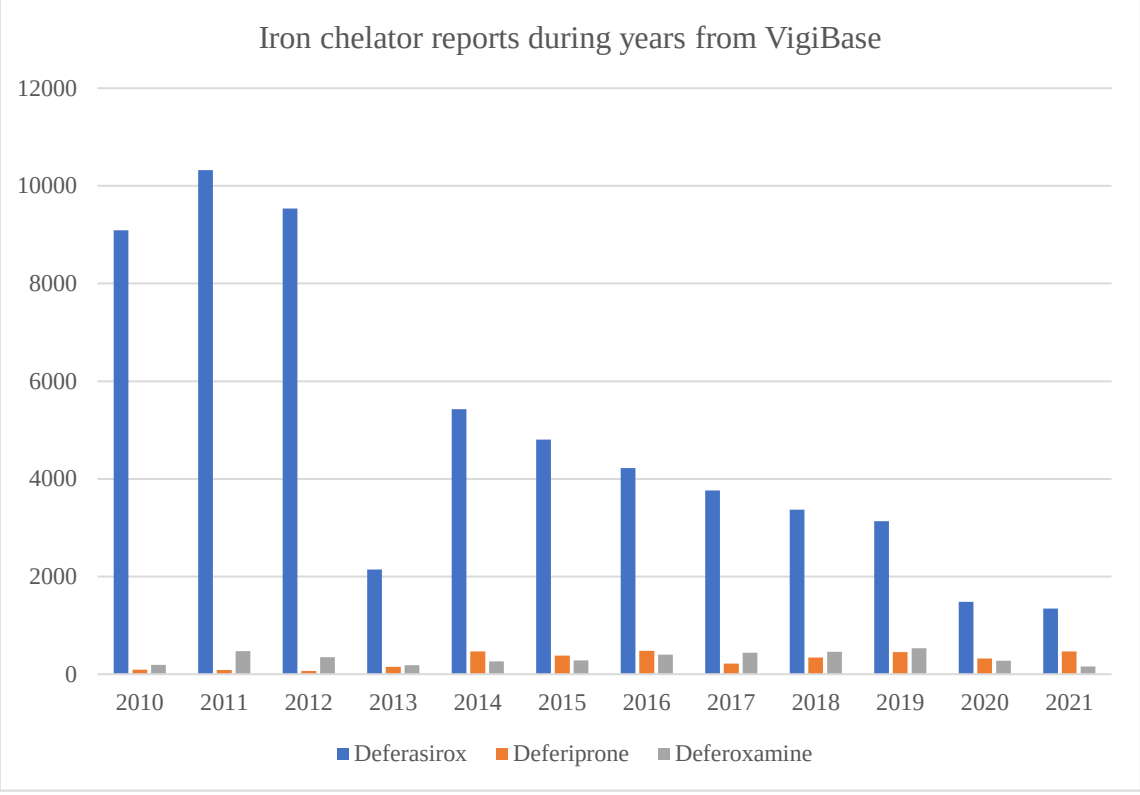

Figure *13.* Iron chelator reports during years from VigiBase

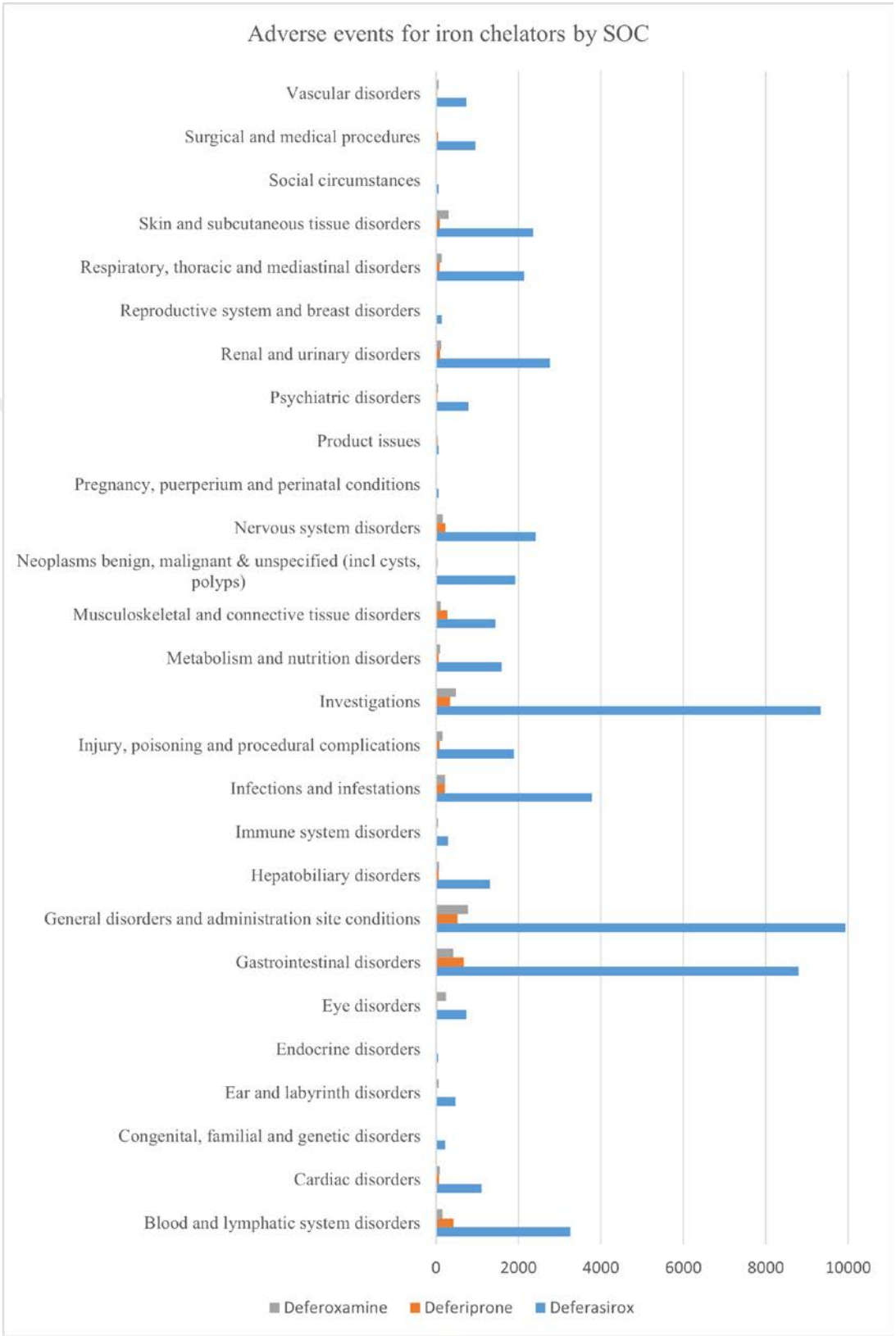

Figure *14.* Reported adverse reactions for iron chelators per their SOC from VigiBase

As seen in Figure 14, the term ‘General disorders and administration site conditions’ is the most frequent SOC reported in relation to deferasirox use (17 %) in VigiBase, followed by the SOC ‘investigations’ (16 %), which, when combined, account for 33 % of all ADRs reported for this drug. Similarly, the term ‘Gastrointestinal disorders’ is the most frequent SOC reported in relation to deferiprone use (19 %) in VigiBase, followed by the SOC ‘General disorders and administration site conditions’ (15 %), which, when combined, account for 34 % of all ADRs reported for this drug. The term ‘General disorders and administration site conditions’ is the most frequent SOC reported in relation to deferoxamine use (19 %) in VigiBase, followed by the SOC ‘investigations’ (12 %), which, when combined, account for 31 % of all ADRs reported for this drug.

As “General disorders and administration site conditions” were the most reported SOC for iron chelators as per the data from VigiBase, the adverse events belonging to this System organ class were examined. As per Figure 15, which shows these adverse events as per their Preferred term names, for cases under “General disorders and administration site conditions”, it was seen that “death” was entered for many cases. However, actually "death" is not an adverse event but the result of an adverse event. For this reason, death cases in detail in a separate section were reviewed. Other than death; pyrexia, malaise, fatigue and asthenia were most reported adverse events for this SOC. Upon reviewing the listed adverse reactions in local label, it was noted that for deferiprone, fatigue was listed as common (148). For deferoxamine, pyrexia was listed as common (149). Interpretation is possible for deferasirox and for other iron chelators, more information is needed, as for some of the adverse events, there are even no reports related to deferoxamine and deferiprone.

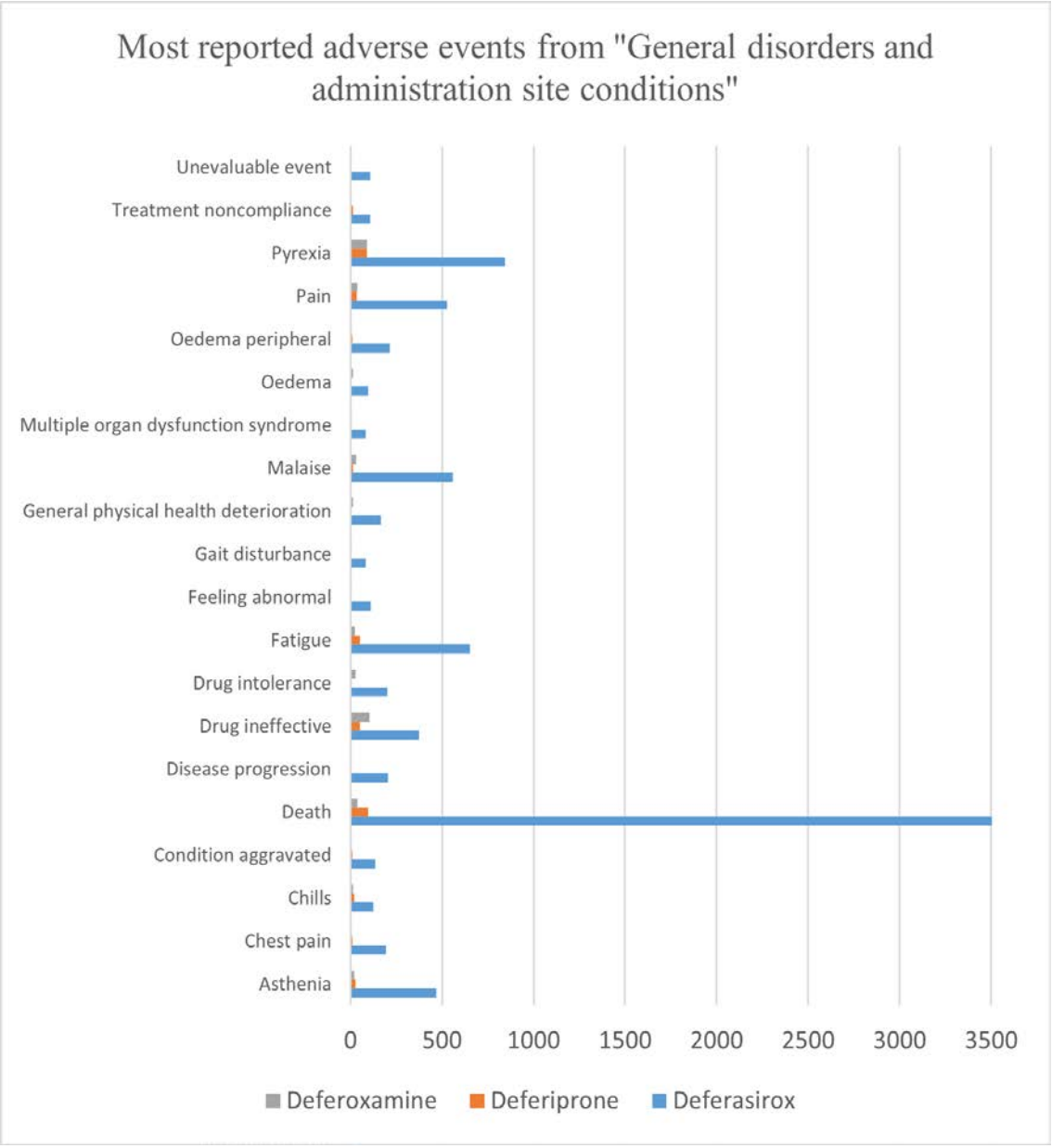

Figure *15*. Numbers of adverse events under the SOC General disorders and administration site conditions from VigiBase

The SOC “Investigations” refers to measurable data such as ECG data, blood pressure, and blood test results like red blood cell counts, bilirubin (150). This SOC has the second most cases for iron chelators as per the data from VigiBase.

As per Figure 16, for cases under “Investigations”, it is identified that serum ferritin increased, blood creatinine increased, haemoglobin decreased, and platelet count decreased were most reported adverse events for this SOC. Upon reviewing the listed

adverse reactions in local label, it was noted that for deferiprone, increases in AST in ALT levels were listed as common (148).

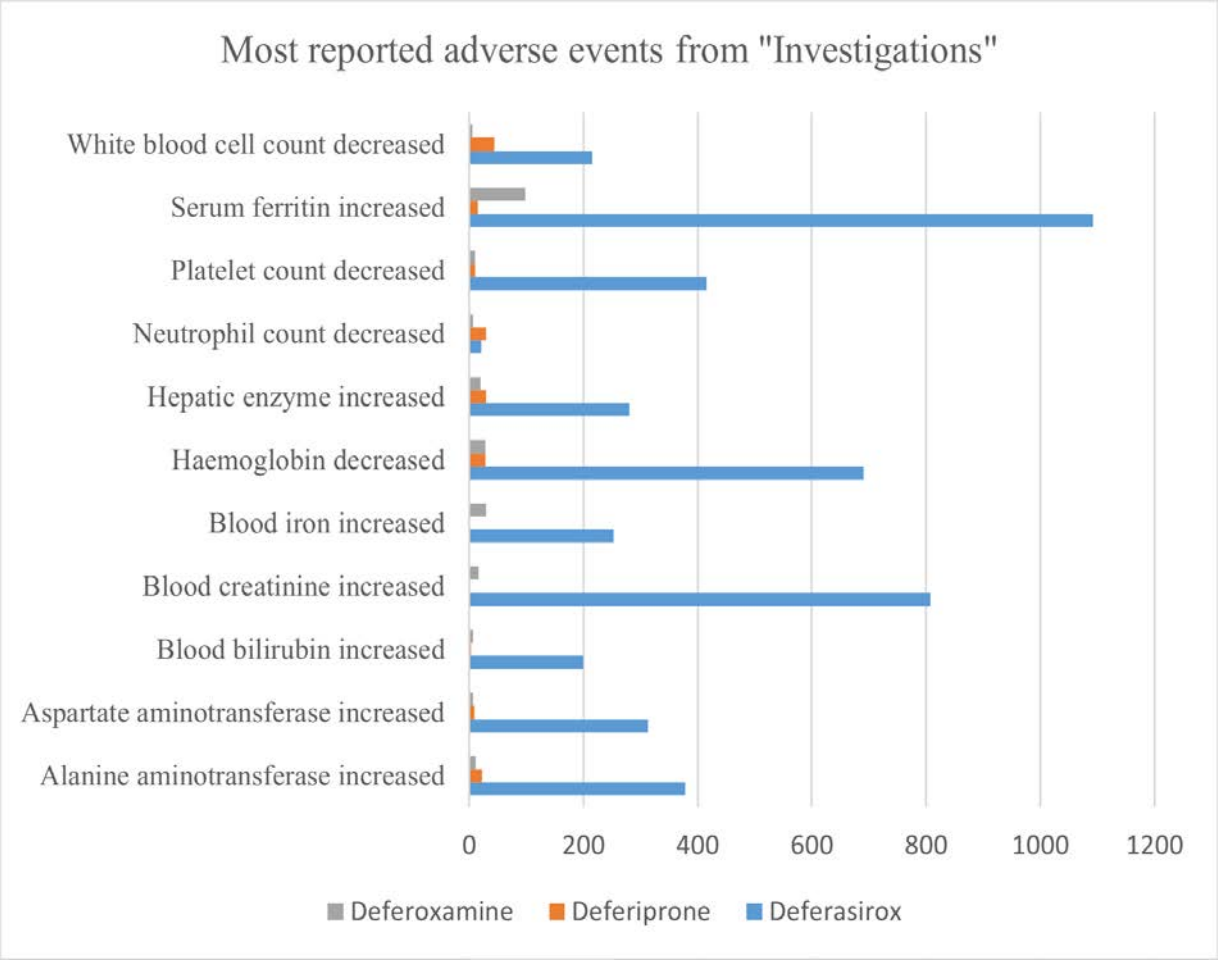

Figure *16*. Numbers of adverse events under the SOC Investigations from VigiBase

As per Figure 17, for cases under “Gastrointestinal disorders”, which is the third most reported SOC, it is identified that diarrhoea, nausea, vomiting and abdominal pain were most reported adverse events for this SOC. Upon reviewing the listed adverse reactions in local label, it was noted that for deferiprone, abdominal pain vomiting and nausea were also listed as very common (148). For deferasirox, diarrhoea, constipation, nausea, abdominal pain and dyspepsia were listed as common (143). For deferoxamine, nausea was listed as common and vomiting and abdominal pain were listed as rare. Diarrhoea was listed as very rare (145). Similarly, more information is needed for deferoxamine and deferiprone.

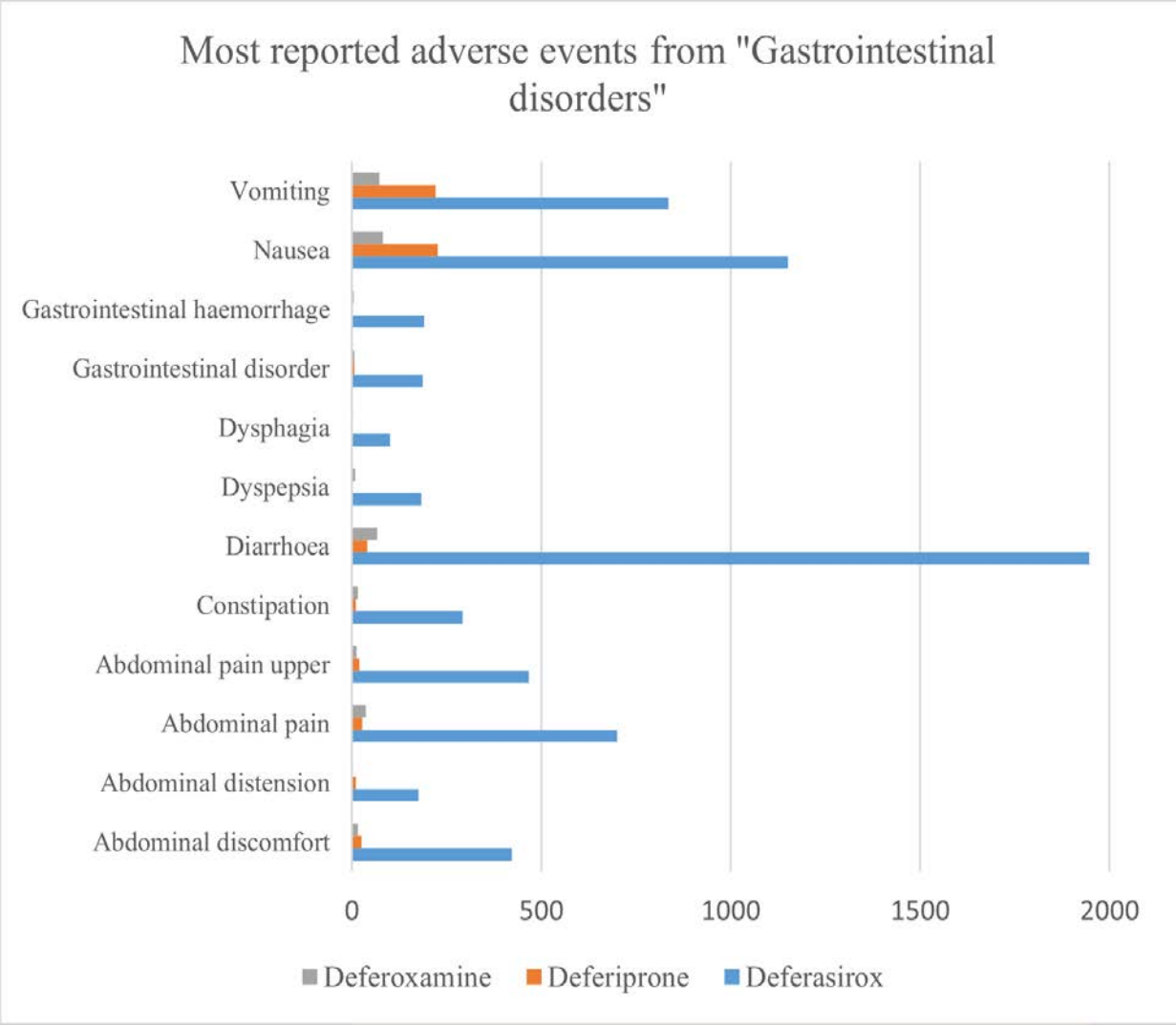

Figure *17.* Numbers of adverse events under the SOC Gastrointestinal disorders from VigiBase

As per Figure 18, it is evident that data from the region “Americas” is more abundant compared to other regions. This is followed by data from European countries and there is a small amount of information for Oceania and Africa. Reported adverse events from Asia are comparatively higher for SOCs Gastrointestinal Disorders, Investigations and General Disorders and Administration Site Conditions. For most of other SOCs, the information from Asia is limited, similar to Oceania and Africa.

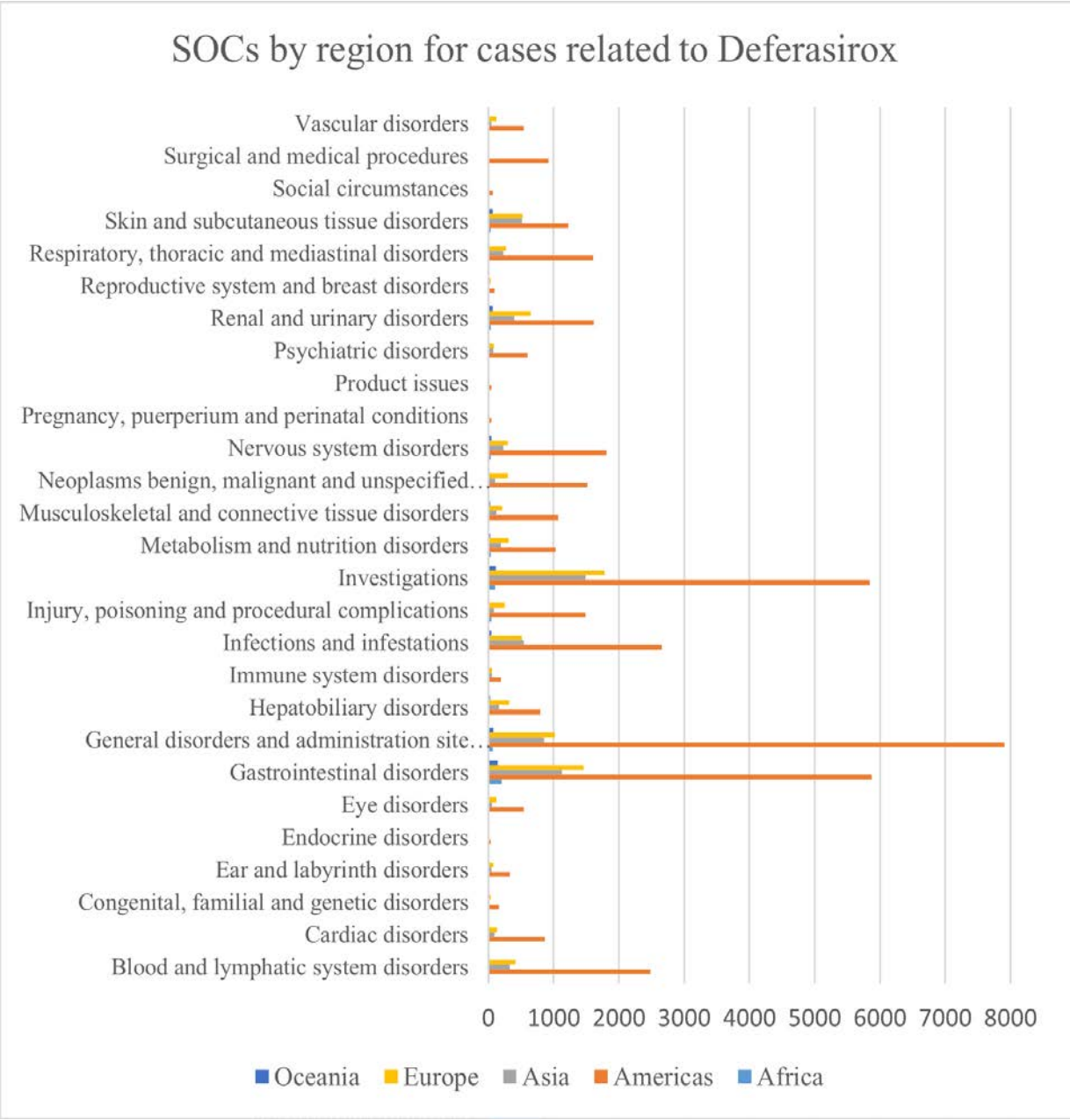

Figure *18*. SOCs by region for cases related to Deferasirox from VigiBase

As per Figure 19, which is relatively similar to Figure 17, it is also evident that data from the region "Americas" is more abundant compared to other regions. Differently, there are more data from Asian countries related to SOCs Gastrointestinal Disorders, Musculoskeletal and connective tissue disorders, General conditions and administration site conditions and blood lymphatic system disorders. For product issues, only available data is from Asian countries as well.

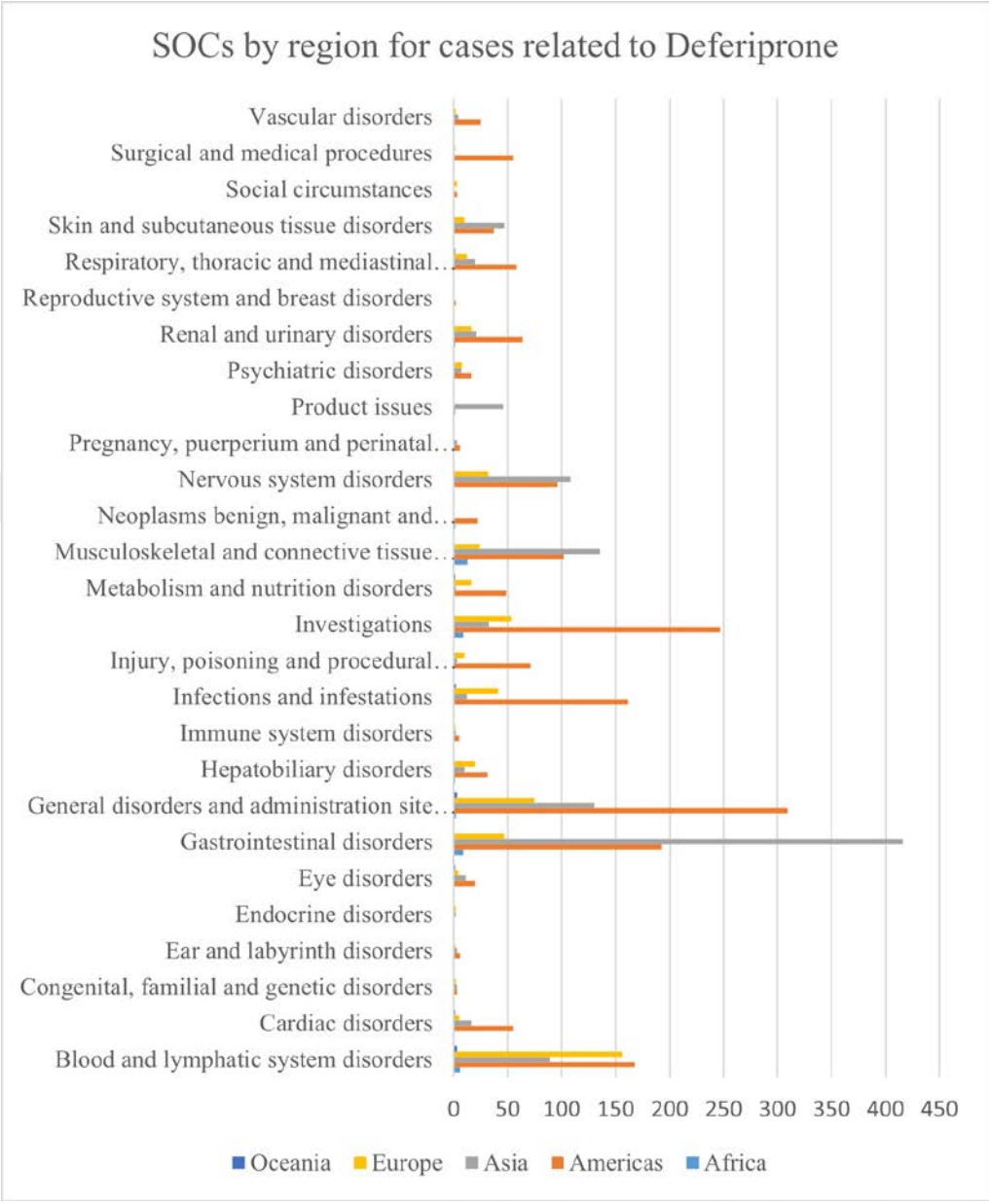

Figure *19*. SOCs by region for cases related to Deferiprone from VigiBase

As per Figure 20, which lists SOCs by region for deferoxamine related cases, more data is obtained from European countries. This is followed by Americas. Information related to SOC Social circumstances is missing from almost all regions. For some SOCs, such as Eye disorders in Europe and Skin and Subcutaneous tissue disorders in Asia, there is a higher ratio in the reports, which can be worth investigating.

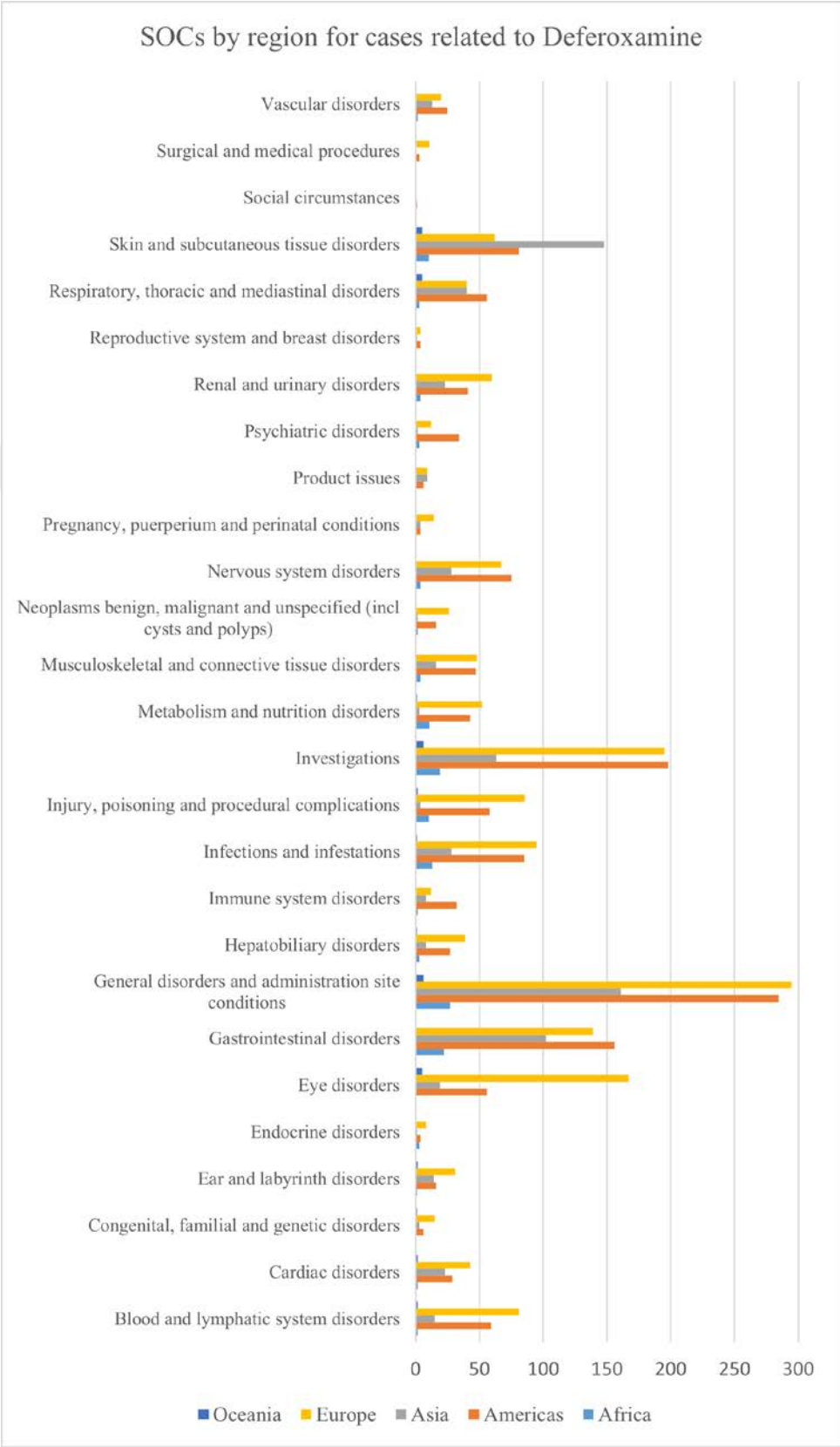

Figure *20*. SOCs by region for cases related to Deferoxamine from VigiBase

The term ‘Sepsis’ was reported 319 out of 58629 times in relation to deferasirox use, which makes the ratio around % 0.54. The same term was reported 22 out of 3525 times in relation to deferiprone use, which makes the ratio around % 0.62. It was also reported 16 out of 4005 times in relation to deferoxamine use, which makes the ratio around % 0.40.

As per Figure 21, it is seen that most sepsis cases for deferasirox originated from Americas, and it is followed by Asia. Sepsis reports for all three chelators are mostly from Americas. For deferiprone and deferoxamine, there are slightly more reports compared to Asia.

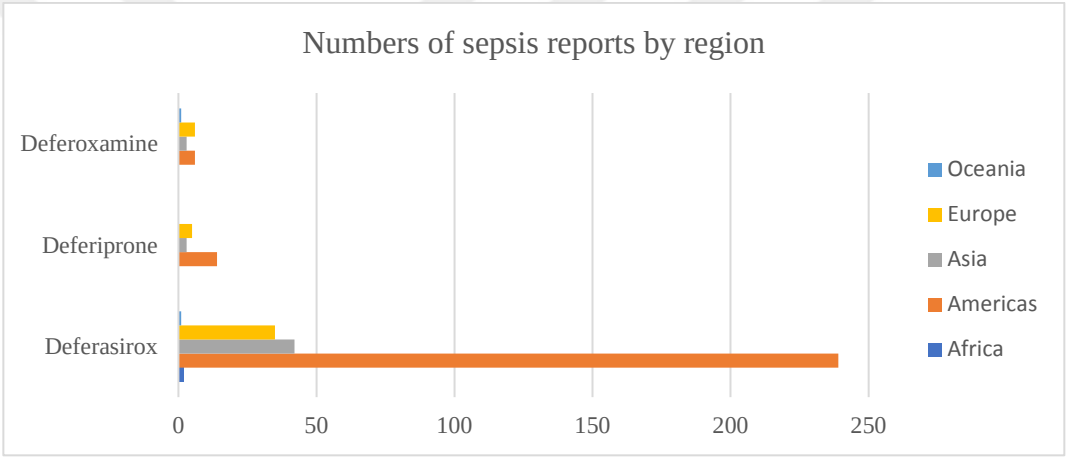

Figure 21. Number of sepsis reports for iron chelators per region in VigiBase

Table 14 summarizes details of sepsis cases related to iron chelators. While the patient’s gender ratio differs between chelators, there is a similarity between indications, age group and outcomes of the cases. It is clear that most of the patients that experiences sepsis were over the age of 18. For deferoxamine, most of the patients were over 75. There were 2 babies who were given deferasirox and deferoxamine, who experienced sepsis. It should be noted that due to the nature of sepsis, all cases are serious, and a significant proportion are fatal. Most common reasons for iron chelator administration were thalassemia, haemochromatosis, iron overload and myelodysplastic syndrome.

Table 14. Numbers of sepsis cases and case details including patient demographics for iron chelators according to data from VigiBase

	Deferasirox case numbers and percentages		Deferiprone case numbers and percentages		Deferoxamine case numbers and percentages	
GENDER						
Male	311	%60	18	%49	7	%12
Female	187	%36	19	%51	49	%86
UNK	14	%2.7	-	-	1	%1.7
AGE GROUP						
28 days to 23 months	1	%0.2	-	-	1	%1.7
2-11	1	%0.2	-	-	2	%3.4
12-17	8	%1	2	%5.4	1	%1.7
18-44	15	%29	17	%46	-	-
45-64	36	%7	3	%8	-	-
65-74	83	%16	1	%2.7	8	%14
≥75	34	%6	5	%13	39	%68
UNK	334	%65	7	%19	6	%67
SERIOUSNESS						
Caused/Pro. Hosp.	58	%11	16	%43	1	%1.7
Caused/Pro. Hosp., Other	67	%13	5	%13	19	%33
Disabling/Incap.	1	%0.2	-	-	-	-
Disabling/Incap., Other	1	%0.2	-	-	-	-
Death, Caused/Pro Hosp.	98	%19	3	%8	-	-
Death, Caused/Pro Hosp., Other	79	%15	3	%8	-	-
Death, Life threatening,	1	%0.2	4	%10	-	-

Caused/Pro Hosp., Disabling/Incap., Other						
Death	105	%20	2	%5.4	16	%28
Life Threatening	25	%5	-	-	2	%3.5
Other	16	%3	4	%10	4	%7
UNK	38	%7	-	-	4	%7
INDICATION						
Acute lymphocytic/myeloid leukaemia	10	%2	-	-	-	-
Anaemia/Aplastic anaemia	14	%2.7	2	%5.4	1	%1.7
Beta thassaemia	-	-	6	16.2	-	-
Blood disorder	6	%1.2	-	-	-	-
Blood iron increased	1	%0.2	-	-	-	-
Breast cancer	1	%0.2	-	-	9	%16
Chelation therapy	-	-	-	-	1	%1.7
Chronic lymphocytic/myeloid leukemia	6	%1.2	-	-	-	-
Diamond-blackfan anaemia	2	%0.45	-	-	-	-
Essential thrombocythaemia	1	%0.2	-	-	-	-
Haematopoietic neoplasm	1	%0.2	-	-	-	-
Haemochromatosis	10	%2	9	%24	5	-
Haemosiderosis	5	%1	2	%5.4		-
Iron metabolism disorder	18	%3.5	3	%8.1	-	-
Iron overload	88	%17	3	%8.1	1	%1.7

Lung neoplasm malignant	1	%0.2	-	-	-	-
Lymphatic disorder	4	%0.8	-	-	-	-
Lymphoma	2	%0.4	-	-	-	-
Multiple myeloma	2	%0.4	-	-	-	-
Myelodysplastic syndrome	125	%24	2	%5.4	32	%56
Myelofibrosis	4	%0.8	-	-	-	-
Neoplasm	12	%2	1	%2.7	-	-
Pearson's syndrome	1	%0.2	-	-	-	-
Refractory cytopenia with unilineage dysplasia	1	%0.2	1	%2.7	-	-
Schistosomiasis	1	%0.2	-	-	-	-
Sickle cell anaemia	13	%2.5	2	%5.4	-	-
Thalassaemia	5	%1	4	%10.8	3	5.2
Thalassemia major	1	%0.2	-	-	-	-
Transfusion	3	%0.6	1	%2.7	-	-
Unevaluable event	7	%1.4	-	-	-	-
UNK	153	%30	-	-	11	%19
OUTCOME						
Fatal	235	%46	2	%5.4	11	%19
Not recovered	9	%1.7	7	%19	-	-
Recovered	49	%9.6	12	%32	36	%63
Recovering	19	%3.7	1	%2.7	1	%1.8
UNK	200	%39	15	%40	9	%16
REPORTER TYPE						

Consumer/Non-HCP	91	%17	6	%16	12	%21
Other Healthcare Professional	64	%12	8	%21	15	%26
Pharmacist	9	%1.7	10	%27	2	%3.5
Physician	177	%34	13	%35	26	%45
UNK	171	%33	-	-	2	%3.5

*Pro. Hosp: Prolonged Hospitalization, Incap: Incapacitating, UNK: Unknown

The term ‘Vision blurred’ was reported 108 out of 58629 times in relation to deferasirox use, which makes the ratio around % 0.18. The same term was reported 3 out of 3525 times in relation to deferiprone use, which makes the ratio around % 0.08. It was also reported 17 out of 4005 times in relation to deferoxamine use, which makes the ratio around % 0.42.

As per Figure 22, it is also seen that most blurred vision cases for deferasirox originated from Americas and most blurred vision cases for deferiprone and deferoxamine originated from Europe.

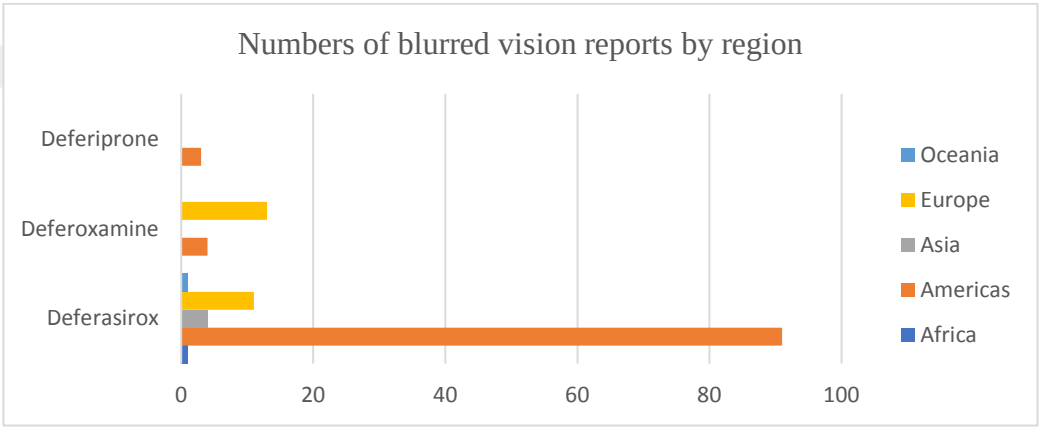

Figure *22*. Number of blurred vision reports for iron chelators per region in VigiBase

As per Table 15 and blurred vision cases, at first glance, it is clear that a lot of information is not shared by the reporter. This imposes restrictions on our comments. Especially for case criteria like outcome, seriousness and age group, information was not given. With this being said, a limited interpretation can be made. For gender, ratio for female patients is higher for deferasirox and deferiprone. It is difficult to comment on the age range because the data for all 3 iron chelators is not homogeneous. For deferasirox, it is clear that most cases are reported for patients over the age of 18. Seriousness and outcome information is lacking as well, for this reason, a separate filter for fatal cases was applied. For indications, the ratio difference for iron overload, myelodysplastic syndrome and haemochromatosis is slightly higher than other indications. Reporter information gives an idea about the cases’ medical approval, as it is important to know that case was examined by someone with medical knowledge. For all 3 iron chelators, most of the cases were reported by HCPs.

Table 15. Numbers of blurred vision cases and case details including patient demographics for iron chelators according to data from VigiBase

	Deferasirox		**Deferiprone**		**Deferoxamine**	
	case numbers and percentages		**case numbers and percentages**		**case numbers and percentages**	
GENDER						
Male	79	%36	2	%40	-	-
Female	134	%61	3	%60	-	-
UNK	6	%3	-	-	6	%100
AGE GROUP						
28 days to 23 months	1	%0.5	-	-	-	-
2-11	1	%0.5	1	%20	-	-
12-17	2	%0.9	-	-	-	-
18-44	9	%4	2	%40	1	%17
45-64	13	%6	-	-	1	%17
65-74	31	%14	-	-	-	-
≥75	24	%11	-	-	-	-
UNK	138	%63	2	%40	4	%67
SERIOUSNESS						
Caused/Pro. Hosp.	23	%11	1	%20	-	-
Caused/Pro. Hosp., Other	45	%21	-	-	-	-
Disabling/Incap.	2	%1	2	%40	-	-
Disabling/Incap., Other	1	%0.5	-	-	-	-
Death, Caused/Pro Hosp.	8	%4	-	-	-	-
Death, Caused/Pro Hosp., Other	5	%2	-	-	-	-
Death, Life threatening,	3	%1	-	-	-	-

Caused/Pro Hosp., Disabling/Incap., Other						
Death	1	%0.5	-	-	-	-
Life Threatening	2	%1	-	-	-	-
Other	92	%42	-	-	-	-
UNK	37	%17	2	%40	6	%100
INDICATION						
Acute lymphocytic leukaemia (in remission)	1	%0.45	-	-	-	-
Anaemia/Aplastic anaemia	4	%2	-	-	-	-
Beta thassaemia	2	%1	-	-	-	-
Blood iron increased	3	%1.4	-	-	-	-
Catatonia	1	%0.45	-	-	-	-
Chelation therapy	1	%0.45	-	-	-	-
Haemochromatosis	4	%2	2	%40	-	-
Haemosiderosis	5	%2.7	-	-	2	%33
Hemolytic anemia	2	%1	-	-	-	-
Iron metabolism disorder	2	%1	-	-	-	-
Iron overload	37	%17	-	-	-	-
Leukaemia plasmacytic	1	%0.45	-	-	-	-
Lymphatic disorder	1	%0.45	-	-	-	-
Lymphatic system neoplasm	1	%0.45	-	-	-	-
Multiple myeloma	1	%0.45	-	-	-	-
Myelodysplastic syndrome	18	%8	-	-	-	-

Myelofibrosis	1	%0.45	-	-	-	-
Neoplasm	1	%0.45	-	-	-	-
Serum ferritin increased	9	%4	-	-	-	-
Sickle cell anaemia	6	%3	1	%20	-	-
Sickle cell anaemia with crisis	1	%0.45	-	-	-	-
Sickle cell disease	1	%0.45	1	%20	-	-
Thalassaemia	1	%0.45	1	%20	-	-
Thalassemia intermedia	1	%0.45	-	-	-	-
Thalassemia major	1	%0.45	-	-	-	-
Transfusion	1	%0.45	-	-	-	-
Unevaluable event	1	%0.45	-	-	-	-
UNK	113	%51	-	-	4	%67
OUTCOME						
Not recovered	21	%10	-	-	-	-
Recovered	12	%5	-	-	-	-
Recovering	16	%7	2	%40	-	-
UNK	170	%78	3	%60	6	%100
REPORTER TYPE						
Consumer/Non-HCP	53	%24	-	-	2	%33
Other Healthcare Professional	36	%16	-	-	2	%33
Pharmacist	9	%4	5	%100	-	-
Physician	47	%21	-	-	-	-
UNK	74	%34	-	-	2	%33

*Pro. Hosp: Prolonged Hospitalization, Incap: Incapacitating, UNK: Unknown

‘Headache’ was reported 340 out of 58629 times in relation to deferasirox use, which makes the ratio around % 0.57. The same term was reported 45 out of 3525 times in relation to deferiprone use, which makes the ratio around % 1.27. It was reported 30 out of 4005 times in relation to deferoxamine use, which makes the ratio around % 0.75.

As per Figure 23, in total, most of the cases originated from Americas. There are almost same amount of cases for headache related to deferiprone and deferasirox from Americas. Similar to this, there are also the same amount of cases related to deferiprone and deferasirox from Asia.

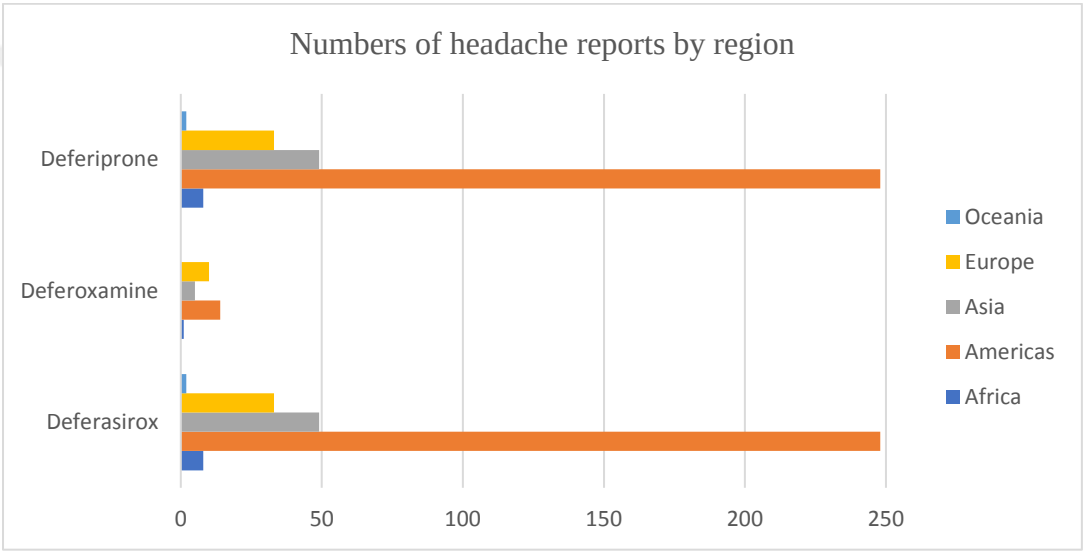

Figure *23*. Number of headache reports for iron chelators per region in VigiBase

As per Table 16, a lot of information is not shared, however, the case volume in total is higher. Also criteria like outcome, seriousness and age group, information was not given, so a limited interpretation is possible. Female patient ratio is higher for deferasirox and deferiprone. Regarding age group, the information for deferoxamine is limited. For deferasirox and deferiprone, a limited interpretation is possible, as it is evident that most of the reports are for patients over the age of 18. Seriousness and outcome are lacking; hence a separate filter was applied. For indications, the ratio difference for iron overload, MDS, iron metabolism disorder, sickle cell anemia, haemochromatosis and thalassemia are higher than other indications. Reporter is important for medical approval; if the case was examined by someone with medical knowledge. For all 3 iron chelators, most cases were reported by HCPs.

Table 16. Numbers of headache cases and case details including patient demographics for iron chelators according to data from VigiBase

	Deferasirox		**Deferiprone**		**Deferoxamine**	
	case numbers and percentages		**case numbers and percentages**		**case numbers and percentages**	
GENDER						
Male	252	%40	34	%46	-	-
Female	362	%57	40	%54	-	-
UNK	19	%3	-	-	8	%100
AGE GROUP						
2-11	17	%3	5	%7	-	-
12-17	30	%5	2	%2.7	-	-
18-44	90	%15	36	%49	-	-
45-64	129	%20	13	%17	-	-
65-74	71	%11	3	%4	-	-
≥75	51	%8	-	-	-	-
UNK	245	%39	15	%20	8	%100
SERIOUSNESS						
Caused/Pro. Hosp.	108	%17	3	%4	-	-
Caused/Pro. Hosp., Other	87	%14	9	%12	1	%12
Disabling/Incap.	1	%0.2	-	-	-	-
Death, Caused/Pro Hosp.	25	%4	-	-	-	-
Death, Caused/Pro Hosp., Other	13	%2	-	-	-	-
Death	28	%4.5	-	-	-	-
Life Threatening	7	%1	-	-	-	-

Life Threatening, Other	1	%0.2	-	-	-	-
Other	178	%28	26	%35	-	-
UNK	179	%28	34	%45	7	%88
INDICATION						
Acute lymphocytic leukaemia	5	%0.8	-	-	-	-
Anaemia/Aplastic anaemia	7	%1.1	1	%1.3	-	-
Beta thassaemia	1	%0.1	1	%1.3	-	-
Blood disorder/blood iron abnormal	3	%0.47				
Blood iron increased	4	%0.63	-	-	-	-
Chelation therapy	6	%0.9	-	-	-	-
Erythroblastopenia	1	%0.1			-	-
Ferritin high	1	%0.1				
Haemochromatosis	9	%1.4	10	%13	-	-
Haemoglobin e-thalassaemia disease	-	-	1	%1.3	-	-
Haemosiderosis	9	%1.4	1	%1.3	-	-
Hemolytic anemia	0	%1	1	%1.3	-	-
Haematopoietic neoplasm	1	%0.1	-		-	-
Iron metabolism disorder	12	%1.9	2	%2.7	-	-
Iron overload	93	%15	15	%20	-	-
Leukaemia (chronic, myeloid or unspecified)	3	%0.47	-	-	-	-
Lymphoma	1	%0.1			-	-

Lymphatic disorder	4	%0.63	-	-	-	-
Myelodysplastic syndrome	58	%9	-	-	-	-
Myelofibrosis	4	%0.63	-	-	-	-
Neoplasm	1	%0.1	-	-	-	-
Polycythaemia vera	1	%0.1			-	-
Serum ferritin decreased	2	%0.3			-	-
Serum ferritin increased	10	%1.6	-	-	-	-
Sickle cell anaemia	33	%5.2	2	%2.7	-	-
Sickle cell anaemia with crisis	2	%0.3	1	%1.3	-	-
Sickle cell disease	8	%1.3	1	%1.3	-	-
Sickle cell trait	1	%0.1	-	-	-	-
Superficial siderosis of central nervous system	-	-	3	%4	-	-
Pancytopenia	-	-	1	%1.3	-	-
Thalassaemia	10	%1.6	12	%16	-	-
Thalassemia major	1	%0.1	3	%4	-	-
Transfusion	1	%0.1	-	-	1	%12
UNK	315	%50	19	%25	7	%88
Vertigo of central origin	2	%0.3	-	-	-	-
OUTCOME						
Fatal	7	%1.1	-	-	-	-
Not recovered	38	%6	2	%2.7	-	-
Recovered	140	22	36	%49	1	%12
Recovered with sequelae	3	%0.47	2	%2.7	-	-

Recovering	35	%5.5	20	%27	-	-
UNK	410	%66	14	%19	7	%88
REPORTER TYPE						
Consumer/Non-HCP	230	%36	6	%8	4	%50
Lawyer	1	%0.1	-	-	-	-
Other Healthcare Professional	68	%11	7	%9	-	-
Pharmacist	30	%4.7	30	%40	-	-
Physician	178	%28	30	%40	3	%37.5
UNK	126	%20	1	%1.3	1	%12.5

*Pro. Hosp: Prolonged Hospitalization, Incap: Incapacitating, UNK: Unknown

3.2.1.1.Lack of Efficacy Cases from VigiBase

Cases where the iron chelator was ineffective were also reviewed. Table Figure 24 summarizes lack of efficacy cases.

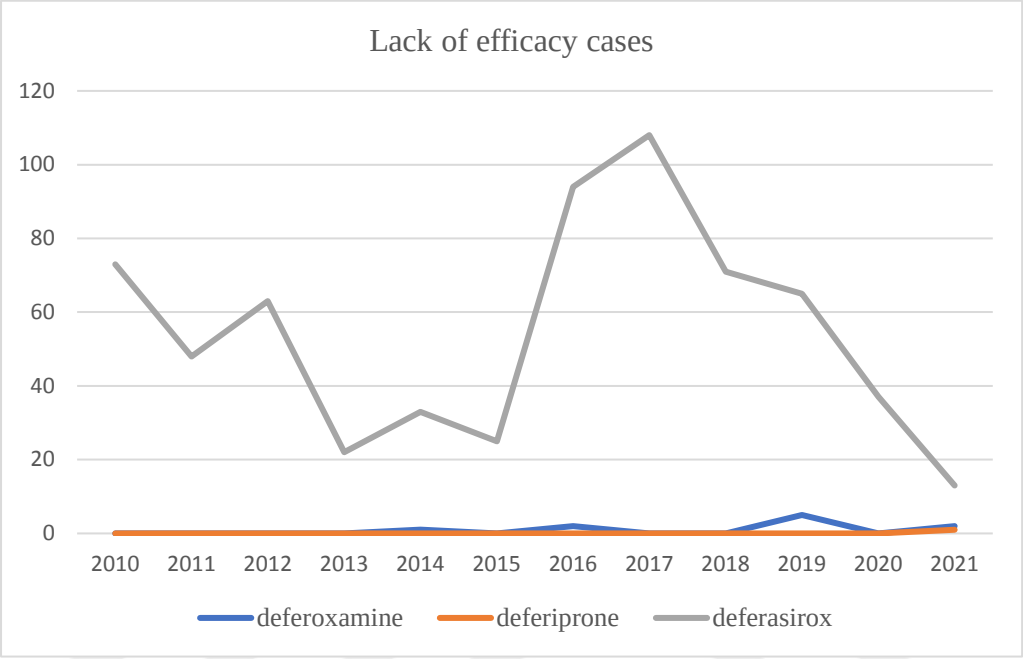

Figure *24*. Number of lack of efficacy cases related to iron chelators from VigiBase

As per Figure 24, some peaks for lack of efficacy cases related to deferasirox were noted. These peaks happened in 2012 and 2016-2017. After year 2017, there is a constant decrease. For lack of efficacy cases related to deferoxamine and deferiprone, a significant difference is not noted.

3.2.1.2.Fatal Cases from VigiBase

Cases that resulted in death were reviewed separetely. For this purpose, fatal cases were filtered, regardless of the reported adverse event. Figure 25 summarizes the fatal cases throughout the years related to iron chelators.

As per Figure 25, it was noted that from 2010 to 2013, there was a decrease in reported fatal cases for deferasirox. After 2013, it was noted there are some peaks for fatal cases in 2014, 2016 and 2019. For fatal cases related to deferoxamine and deferiprone, there is no significant difference.

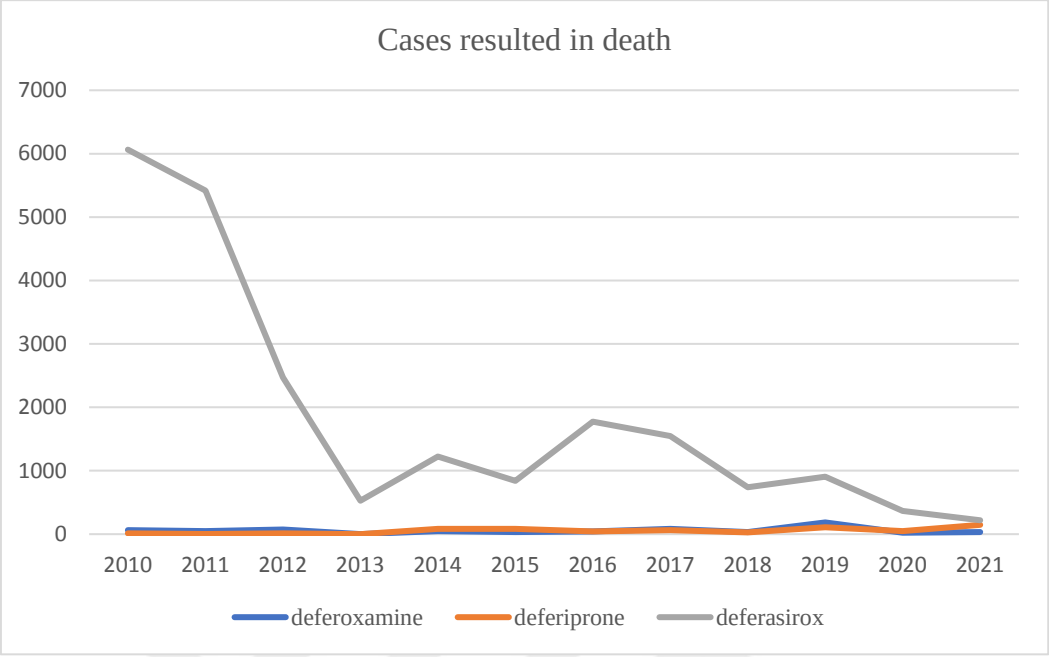

Figure *25*. Number of fatal cases related to iron chelators from VigiBase

Death and life-threatening cases were also filtered, to see if there were significant differences in certain adverse event reports. For this reason, cases reported due to an unwanted adverse event of “blurred vision”, “headache” and “sepsis”.

For blurred vision, there were no death or life-threatening cases related to deferoxamine and deferiprone. There were fatal cases related to deferasirox that also resulted in blurred vision. In total, there are 19 cases with these criteria. 18 out of 19 cases are from Americas region, and 1 out of 19 cases is from Western Pacific Region. As shown in Figure 26, for blurred vision, similar to all other reviewed cases, all cases except one, were reported for female patients. There is also a similarity in the age group, if the reports for which patient age was not mentioned are neglected, patients were mostly over 65 years of age.

For fatal headache cases, in total, there are 72 entries. 70 out of 72 cases are from Americas region, and 2 cases were reported from Europe. As shown in Figure 28, surprisingly, for headache, exactly half of the cases were reported for female patients and male patients respectively. Most of the patients are over 45 years old.

512 sepsis cases related to deferasirox, 37 sepsis cases related to deferiprone and 16 sepsis cases related to deferoxamine resulted in death. As per Figure 31, most of the patients were male, which was different than other adverse events that were

investigated throughout our study. It was also seen that there were some fatal sepsis cases for patients under the age of 18, and even babies. Similarly, for most of the cases, age was not indicated.

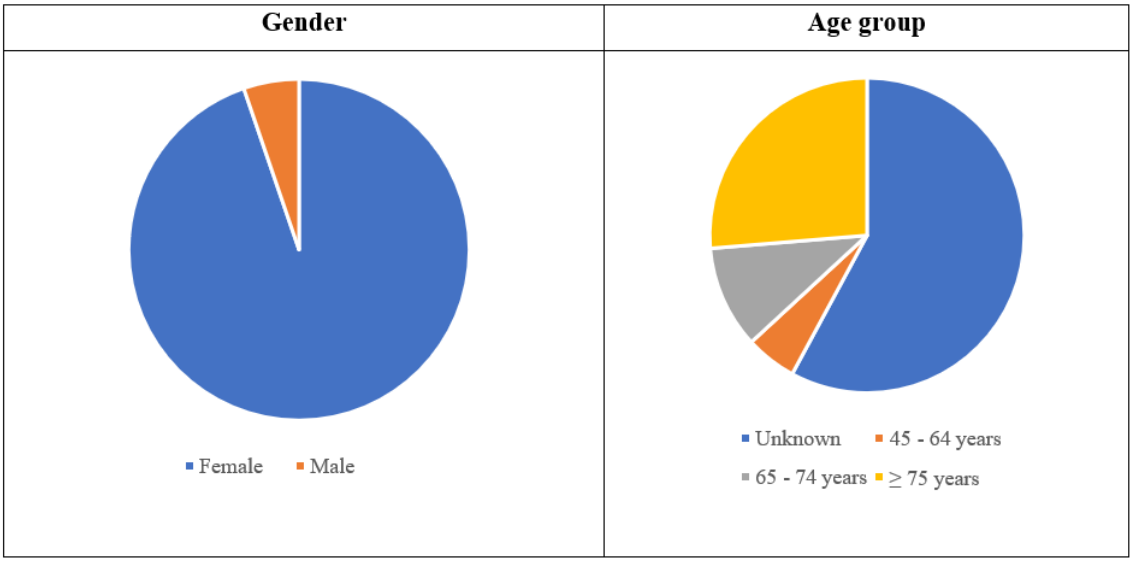

Figure *26.* Fatal cases' details from VigiBase related to blurred vision

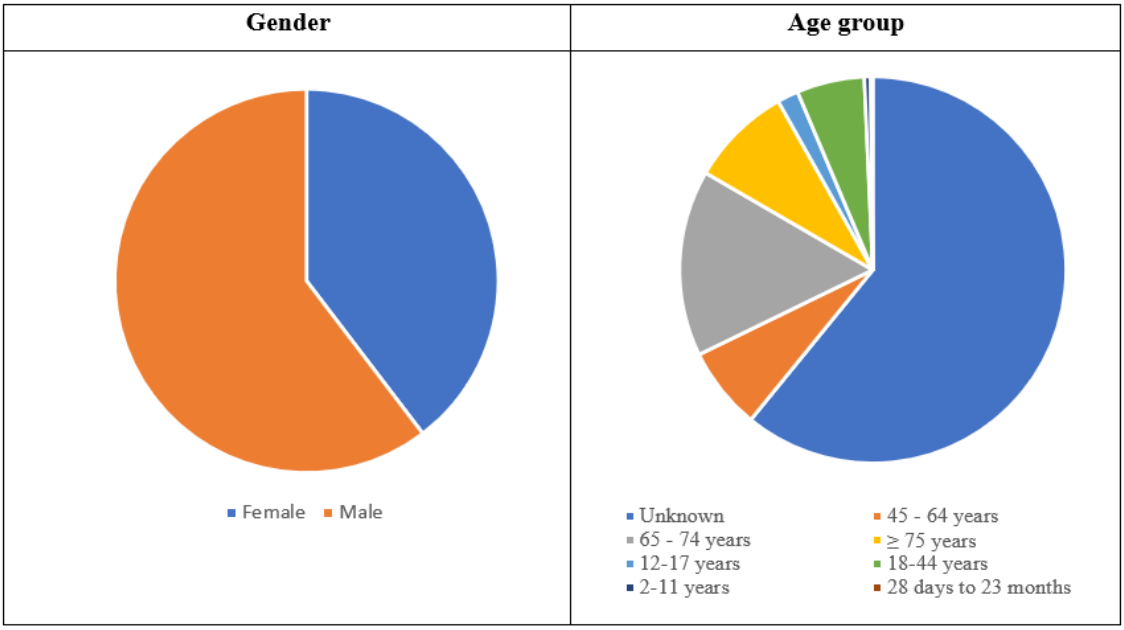

Figure 27. Fatal cases' details from VigiBase related to sepsis

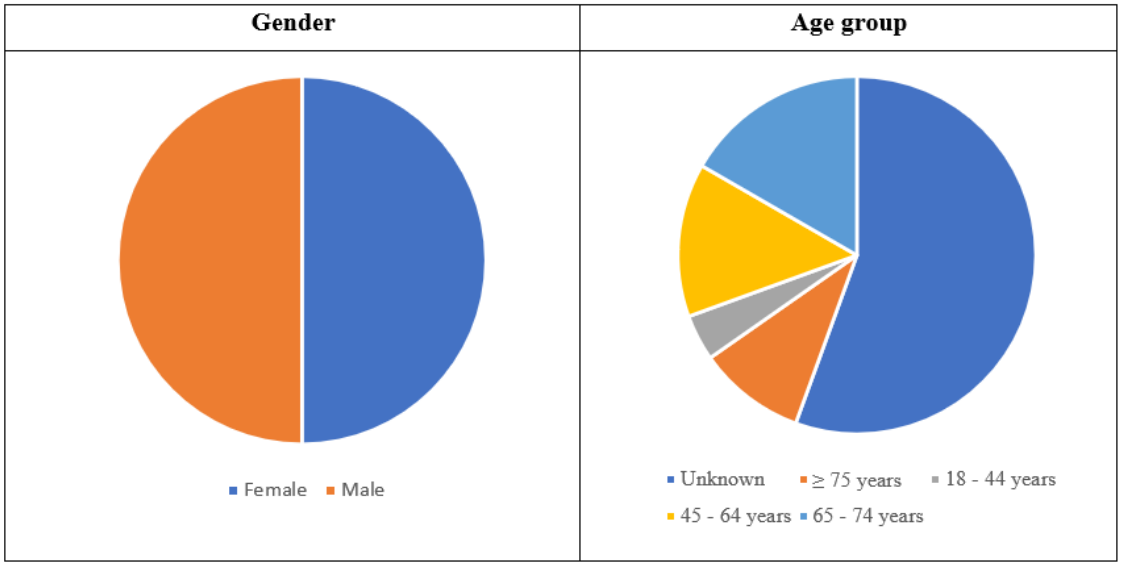

Figure *28*. Fatal cases' details from VigiBase related to headache

According to Table 17, which summarizes indication and dose details for fatal blurred vision and headache cases, it is seen that mostly indication was not provided. For cases where this information was provided, it should be noted that the indication of deferasirox was either Myelodysplastic syndrome or iron overload.

The situation for one of the blurred vision cases that was given deferasirox for Myelodysplastic syndrome is life threatening. This patient has received 5 mg/day of deferasirox orally, which is 100 times lower compared to other patients who were given deferasirox for Myelodysplastic syndrome or iron overload.

Going further and looking at these cases, it should be noted that some other adverse events were reported as well. For the patient that received 500 mg/day and 750 mg/day of deferasirox; disease progression, myalgia, dysarthria, pruritus, abdominal distension, Malignant neoplasm progression, dysphonia, pancytopenia, sepsis, respiratory tract congestion and many other events were reported alongside blurred vision.

For the patient that received 1500 mg/day of deferasirox, dyspepsia, bone pain, constipation, diarrhea, blood sodium decreased, alopecia, liver disorder, cystitis, poor quality sleep, kidney infection, hemorrhoids and many other events were reported alongside blurred vision.

It must be noted that almost all sepsis cases resulted in death. If not, they resulted in life threatening situations. As per Table 17, it is evident that data for deferasirox is more compared to deferiprone and deferoxamine. Some of the most reported indications for irone chelators are iron metabolism disorder, multiple myeloma, transfusion, iron overload and myelodysplastic syndrome.

As per Table 18, some reporters did not want to share the iron chelator doses. An interpretation can be made with the reported information. It must be noted that for most of the cases, patients were receiving higher doses of iron chelators.

On the other hand, according to the data shared by UMC, a patient received 28000 mg of deferasirox, which experienced sepsis but did not die.

For headache cases that resulted in fatal outcomes, one patient was given 500 mg/day and 750 mg/day of deferasirox orally for iron overload and Myelodysplastic syndrome. One patient was given 1500 mg/day of deferasirox orally for Myelodysplastic syndrome. As per the summary of product characteristics of Exjade, maximum amount is 28 mg/kg per day (151). As per our calculation, considering that the patients weigh around 60 to 90 kg, their daily dose doesn't exceed the recommended maximum dose.

Exjade's summary of product characteristics does not provide a guidance for overdoses, whether they be intentional or unintentional (143). However, it does include that early signs of acute overdose can show up as digestive reactions including abdominal pain, diarrhea, nausea and vomiting. It was also noted that an incorrectly given single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment (151).

Table 17. Indications related to fatal headache, sepsis and blurred vision cases

	Fatal cases resulted in headache		Fatal cases resulted in sepsis			Fatal cases resulted in blurred vision
	Deferasirox	Deferoxamine	Deferasirox	Deferiprone	Deferoxamine	Deferasirox
Indications						
Aplasia pure red cell	-	-	-	1	-	-
Acute lymphocytic/myeloid leukaemia	1	-	9	-	-	-
Anaemia	3	-	4	1	-	-
Blood disorder	-	-	1	-	-	-
Blood iron increased	-	-	6	-	-	-
Breast cancer	-	-	1	-	-	-
Chelation therapy	1	-	1	-	-	-
Chronic lymphocytic/myeloid leukaemia	-	-	1	-	-	-
Essential thrombocythaemia	-	-	5	-	-	-
Haemochromatosis	-	-	1	-	-	-
Haemosiderosis	1	-	1	-	-	-
Iron binding capacity total abnormal	-	-	5	2	1	-
Iron metabolism disorder	-		1	1	-	-
Iron overload	11	1	1	-	-	1
Lymphatic disorder	-	-	7	3	-	-
Lymphocytic leukaemia	1	-	46	3	2	-
Multiple myeloma	-	-	4	-	-	-
Myelodysplastic syndrome	11	-	3	-	-	2
Myelofibrosis	1	-	1	-	-	-
Neoplasm	-	-	48	2	2	-
Refractory anaemia	-	-	1	-	-	-
Schistosomiasis	-	-	10	1	-	-
Serum ferritin increased	-	-	1	1	-	-
Sickle cell anaemia	-	-	1	-	-	-
Thalassaemia	-	-	3	-	-	-
Transfusion	-	-	5	1	-	-
Unknown	21	1	2	3	-	-
Waldenstrom's macroglobulinaemia	-	-	3	-	-	-

Table 18. Dose details for fatal headache, sepsis and blurred vision cases

	Fatal cases resulted in headache		Fatal cases resulted in sepsis			Fatal cases resulted in blurred vision
	Deferasirox	Deferoxamine	Deferasirox	Deferiprone	Deferoxamine	Deferasirox
Chelator dose (in mg)						
Unknown	11	2	21	4	7	1
Irregular doses (1, 4, 5, 7, up to 80)	3	-	6	5	4	-
120	-	-	-	1	-	-
125	-	-	-	2	-	-
200	-	-	-	1	-	-
250	1	-	4	-	-	-
375	1	-	1	-	-	-
500	8	-	5	-	-	-
600	-	-	1	-	-	-
625	-	-	16	-	-	-
720	-	-	1	-	-	-
750	2	-	1	-	-	1
1000	9	-	1	-	-	1
1080	-	-	4	-	-	-
1250	4	-	25	-	-	1
1500	8	-	2	-	-	1
1625	-	-	9	-	-	-
1750	-	-	29	-	-	-
2000	5	-	1	-	-	-
2125	1	-	2	-	-	-
>2150	5	-	14	-	1	-

3.2.1.3.Adverse Events Listed as “very rare”

Regarding very rare adverse events related to iron chelators as per local labeling in Turkey, a further analysis was necessary. The cases with reporting odds ratio greater than 1, hence which can be considered associated with higher odds, were examined. For this reason, disproportionality results by their reporting odds ratio and confidence intervals were filtered. For deferiprone and deferasirox, no adverse event was listed as very rare, but for deferoxamine, the adverse events in Table 19 were listed as very rare. According to that, a strong connection between deferoxamine and encephalopathy, acute respiratory distress, diarrhea, leukopenia, lung infiltration, thrombocytopenia and Yersinia gastroenteritis, can be assumed.

Table 19. Very rare adverse events of deferoxamine with corresponding events in VigiBase

Very rare adverse events and corresponding names in Vigibase for deferoxamine	ROR	Confidence interval	ROR >1?
Acceleration or exacerbation of aluminum-related dialysis encephalopathy (As encephalopathy)	5.48	2.05-14.62	Yes
Acute respiratory distress	5.04	1.26-20.17	Yes
Anaphylactic reaction	0.78	0.35-1.74	-
Anaphylactic shock	0.42	0.11-1.7	-
Angioneurotic edema	-	-	-
Common rash (As rash)	0.75	0.56-1.01	-
Diarrhea	1.63	1.27-2.09	Yes
Dizziness	0.37	0.24-0.56	-
Leukopenia	1.98	0.99-3.97	Yes
Lung infiltration	6.55	1.64-26.24	Yes
Paresthesia	0.29	0.11-0.76	-
Thrombocytopenia	2.71	1.7-4.31	Yes
Yersinia gastroenteritis (As yersinia infection)	388.88	53.59-2821.95	Yes

3.2.1.4.Adverse Events Listed as “unknown”

Regarding unknown adverse events related to iron chelators as per local labeling, a further analysis was necessary. This information can be useful for changing the frequencies of existing adverse reactions. This information can also lead to a new signal, as new safety data will be discovered. The cases with ROR greater than 1,

hence which can be considered associated with higher odds were examined. For this reason, disproportionality results by their ROR and confidence intervals were filtered.

According to Table 20, a strong connection between deferasirox and erythema multiforme, GI perforation, liver failure, metabolic acidosis, nephrolithiasis, neutropenia, pancytopenia, renal tubular necrosis and thrombocytopenia can be assumed. There is still no sufficient information regarding acute pancreatitis, acute renal failure, hypersensitive vasculitis and worsening of anemia.

Table 20. Unknown adverse events of deferasirox with corresponding events in VigiBase

Adverse events with unknown frequencies and corresponding names in Vigibase for deferasirox	ROR	Confidence interval	ROR >1?
Acute pancreatitis	-	-	-
Acute renal failure	-	-	-
Alopecia	0.39	0.31-0.5	-
Anaphylactic reaction	0.11	0.07-0.19	-
Angioedema	0.25	0.17-0.36	-
Erythema multiforme	1.16	0.72-1.87	Yes
Gastrointestinal perforation	2.32	0.96-5.58	Yes
Hypersensitive vasculitis	-	-	-
Liver failure (As hepatic failure)	10.46	8.77-12.48	Yes
Metabolic acidosis	9.89	8.04-12.16	Yes
Nephrolithiasis	5.23	4.34-6.29	Yes
Neutropenia	2.03	1.78-2.31	Yes
Pancytopenia	5.33	4.56-6.25	Yes
Pruritus	0.32	0.28-0.35	-
Renal tubular necrosis	4.43	2.71-7.24	Yes
Stevens-Johnson Syndrome	0.68	0.42-1.09	-
Thrombocytopenia	2.77	2.47-3.11	Yes
Toxic epidermal necrolysis (TEN)	0.21	0.05-0.83	-
Tubulointerstitial nephritis	0.77	0.39-1.55	-
Urticaria	0.30	0.25-0.35	-
Worsening of anemia	-	-	-

Regarding adverse events with unknown frequencies and their corresponding names in VigiBase for deferiprone, given the fact that the list was longer, the data for deferiprone was split into 2, for adverse events that have corresponding reports, and for adverse events that don’t have corresponding reports in VigiBase.

Table 21. Unknown adverse events of deferiprone with corresponding events in VigiBase

Adverse events with unknown frequencies and corresponding names in Vigibase for deferiprone	ROR	Confidence interval	ROR >1?
Acute respiratory distress syndrome	4.11	1.02-16.46	Yes
Anaphylactic shock	0.17	0.02-1.23	-
Anemia	0.47	0.2-1.13	-
Atrial fibrillation	1.20	0.5-2.88	Yes
Blood increase in bilirubin	2.47	0.8-7.66	Yes
Cerebellar syndrome	13.50	1.9-95.95	Yes
Cerebral hemorrhage	1.34	0.43-4.17	Yes
Chills	0.47	0.31-0.72	-
Dehydration	1.86	0.1-3.46	Yes
Depression	0.18	0.05-0.73	-
Diplopia	1.32	0.33-5.29	Yes
Epistaxis	0.50	0.16-1.54	-
Furuncle	2.30	0.32-16.32	Yes
Gait disturbance	0.39	0.15-1.04	-
Gastric ulcer	1.26	0.18-8.92	Yes
Glycosuria	29.67	7.4-118.89	Yes
Heart failure (As cardiac failure)	3.51	1.88-6.53	Yes
Hepatomegaly	9.18	2.96-28.5	Yes
Hyperhidrosis	0.18	0.05-0.55	-
Hypersensitivity	0.28	0.11-0.75	-
Hypotension	0.88	0.49-1.59	-
Jaundice	1.29	0.32-5.16	Yes
Pancreatitis	0.43	0.06-3.07	-
Pancytopenia	2.24	0.93-5.37	Yes
Periorbital edema	1.16	0.44-3.1	Yes
Pharyngitis	6.11	2.74-13.62	Yes
Pneumonia	1.58	1.04-2.41	Yes
Pruritus	0.24	0.15-0.38	-
Pulmonary embolism	0.18	0.03-1.28	-
Pyramidal pathway syndrome (As pyramidal tract syndrome)	67.92	9.52-484.65	Yes
Rash	0.30	0.2-0.45	-
Retinal toxicity (As retinal degeneration)	25.71	3.61-182.93	Yes
Sepsis	5.61	3.68-8.55	Yes
Sickle Cell Disease	148.34	36.81-597.81	Yes
Somnolence	0.73	0.42-1.26	-
Urticaria	0.47	0.3-0.75	-

As per Table 21, a strong connection between deferiprone and acute respiratory distress syndrome, atrial fibrillation, blood increase in bilirubin, cerebellar syndrome, cerebral hemorrhage, dehydration, diplopia, furuncle, gastric ulcer, glycosuria, heart failure, hepatomegaly, jaundice, pancytopenia, periorbital edema, pharyngitis,

pneumonia, pyramidal pathway syndrome, retinal toxicity, sepsis, sickle cell disease can be assumed. Adverse events listed in Table 22 had no corresponding reports in VigiBase, hence a connection cannot be assumed. In the future, as the case volume increases, more information can be obtained.

Table 22. Unknown adverse events of deferiprone, that were not reported to VigiBase

Adverse events with unknown frequencies with no reports in Vigibase for deferiprone
Anaphylactic shock
Anemia
Bruxism, trismus
Chills
Chondropathy
Convulsions
Cryptococcal cutaneous infection
Depression
Enterocolitis, Enteroviral encephalitis
Epistaxis
Gait disturbance
Hemoglobinuria
Hemoptysis
Henoch-Schönlein purpura
Hyperhidrosis
Hypersensitivity, photosensitivity
Hypertension
Hypospadia
Hypotension
Impaired psychomotor skills
Increase in blood creatine phosphokinase
Increased intracranial pressure
Infectious hepatitis
Metabolic acidosis
Multi-organ failure
Myositis
Obsessive compulsive disorder
Pancreatitis
Papilledema
Parotid gland enlargement
Peripheral edema
Pruritus
Pulmonary embolism
Pustular rash, rash, urticaria
Rectal bleeding
Somnolence
Subcutaneous abscess
Thrombocytosis

As per Table 23, a strong connection between deferoxamine and adverse events blood creatinine elevation and renal tubular disorder can be assumed. For other adverse events like acute renal failure, convulsions and muscle spasms, more safety information is needed.

Table 23. Unknown adverse events of deferoxamine with corresponding events in VigiBase

Adverse events with unknown frequencies and corresponding names in Vigibase for deferoxamine	ROR	Confidence interval	ROR >1?
Acute renal failure	-	-	-
Blood creatinine elevation (As blood creatinine increased)	6.18	3.77-10.12	Yes
Convulsions	-	-	-
Muscle spasms	0.80	0.4-1.61	-
Renal tubular disorder	49.45	18.51-132.14	Yes

3.2.1.5. Unlisted Adverse Events from VigiBase

Unlisted adverse events for deferasirox, deferiprone and deferoxamine with reporting odds ratios greater than 1, were selected. As per Table 24, many adverse events can be considered as new information that was not previously included in the local labels. As the results fall between confidence interval, the result is strong enough to warrant further investigation. Upon further investigations, these adverse events may become listed in the future, if there is enough information. They can then be further evaluated with solicited resources such as post marketing studies, patient support programs, additional monitoring, literature articles or by raising the reporting awareness.

Table 24. Adverse events from VigiBase that are not listed in Local Labels

Iron Chelator	Adverse event	ROR	PRR
Deferasirox	Abortion	1.29	1.29
Deferasirox	Atonic seizures	1.93	1.93
Deferasirox	Breast calcifications	2.36	2.36
Deferasirox	Cardiac tamponade	1.57	1.57
Deferasirox	Cellulitis	1.71	1.71
Deferasirox	Compartment syndrome	1.91	1.91
Deferasirox	Confusional state	1.15	1.15
Deferasirox	Coronary artery disease	1.74	1.74
Deferasirox	Dermatosis	1.86	1.86
Deferasirox	Folliculitis	1.85	1.85
Deferasirox	Gingival bleeding	1.26	1.25
Deferasirox	Gingivitis	1.61	1.61
Deferasirox	Incisional hernia	1.52	1.52
Deferasirox	Intestinal ischaemia	2.19	2.19
Deferasirox	Joint noise	1.47	1.46
Deferasirox	Learning disorder	1.22	1.22
Deferasirox	Mastoiditis	1.93	1.93
Deferasirox	Meningitis cryptococcal	1.93	1.93
Deferasirox	Mitral valve stenosis	1.38	1.38
Deferasirox	Nocardiosis	1.22	1.22
Deferasirox	Obstructive airways disorder	1.37	1.37
Deferasirox	Ovarian cyst	1.08	1.09
Deferasirox	Reflux gastritis	2.46	2.46
Deferasirox	Sinus node dysfunction	2.06	2.06
Deferasirox	Spider vein	1.73	1.73
Deferasirox	Tonsillitis	2.35	2.35
Deferasirox	Varicella	1.20	1.21
Deferasirox	Venous occlusion	1.46	1.46
Deferiprone	Anal incontinence	1.69	1.69
Deferiprone	Lower GI haemorrhage	2.14	2.14
Deferoxamine	Cardiac failure congestive	1.57	1.57
Deferoxamine	Foot fracture	1.58	1.58
Deferoxamine	Musculoskeletal chest pain	2.53	2.52

3.3. Data from SIDER

Upon reviewing the SIDER data, it was not possible to conduct a disproportionality analysis, as the frequency of the adverse events were not provided. So, it was only possible to look for these adverse events to see if they were reported previously and hence listed in the local labels. Cases that were entered as “post marketing” were filtered, as cases with frequency labels were coming from product

labels. This filtering showed that there was no unlisted adverse event related to deferoxamine from SIDER. However, there were some unlisted adverse events related to deferasirox and deferiprone, To understand their association, their corresponding adverse events from VigiBase were checked (124).

As per Table 25, a strong association between deferasirox and iron overload, multi organ failure and urinary tract disorder as adverse events can be assumed. Also, an association between deferiprone and furuncle and malnutrition as adverse events can be assumed.

Table 25. Unlisted cases from SIDER with disproportionality results from VigiBase data

Iron Chelator	Unlisted adverse events from SIDER	ROR from Vigibase	PRR from Vigibase	ROR >1?
Deferasirox	Iron overload	263.54	262.07	Yes
	Leukocytoclastic vasculitis	-	-	-
	Multi-organ failure (As multi organ dysfunction syndrome)	5.97	5.95	Yes
	Urethral disorder	-	-	-
	Urinary tract disorder	2.47	2.47	Yes
Deferiprone	Angiopathy	-	-	-
	Body temperature increased	0.46	0.46	-
	Chills	0.47	0.48	-
	Convulsion	-	-	-
	Epistaxis	0.49	0.49	-
	Furuncle	2.29	2.29	Yes
	Gait disturbance	0.38	0.39	-
	Malnutrition	3.35	3.35	Yes
	Nephropathy	-	-	-
	Subcutaneous abscess	-	-	-

3.4. Signals

As per our analysis with the published data by FDA and EMA on their respective websites, there were no confirmed signals related to iron chelators since 2012.

3.5. Disproportionality Analysis

3.5.1. Disproportionality Analysis Using Data from FAERS Database

The possibility and probability of a specific event by disproportionality analysis can be investigated, using the below equation:

$$\underline{\textit{Reporting Odds Ratio (ROR)} = [a \div b] / [c \div (d)]}$$

3.5.1.1. Deferasirox Associated Blurred vision, Headache and Sepsis from FAERS

As per Table 26, among 107627 reports of blurred vision, 130 of them were reported by consumers taking only Deferasirox, among 557233 reports of headache, 340 of them were reported by consumers taking only Deferasirox and among 68752 reports of sepsis, 59 of them were reported by consumers taking only Deferasirox.

Table 26. Deferasirox associated case numbers from FAERS

	Blurred vision	Headache	Sepsis	All adverse events
Deferasirox	130	340	59	19699
All products	107627	557233	68752	22100000

Table 27 summarizes the calculation of ROR for deferasirox associated blurred vision, headache and sepsis cases and expectedness of these events based on the result of this calculation.

Table 27. Results for Deferasirox related blurred vision, headache and sepsis

	ROR	Confidence interval	Result
Deferasirox related blurred vision	1.35	1.26-1.59	As ROR is greater than 1, it should be noted that exposure to deferasirox is associated with higher odds of impaired or blurred vision as an adverse reaction. Since the 95% CI is between 1.26 to 1.59, the ROR 1.35 of blurred vision reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.
Deferasirox related headache	0.06	0.05-0.06	As ROR is smaller than 1, it should be noted that exposure to deferasirox is associated with lower odds of headache as an adverse reaction. Since the 95% CI is between 0.054 to 0.067, the ROR 0.06 of headache reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.
Deferasirox related sepsis	0.04	-0.20-0.30	As ROR is smaller than 1, it should be noted that exposure to deferasirox is associated with lower odds of sepsis as an adverse reaction. Since the 95% CI is between -0.20 to 0.30, the ROR 0.04 of sepsis reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.

3.5.1.2. Deferiprone Associated Blurred vision, Headache and Sepsis from FAERS

As per Table 28, among 107627 reports of blurred vision, 3 of them were reported by consumers taking only Deferiprone, among 557233 reports of headache, 45 of them were reported by consumers taking only Deferiprone and among 68752 reports of sepsis, 3 of them were reported by consumers taking only Deferiprone.

Table 28. Deferiprone associated case numbers from FAERS

	Blurred vision	Headache	Sepsis	All adverse events
Deferiprone	3	45	3	809
All products	107627	557233	68752	22100000

Table 29 summarizes the calculation of ROR for deferiprone associated blurred vision, headache and sepsis cases and expectedness of these events based on the result of this calculation.

Table 29. Results for Deferiprone related blurred vision, headache and sepsis

	ROR	Confidence interval	Result
Deferiprone related blurred vision	0.76	0.23-2.72	As ROR is smaller than 1, it should be noted that exposure to deferiprone is associated with lower odds of blurred vision as an adverse reaction. Since the 95% CI is between 2.72 to 0.23, the ROR 0.76 of blurred vision reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.
Deferiprone related headache	2.2	1.50-2.63	As ROR is greater than 1, it should be noted that exposure to deferiprone is associated with higher odds of headache as an adverse reaction. Since the 95% CI is between 1.50 to 2.63, the ROR 2.2 of headache reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.
Deferiprone related sepsis	135.10	132.88-135.12	As ROR is greater than 1, it should be noted that exposure to deferiprone is associated with higher odds of sepsis as an adverse reaction. Since the 95% CI is between 132.88 to 135.12, the ROR 135.10 of sepsis reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.

3.5.1.3. Deferoxamine Associated Blurred vision, Headache and Sepsis from FAERS

As per Table 30, among 107627 reports of blurred vision, 23 of them were reported by consumers taking only Deferoxamine, among 557233 reports of headache, 30 of them were reported by consumers taking only Deferoxamine and among 68752 reports of sepsis, 3 of them were reported by consumers taking only Deferoxamine.

Table 30. Deferoxamine associated case numbers from FAERS

	Blurred vision	Headache	Sepsis	All adverse events
Deferoxamine	23	30	3	1668
All products	107627	557233	68752	22100000

Table 31 summarizes the calculation of ROR for deferiprone associated blurred vision, headache and sepsis cases and expectedness of these events based on the result of this calculation.

Table 31. Results for Deferoxamine related blurred vision, headache and sepsis

	ROR	Confidence interval	Result
Deferoxamine related blurred vision	2.83	2.01-4.27	As ROR is greater than 1, it should be noted that exposure to deferoxamine is associated with higher odds of an impaired or blurred vision as an adverse reaction. Since the 95% CI is between 2.015 to 4.27, the ROR 2.83 of blurred vision reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.
Deferoxamine related headache	0.71	0.47-1.01	As ROR is smaller than 1, it should be noted that exposure to deferoxamine is associated with lower odds of headache as an adverse. Since the 95% CI is between 0.47 to 1.01, the ROR 0.71 of headache reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.
Deferoxamine related sepsis	0.58	-0.56-1.67	As ROR is smaller than 1, it should be noted that exposure to deferoxamine is associated with lower odds of sepsis as an adverse. Since the 95% CI is between -0.56 to 1.67, the ROR 0.58 of sepsis reaches statistical significance. This means that the true value of odds ratio is contained in this interval, by 95% confidence level.

3.5.2. Disproportionality Analysis Using Data from VigiBase

Odds ratio and Proportional reporting ratio results for blurred vision cases related to iron chelators were similar. According to Table 32, while deferasirox and deferiprone cannot be associated with blurred vision, deferoxamine can be.

Table 32. Disproportionality analysis results for iron chelators and blurred vision

	# of events	Total events	Odds Ratio	PRR
Deferasirox	108	58629	0.89	0.89
Deferiprone	3	3525	0.33	0.33
Deferoxamine	17	4005	2.29	2.28

Odds ratio and Proportional reporting ratio results for headache cases related to iron chelators were similar. According to Table 33, deferasirox, deferiprone and deferoxamine cannot be associated with blurred vision.

Table 33. Disproportionality analysis results for iron chelators and headache

	# of events	Total events	Odds Ratio	PRR
Deferasirox	340	58629	0.24	0.25
Deferiprone	45	3525	0.43	0.44
Deferoxamine	30	4005	0.35	0.36

Odds ratio and Proportional reporting ratio results for sepsis cases related to iron chelators were similar. According to Table 34, deferasirox, deferiprone and deferoxamine can all be associated with sepsis.

Table 34. Disproportionality analysis results for iron chelators and sepsis

	# of events	Total events	Odds Ratio	PRR
Deferasirox	319	58629	6.20	6.13
Deferiprone	22	3525	5.61	5.55
Deferoxamine	16	4005	4.99	4.94

3.5.3. Comparison of Disproportionality Analysis Results from VigiBase and FAERS

The disproportionality results for headache, sepsis and blurred vision using 2 different databases were listed and compared in Table 35. According to this data, there is an inconsistency. While the same results for both analysis were expected, it is seen that there are differences between databases related to deferasirox and blurred vision association, deferiprone and headache association as well as deferasirox and deferoxamine sepsis association. On the other hand, same results were obtained regarding deferoxamine being associated to blurred vision, deferiprone being associated to sepsis and deferiprone not being associated to blurred vision, deferasirox not being associated to headache and deferoxamine not being associated to headache.

Table 35. Comparison of ROR results from VigiBase and FAERS

	FAERS			Vigibase		
	Blurred vision	Sepsis	Headache	Blurred vision	Sepsis	Headache
Deferasirox	ROR>1 (130 cases)	ROR<1 (59 cases)	ROR<1 (340 cases)	ROR<1 (108 cases)	ROR>1 (319 cases)	ROR<1 (340 cases)
Deferiprone	ROR<1 (3 cases)	ROR>1 (3 cases)	ROR>1 (45 cases)	ROR<1 (3 cases)	ROR>1 (22 cases)	ROR<1 (45 cases)
Deferoxamine	ROR>1 (23 cases)	ROR<1 (3 cases)	ROR<1 (30 cases)	ROR>1 (17 cases)	ROR>1 (16 cases)	ROR<1 (30 cases)

4. DISCUSSION

The importance of iron for human body is undeniable. In parallel with this, iron supplements are often used. Additionally, some countries, including Turkey, have genetic predisposition for iron deficiencies and associated complications. People from these countries may suffer from decreased production of hemoglobin and a microcytic, hypochromic anemia. Hence supplementary iron is widely used for the prevention and treatment of iron deficiency anemia, as well as for its immune-enhancing, anticarcinogenic and cognition-enhancing activities (10,58).

With this common practice, in some situations, iron toxicities, unintentional ingestions, overdoses are inevitable. That is moreover why iron chelation therapy and treating iron toxicity are just as important as iron deficiency. The primary intention of iron chelation therapy is to prevent the accumulation of iron reaching harmful levels by binding to free iron from blood transfusion, with iron excreted by iron chelation (152). Therefore, iron chelators' vital importance should be emphasized. As long as iron supplementation is needed, the iron levels in blood must be checked to prevent high levels of iron. Under these circumstances, the importance of iron chelators should not be overlooked.

When it comes to the possible toxic manifestations of iron chelators, published information is very limited, as usually, after an iron chelator treatment and an overdose, given the situation and its urgency, chelators are usually given in an immediate manner. The focus is more so on reversing iron's toxic effects and the side effect of the antidote is usually neglected. Given the fact that spontaneous reporting for iron chelators is reasonably low, information from different resources to fully understand the safety profile were gathered. However, spontaneous adverse events and pharmacovigilance databases were still strong sources for our investigation. Our goal was to reach as much accurate data as possible, from all around the world. So, in our thesis, safety data that was collected from different sources including but not limited to literature, Pharmacovigilance database entries, local labels, and signals, were gathered and reviewed. Our aim was to combine the data and examine it further.

As the mechanism of actions are different for each iron chelating molecule (65,67,68), their toxicities are through different pathways as well. It is necessary to understand that these differences are completely understandable since these agents have different modes of action.

As an example to this, in many studies, for iron's cardiac overload and need for removal, deferasirox monotherapy was shown to be effective as it preserved systolic function with clearance rates similar to deferoxamine (153,154). Synergistic effect between deferiprone and deferoxamine was studied and proven for combination therapy, as there was evident improvement in cardiac and hepatic iron clearance. The option to combine deferiprone and deferasirox is also being investigated. At the time of this study, there were relatively limited data on the utility of this combination (154).

The oldest iron chelator is deferoxamine, which is not absorbed effectively by the GI tract (68,89). Given the fact that this product has also a short plasma half-life, it is generally given subcutaneously. This route of administration introduces local infusion site reactions such as erythema, swelling, and itching, and some other adverse reactions due to use of deferoxamine may as well be ophthalmologic and audiologic complications, renal toxicity and for high doses, adult respiratory distress syndrome (155–158). Moreover, deferiprone is rapidly absorbed from the upper GI tract and is administered three times a day orally, because of its short half-life. This iron chelate is excreted renally (67). Nausea, vomiting, abdominal pain and increase of liver enzymes are common adverse reactions. Agranulocytosis and neutropenia are more serious side effects that might occur, and this situation may require either temporary or permanent cessation of therapy (148). Lastly, deferasirox is rapidly absorbed from the GI tract and, due to its longer half-life, administration once per day is possible (2,56,72). The main route of excretion is through defecation. Unsurprisingly, adverse reactions may include GI disturbances including nausea, vomiting, diarrhea, and abdominal pain, as well as diffuse maculopapular skin rash, and increased alanine aminotransferase and serum creatinine. More severe adverse reactions may include Fanconi syndrome and auditory and ocular toxicities (154).

Some studies have showed that early and intensive deferoxamine chelation may result in many different consequences such as impairment in linear growth, severe bone lesions (159), ocular toxicity and neurosensory hearing loss (157,160).

Boston Children's Hospital lists impaired or blurred vision, rash or hives, itching, vomiting, diarrhea, stomach or leg cramps, rapid heartbeat, hypotension and dizziness as common side effects of iron chelators (161).

Literature resources are abundant and fruitful, as healthcare professionals are eager to share various and sometimes challenging experiences with other healthcare professionals. Literature articles from Mediterranean countries like Turkey were great resources to comprehend patient profile and the frequency of adverse events.

The benefit of the administration of a chelating agent usually outweighs the risk (71). However, this does not mean that these adverse reactions cannot be predicted and prevented. Many articles, safety studies, clinical trials and product labels provide valuable information to do so (70,72,73,152,154,155). During many years of these products being available to patients, expecting and potentially preventing new adverse reactions were also studied. During our review of the safety profiles of the mentioned products, it was identified that following the warnings and precautions play a huge role in the prevention of adverse reactions. Many precautions were suggested based on known adverse events and population groups with different diseases (143,148,149).

The importance of pharmacovigilance and how it plays a big role in our daily lives, should be emphasized here. Pharmacovigilance is a science with increasing awareness and its activities are to improve patient care and safety in relation to the use of medicines; and to support public health programs by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines (9). Collection of adverse events, meaning any untoward medical occurrence associated with the use of a drug in humans, is contributing greatly to safety profiles of products (93). Pharmacovigilance databases may not be the first step when researching treatments, but this might change and the importance of databases will be revealed.

While collecting the data and comparing the countries of origin, it was realized that duplicated information can be included. Although national authorities already perform duplication search to minimize same case entries, as an example, mining data from

Eudravigilance and any other European database could cause many duplicated cases. As all relevant case information are not shared with public, it was not possible to do a duplication search, cross databases. To avoid this potential duplication, and to include as many cases as possible, mining data from FAERS for cases from Americas region, as well as WHO's VigiBase for cases from all over the world was preferred.

Our goal was to reach as much accurate data as possible, from all around the world. It is known that adverse event reporting databases do not include cases from social media, meaning there were currently no effective system in place for adverse event recognition in order to identify and transfer adverse events or safety reports (162).

As is evident from our research, not all authorities are disclosing their archived cases and databases. On another note, the shared information from these databases differed, as some databases were only including relevant information. It was up to the authority to include details that might be considered private data such as the country of reporting. In spite of that, there would also be a disadvantage to only review reports from adverse event databases. While databases are great resources, and they differ from the findings of literature, they may lack homogeneity. It is important to note that these reports may or may not include a healthcare professional opinion, as everyone can report an adverse event, regardless of their profession. This also brings to mind the selectivity in reporting, which is not the case in the literature data. These two points are the strong points of literature data that reports from databases are lacking.

Evidently, the data included in our study from VigiBase is reviewed and evaluated by the Uppsala Monitoring Center (129), but this evaluation is not yet in place for some National Health Authorities. Nevertheless, this confirms how important both data sources are and that it makes sense to combine the data from various resources.

It was also identified that safety monitoring programs and risk management plans (112,113,118) play a huge role: it was noted for deferasirox, safety monitoring programs were suggested (112). This can be helpful to prevent product usage mistakes related to route of administration as well as dosage. Currently in EU, both deferasirox and deferiprone have risk management plans (120,122). It must also be noted that all products containing Deferasirox are under additional monitoring, according to the list published by Turkish Ministry of Health, effective as of 18 May 2022. Deferasirox was

added to this list of products under additional monitoring on 15 July 2014 (163). This means that the Marketing Authorization Holder needs to make additional efforts to enhance reporting of suspected adverse drug reactions. The main goals are to collect information as early as possible to further inform the safe and effective use of them as well as their benefit-risk profile when used in everyday medical practice (112). This principle is further explained with examples in section named “Additional Monitoring Programs”.

Apart from the aforementioned methods and the measures taken by local and international health authorities, patients and health care professionals play a very important role in these processes. It is critical that patients know the product they will use, use it correctly, and hence increase patient compliance. In this way, it may be possible to increase the effectiveness of this drug and minimize its side effects. Even though many precautions are taken and some adverse events are predicted and hence prevented, some serious adverse events still cannot be eliminated. Therefore, it was important to perform a disproportionality analysis, especially for unlisted cases, to discover unknown parts about a product’s safety profile.

While reviewing reports from FAERS, it was noted that over 20 million reported cases are stored in FDA’s reporting database FAERS (7), but only 2229 cases are related to Deferoxamine mesylate. This low percentage (~%0,011) and the lack of reporting for other iron chelators clearly demonstrate that awareness and vigilance is low for antidotes even globally and that the data can be further evaluated. This leads us to think that commonly known adverse reactions are not necessarily reported. This might be due to reporters or consumers thinking that reporting known reactions do not have an impact on the safety profile, which is not the reality. Fact remains that reporting an adverse reaction that is already recognized can alter the frequency of occurrence of such adverse events.

As per the results from FAERS, most cases were reported by patients who were exposed to Deferasirox. Since the sales data in Americas region was not available, no comment can be made on the peaks during the years, but the marketing dates of the products did have an impact on these peaks and waves. A product being easier to use also plays an important role in these peaks and waves. As an example to this,

deferasirox is the only available iron chelator for oral usage in the US. Deferoxamine is available if given subcutaneously (161). Deferiprone on the other hand, was approved by the FDA in 2011. This could explain the number of cases, as it is relatively new compared to Deferoxamine, which was approved in 1968 (164) and Deferasirox, which was approved in 2005 (165). It should be noted that a raise in reporting of Deferasirox and Deferiprone cases after 2010 was seen, compared to before 2010. For deferasirox, although there was a decrease in reporting in 2012 and, there was a peak in 2015. Deferiprone had two peaks in 2015 and 2021. Second peak in 2021 can be related to deferiprone's first generic product being marketed this year (67).

It was noted that there is no significant difference to compare the reports based on patients' sex. Overall, more male patients were reported, which was unexpected, considering the fact that iron deficiency is more likely to occur in women. The first reason that might be too obvious is male patients being more likely to report. However, at the time of our study, FAERS contains more female cases (over 13 million) than male cases (almost 9 million). Upon further investigation of region-specific adverse events or differences in metabolisms, common prescription practices, and cross-checking other databases, reasons may be identified. Few studies showed that male patients suffered more from certain diseases such as thalassemia major (166), which might be a contributing factor to this unexpected result. There are also studies that suggest that male patients have higher incidence rate of MDS compared to female patients, as well as a significant survival disadvantage (167).

It was noted that patient ages range between 0 and 100, but mostly patients are young or middle aged, and the age mean is overall 35. It was also noted that almost all the reported cases contained serious adverse events, which leads us to think that patient rarely consider reporting, if the experienced side effect is not serious.

While reviewing reports from VigiBase, an increase in reported events during years 2010, 2011 and 2012 were identified. However, since the global sales data was not available to us, a comment can be made according to the release dates of the products. A product being easier to use plays an important role in these peaks and waves. As deferasirox use was more common and easier for patients, and if deferasirox had more active patients compared to deferoxamine and deferiprone, it makes sense to

see a higher number of events. Number of deferoxamine reports were stabile for both US and worldwide data. As deferoxamine was first licensed in US in 1968, a higher number of reports would be expected. This low number of reports might be related to deferoxamine not having any generics in Europe (68).

As license approval dates list by Turkish Ministry of Health (168) was also reviewed. It was identified that the first iron chelator that was licensed in Turkey was deferoxamine in 1984 and for a very long time there was no oral iron chelator available. This was followed by deferasirox when it was licensed in 2007. In 2010, deferiprone was licensed for the first time. Deferasirox's first generic was approved in 2015 and it currently has many generics in Turkish market. Deferoxamine has no generics at the time of this study, and deferiprone's first generic was approved in September 2022 (168). An increase from Turkish adverse event reports for the upcoming years can be expected. However, a solid estimation cannot be made, as Turkish data is included in European data in VigiBase, and European area includes many countries. Obtaining sales data and adverse event reports from Turkey would make it possible to assess whether deferoxamine has received more adverse events due to the long period of time it has been on the market, compared to other iron chelators. The fact that the route of administration of deferoxamine is different than other iron chelators also makes the situation interesting, because IV administration is not suitable for patients to administer at home (65,67,68).

Since the sales data of the products were not available, past events that could affect the sales data such as product withdrawal or distribution of a letter to the healthcare professional were investigated, in order to be able to comment. According to this research, no iron chelator was withdrawn in America, Europe or Turkey (108,169,170). However, some Dear Healthcare Professionals Letters related to these products have been distributed. These letters may create fluctuations in sales.

In 2006, for deferiprone, a Dear Healthcare Professional Letter was distributed to communicate risks to prescribers in the European Community (171).

In 2009, a Dear Healthcare Professional Letter in Canada related to deferasirox and its use in patients with Myelodysplastic Syndrome and in elderly patients regarding renal events and gastrointestinal hemorrhage was distributed (172). Following that, in

Turkey, a Dear Healthcare Professional Letter was distributed related to deferasirox's potential effects of hepatic failure, renal failure, renal tubulopathy, gastrointestinal bleeding an ulceration, in 2009 (117).

In 2011, the black box warning shown in Figure 7, related to agranulocytosis and neutropenia for deferasirox was added, which might have an impact on some physician's prescriptions (115). A slight decrease in sales due to this new warning could explain the first small then big decrease in the number of reports in 2012 and 2013 for deferasirox. After examining the cases from VigiBase, it was identified that there was no significant difference for agranulocytosis reports during 2012 and 2013, however, for neutropenia, there was. While 30 cases were reported for neutropenia in 2012, there were only 8 cases in 2013. This might be due to the success of the black box warning and prescribers being more careful towards patients with this risk. Surprisingly, there was another increase in 2014, where 52 cases related to neutropenia were reported. After examining the case reports from FAERS, it was identified that there was no significant difference for agranulocytosis reports during 2012, 2013 and 2014. However, for neutropenia, while in 2012, there were 28 reports, in 2013 there were 13 and in 2014 there were only 8. This might again be interpreted as the success of the black box warning and prescribers being more careful towards patients with this risk.

In 2016, a Dear Healthcare Professional Letter for deferasirox was distributed related to a new indication: treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older (173). However, there is no increase in report numbers in years 2017 and 2018 following this new communication. Further investigation and looking at case details from FAERS and VigiBase, there were also no increase in child cases in 2017 and 2018. On the contrary, both in FAERS and VigiBase cases, there were decreases in during these years for child cases.

The results from VigiBase show that for all three iron chelators, GI disorders are the most common adverse events reported after exposure. Given the fact that GI symptoms such as nausea, abdominal pain, vomiting, dyspepsia were also recorded as common and known adverse reactions in their product characteristics sheets proves that the real life examples are parallel.

As expected, when route of administration differed, commonly reported adverse events varied as well. According to the results obtained from the databases, application site reactions, such as irritation, erythema, oedema, pain were seen after deferoxamine exposure, because deferoxamine is administered IV or SC (91,174). As also expected, deferasirox and deferiprone being oral medications, GI disturbances were reported more commonly after exposure.

As per the numbers of reports by region, it is evident that Americas received more cases compared to all other geographic regions. In our opinion, this is due to 2 reasons; one of them is that, more active patients lead to more reported events. Second reason is the fact that it was usually in Americas region, where the active ingredients and marketed products were first approved. Deferiprone (Ferriprox) was first marketed in United States of America in 2011 and following this, it was marketed in European Union in 2016 (67). Deferasirox (Exjade) was first marketed in United States of America in 2005, and following this, it was marketed in European Union in 2016 (65).

As mentioned previously, combination of methods and scientific review to understand the obtained data is crucial. Patient characteristics of cases reported under specific adverse event terms were reviewed.

Disproportionality analysis methods were used in our study, as they are inexpensive and quick methods, commonly used to identify statistical associations between products and events. Looking at different disproportionality analysis techniques, it was realized that there is no such thing as “one best technique”, as all techniques have their own advantages and disadvantages. They all aim to detect the ‘unexpectedly’ frequently reported relative compared to other reports. Some techniques are better for when the data amount is less, and for some methods it is the opposite, and it requires additional steps to shrink data. For some techniques, data amount doesn’t affect the results. Since all these techniques of disproportionality are based on the same principles of calculation, and all of them are by using two-by-two tables, results are commonly compatible (127,139).

Calculating the ROR in spontaneous report databases, as well as in our study, happen to be more advantageous compared to PRR. ROR ensures estimation of the

relative risk, and focuses attention on which people or reports should be included or excluded from the control series, permitting more deliberate elimination of biases (141). RORs were calculated manually by using the data from FAERS. In addition to this, disproportionality results for iron chelators for the data from Vigibase, was provided by UMC. According to our review and disproportionality analysis using 2 different databases, an assumption can be made that deferoxamine is associated with blurred vision, and deferiprone is associated with sepsis. However, these results only point towards assumptions and they need to be further discussed to understand other criteria that can effect this adverse drug reaction, such as dose, time of exposure, some patient characteristics, etc. To better analyze and understand the disproportionality, more resource is needed. This way the length of the confidence interval can be decreased, and researchers can reach more accurate and reliable results (139). For some adverse events, despite the low number of reports, disproportionality analysis was performed. There were some inconsistencies for blurred vision, sepsis and headache associations, cross databases. This might be due to region specific diseases as well as differences in sales.
Our search criteria included cases with “Vision Blurred”, “Sepsis” and “Headache” as MedDRA Preferred Term, and Deferasirox, Deferoxamine and Deferiprone as suspected product of the case. Some important details such as the seriousness and outcome of the cases, patient’s gender, age group, and iron chelator indication; numerically and proportionally were obtained.

According to the results obtained from our disproportionality analysis and comparing them to local labels, it was expected that headache was associated with all iron chelators, blurred vision was associated only with deferoxamine, and sepsis was not associated with any chelator agent. However, the results were pointing to different associations, even when the results from FAERS and Vigibase were compared. Headache was only associated with Deferiprone, according to the calculation using FAERS data. Blurred vision may be associated with Deferoxamine according to calculations using data from FAERS and Vigibase, and blurred vision may also be associated with Deferasirox according to the calculation using data from FAERS. Sepsis may be associated with Deferiprone according to the calculations using data from VigiBase and FAERS, and sepsis may also be associated with Deferasirox and

Deferoxamine according to calculation using data from Vigibase. For the reasons of these differences, a further analysis is necessary, however, differences in regions, duplication check, medical assessment of cases may be considered.

For sepsis, the results from FAERS and VigiBase were very different, in terms of the strength of the association. FAERS results point to an association 135 times stronger. This leads to consider region specific differences in metabolism, product quality, number of reports and common reporting practices.

To go further in our study, “very rare” adverse events from local labels were selected, and while doing that, for some adverse events, the closest events when the names did not completely match were selected, such as Yersinia gastroenteritis as yersinia infection. When the disproportionality analysis of the Deferoxamine cases listed as very rare were reviewed, it was seen that all results are within the confidence interval. As odds ratio being higher than 1 means that the result of exposure is associated with higher odds of outcome, a strong correlation for these adverse events can be assumed, that are acceleration or exacerbation of aluminum-related dialysis encephalopathy, acute respiratory distress, diarrhea, leukopenia, lung infiltration, thrombocytopenia and yersinia gastroenteritis.

Adverse events with unknown frequencies, as per the local labels were also reviewed. Upon examining the disproportionality analysis of the iron chelator cases listed as unknown, it is observed that all results are within the confidence interval. However, for only some of the adverse events, a higher association by their ROR being greater than 1 can be considered (139).

Adverse events from VigiBase with higher association possibility were also reviewed and examined. These adverse events were not listed in the local labels, meaning that neither during pre-marketing studies, nor during the post marketing period, these cases were raised as significant adverse events that the consumers need to be aware of. These adverse events may be important and unexpected adverse events may occur at any time. The importance of pharmacovigilance and spontaneous reporting should be emphasized in this case. Eventhough a signal for these adverse events was not created until now (128,131,132), this may change in the future.

Unexpectedly high reporting associations, which as a technical term are called “signals”, were reviewed throughout our thesis, also to assess the causality of our findings (6,125).

A retrospectively review was performed to see whether if there was a signal associated with “blurred vision”, “sepsis” or “headache” were ever confirmed or considered. When past signal reports were examined, it was identified that there is no signal related to them, but these terms are included in the summary of product characteristics. Blurred vision was listed as rare for deferoxamine (149). For deferiprone and deferasirox, this was not the case, but some other eye related disorders are mentioned (66,144).

Signal detection is a subject of ongoing research, and it will remain important as long as medicines stay on the market. Its potential to disclose new risks and benefits cannot be neglected. Analyzing databases retrospectively can strengthen previously revealed data or even enable us to obtain new safety information. Nonetheless, a small part of issued signals are generated by disproportionality practices (100,125,132).

Various statistical measures were considered for the application of computerized signal detection procedures. Data mining includes many different statistical techniques, such as cluster analysis, link analysis, deviation detection and disproportionality assessment, to be used to determine the presence of and to assess the strength of signals (136,175). Hence disproportionality methods are used by many authorities. Although disproportionality analysis is conducted by the national authorities on a regular basis, signal detection is performed using different tools (127,139). The most known tools would be review of designated medical events, information from reported adverse events regarding the survival of the patient and statistical methods, including disproportionality analysis. Examination of additional clinical data is always valuable (120).

National authorities may prefer to follow different tools and rules for their search potential signals. Moreover, different databases have different effectiveness criteria when assessing the safety information. Some promising research areas; including methods based on parametric modelling for time to onset for products for which exposure times can be determined, investigation of MedDRA PT ‘synonyms’, detecting

drug-drug interactions, statistical signal detection within therapeutic/clinical areas, occasional pharmacovigilance initiatives that focus on a specific group of products and cause unrepresentative reporting, were identified. EMA recommends combining these methods and examining results separately. Since disproportionality analysis remains just as impactful on drug regulation actions and, more research related to disproportionality analysis must be conducted and encouraged. That is why, the gathered data from different kinds of sources including adverse event databases was analyzed, in order to understand and examine safety and toxicity data and their relation to patient profile, pharmacodynamics and pharmacokinetics, to increase the knowledge of these chelating agents in a detailed manner. This chelating agent will be re-introduced to patients and healthcare professionals, in a more detailed and clear way.

The results obtained throughout this thesis may point to some signals. Medical evaluation should be performed to confirm these results. In this context, for the data collected from global databases, positive assumption can be made for medical assessment if the reporter was a healthcare professional. However, the same may not be true for SIDER. That may be why some SIDER results were very different from what was expected. For example, "iron overload" was found to be highly associated with iron chelator due to the ROR result. This does not prove the correctness of the result. The reason for this may be that the data came from an uncontrolled reporting, there was no medical evaluation, and no duplicate control was performed. Therefore, the data provided by health authorities is very valuable. If in the future, it is the case that all the collected reports point to “iron overload” related to deferasirox, including data from official sources, the reasons must be investigated. Region specific effects of deferasirox, its bioavailability, and even the possibility of saturation of iron binding capacity due to overusing, therefore the possibility of increased iron in the blood, should be considered.
Although an adverse event is listed, there may still be a new signal related to it. This might alter the frequency listed in local label, warnings and precautions or it might even add a new contraindication as there might be new information regarding to this adverse event and patient profile. Therefore, reporting adverse events that are already listed is also as important. With the obtained data, a better recognition of the product and to by means of promoting the correct usage of the product, by the correct patient profile, and

with the correct posology, was provided. By understanding certain mechanisms, how related toxicities can be minimized or eliminated was revealed, by understanding effects of each iron chelating agent in depth (2,156). While doing this, the difficulties and adverse events that may occur during the use of the product were also mentioned. It was also intended to raise the awareness of reporting of toxicities concerning chelating agents.

In today's conditions, especially in big and crowded cities, the time that physicians can spare to patients may not be enough. Unfortunately, to this extend, it is possible that some important information is missed. Also, due to this lack of time, an important point to eliminate adverse events may be missed: the fact that a patient-based approach must be applied when selecting the chelator. The importance of pharmacists in this process should not be forgotten. The easy accessibility of pharmacists and their close acquaintance with the patients provide great advantages for the patients. Pharmacists are usually the first the discover if there is an incompliance related to difficulty in using any medication. Finally, increasing patient compliance is achieved with scientific data that the patients and consumers can get from their doctor or pharmacist, rather than hearsay, which is very common for developing countries. That is also why a publicly available database for each country would be beneficial.

This research was not limited to Turkey, but if there was a database, a Turkey specific study could be done. This may be possible in the future. For this, reporting awareness should be increased and easier reporting opportunities can be provided. For example, adding a reporting option to the “e-NABIZ” application (176) that was established and made available to those living in Turkey during the COVID-19 pandemic, can be considered.

For future perspectives of this study, purchasing the disproportionality analysis calculation services to SOCs from VigiBase might be beneficial to add a new perspective to the results, considering that there was no SOC information in FAERS.

5. ANNEXES

5.1. Summary of Product Characteristics

5.1.1. Summary of Product Characteristics for Desferal

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: More common with rapid intravenous infusion. Administer intramuscularly or by slow subcutaneous or intravenous infusion. (5.1)
- Auditory and Ocular Toxicity: Have been reported when administered over prolonged periods of time, at high doses, or in patients with low ferritin levels. (5.2)
- Renal Toxicity: Cases of acute renal failure, renal tubular disorders and increase in serum creatinine have occurred. Monitor patients for changes in renal function. (5.3)
- Respiratory Toxicity: Acute respiratory distress syndrome has occurred. Risk increased with high intravenous doses. Recommended daily dose should not be exceeded. (5.4)
- Growth Suppression: Has occurred in pediatric patients treated with high doses and concomitant low ferritin levels. Dose reduction may partially resume growth velocity to pre-treatment rates. (5.5)
- Serious Infections: Cases of mucormycosis and Yersinia infections, some fatal, have occurred. Discontinue Desferal and initiate appropriate treatment immediately. (5.6)
- Cardiac Dysfunction with Concomitant Use of Vitamin C: Avoid coadministration in patients with cardiac failure. Delay Vitamin C for one month after start of Desferal. Avoid exceeding 200 mg daily in adults. Monitor cardiac function with combined treatment. (5.7)
- Risks of Desferal Treatment in Patients with Aluminum Overload: Risks include neurological dysfunction (including seizures), dialysis dementia, and aggravation of hyperparathyroidism. (5.8)
- Effects on Ability to Drive and Use Machines: May cause dizziness. (5.9)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception. (5.10, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions are injection reactions (local and systemic), hypersensitivity reactions, infections with Yersinia and Mucormycosis, cardiovascular, gastrointestinal, hematologic, hepatic, musculoskeletal, urogenital, nervous, respiratory, ocular and hearing. (6)

Figure *29.* "Warnings and Precautions" and "Adverse reactions" listed for Desferal

5.1.2. Summary of Product Characteristics for Deferasirox Mylan

Blood and lymphatic system disorders	
Not known:	Pancytopenia[1], thrombocytopenia[1], anaemia aggravated[1], neutropenia[1]
Immune system disorders	
Not known:	Hypersensitivity reactions (including anaphylactic reactions and angioedema)[1]
Metabolism and nutrition disorders	
Not known:	Metabolic acidosis[1]
Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Cataract, maculopathy
Rare:	Optic neuritis
Ear and labyrinth disorders	
Uncommon:	Deafness
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Laryngeal pain
Gastrointestinal disorders	
Common:	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis
Rare:	Oesophagitis
Not known:	Gastrointestinal perforation[1], acute pancreatitis[1]
Hepatobiliary disorders	
Common:	Transaminases increased
Uncommon:	Hepatitis, cholelithiasis
Not known:	Hepatic failure[1,2]
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Rare:	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Not known:	Stevens-Johnson syndrome[1], hypersensitivity vasculitis[1], urticaria[1], erythema multiforme[1], alopecia[1], toxic epidermal necrolysis (TEN)[1]
Renal and urinary disorders	
Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Renal tubular disorder[2] (acquired Fanconi syndrome), glycosuria
Not known:	Acute renal failure[1,2], tubulointerstitial nephritis[1], nephrolithiasis[1], renal tubular necrosis[1]
General disorders and administration site conditions	
Uncommon:	Pyrexia, oedema, fatigue

Figure *30.* Potential adverse events listed for Desferasirox Mylan

5.1.3. Summary of Product Characteristics for Ferriprox

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Frequency not known
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal pain Vomiting	Diarrhoea	
Skin and subcutaneous tissue disorders			Rash Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders	Chromaturia		
General disorders and administration site conditions		Fatigue	
Investigations		Increased liver enzymes	

Figure *31.* Adverse events and SOCs listed for Ferriprox

5.2. PV Database Dashboards

5.2.1. FAERS Dashboard

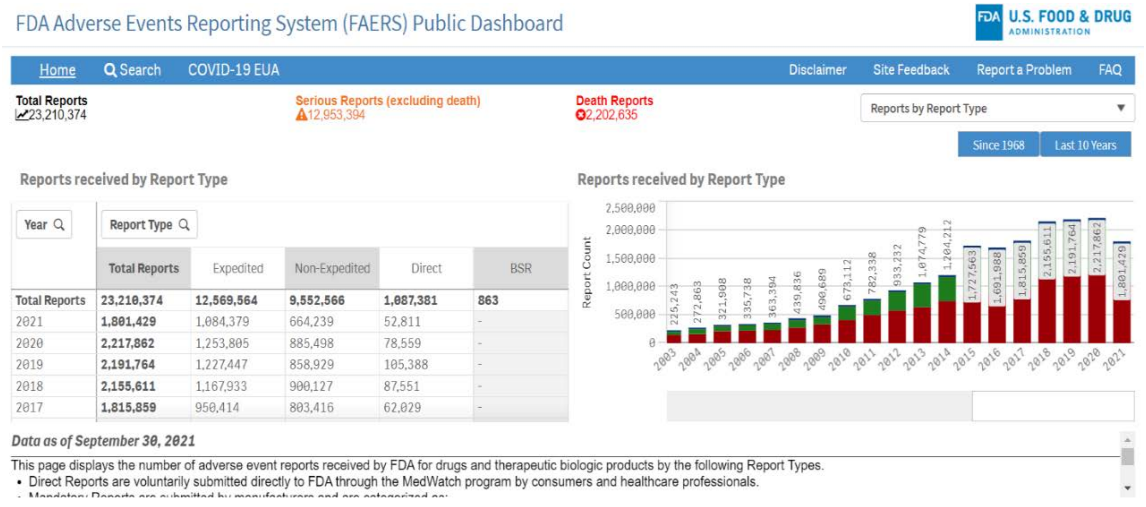

Figure 32. FAERS Dashboard

5.2.2. Eudravigilance Dashboard

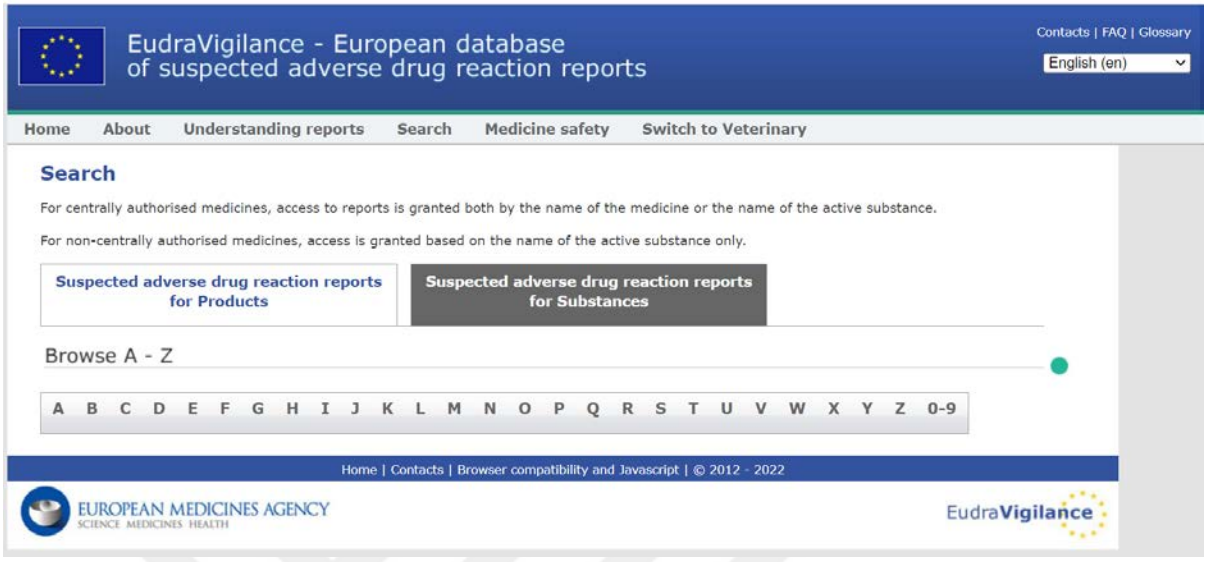

Figure 33. Eudravigilance Dashboard

5.2.3. DAEN Dashboard

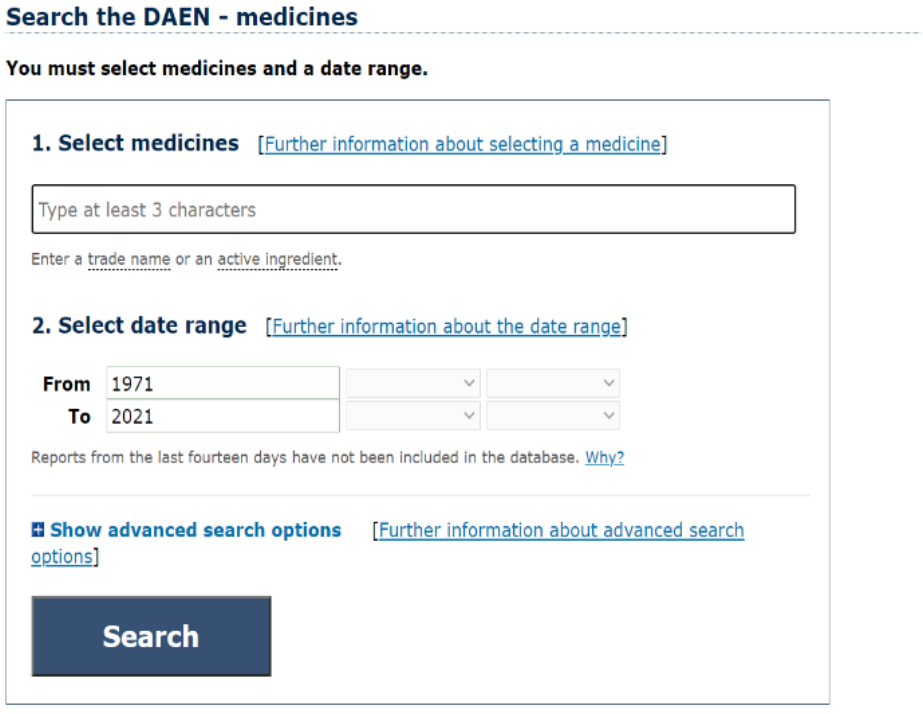

Figure 34. DAEN Dashboard

5.2.4. VigiAccess Dashboard

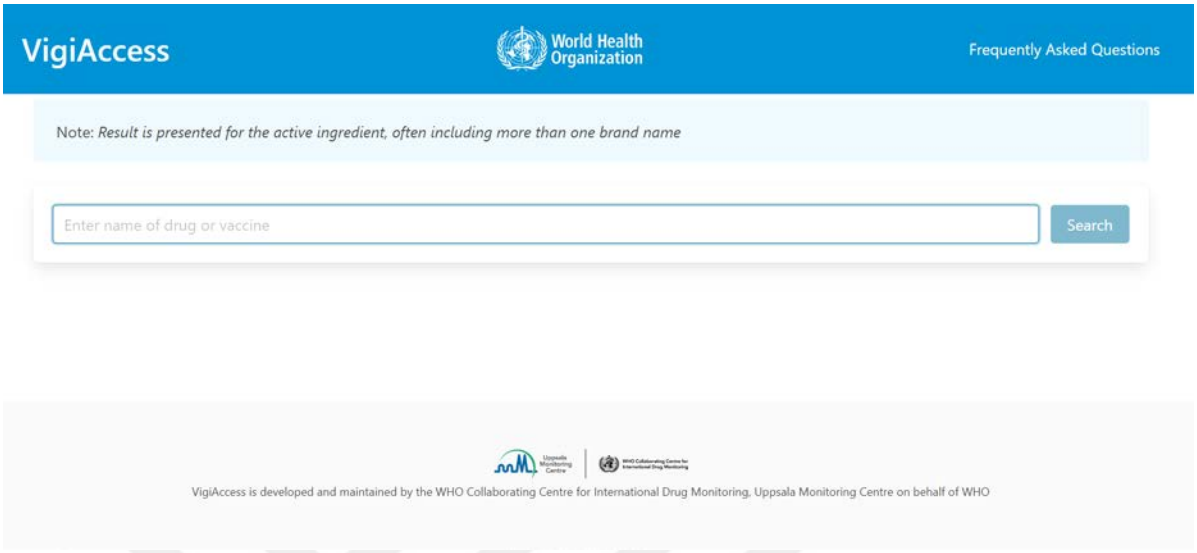

Figure 35. VigiAccess Dashboard

5.3. DEFINITIONS

Adverse event: An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine (177).

Adverse reaction: A noxious and unintended response to a medicine (177).

Disproportionality analysis: The statistical measures of disproportionality analysis express the extent to which the reported adverse drug reaction is associated with the suspected drug compared with the other drugs in the database (127).

Investigations: Investigations includes test names with qualifiers (e.g., increased, decreased, abnormal, normal) and without qualifiers (178).

Pharmacovigilance: Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem (93).

Signal: A safety signal refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect (125).

6. REFERENCES

1. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sci [Internet]. 2014 Feb;19(2):164–74. Available from: https://pubmed.ncbi.nlm.nih.gov/24778671
2. Britton RS, Leicester KL, Bacon BR. Iron Toxicity and Chelation Therapy. Int J Hematol [Internet]. 2002;76(3):219–28. Available from: https://doi.org/10.1007/BF02982791
3. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. Therap Adv Gastroenterol [Internet]. 2011 May;4(3):177–84. Available from: https://pubmed.ncbi.nlm.nih.gov/21694802
4. Gizem Ö, İNCEOĞLU B, SÜZGEÇ S, DURAN NH, TOPALOĞLU G, Burcu A, et al. Pharmacovigilance Activities in the Treatment of COVID-19. Hacettepe Univ J Fac Pharm. 2021;41(2):93–101.
5. Worakunphanich W, Youngkong S, Suwankesawong W, Anderson C, Thavorncharoensap M. Comparison of Patient Adverse Drug Reaction Reporting Systems in Nine Selected Countries. Int J Environ Res Public Health [Internet]. 2022 Apr 7;19(8):4447. Available from: https://pubmed.ncbi.nlm.nih.gov/35457318
6. Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Inf J [Internet]. 2008 Sep 1;42(5):409–19. Available from: https://doi.org/10.1177/009286150804200501
7. FDA Adverse Events Reporting System (FAERS) Public Dashboard [Internet]. Available from: https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis
8. WHO. UMC [Internet]. Available from: https://who-umc.org/vigibase/
9. Pharmacovigilance: Overview [Internet]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview
10. Iron [Internet]. Available from: https://go.drugbank.com/drugs/DB01592
11. Iron-Deficiency Anemia [Internet]. Available from:

https://my.clevelandclinic.org/health/diseases/22824-iron-deficiency-anemia

12. Rossi A, Poverini R, Di Lullo G, Modesti A, Modica A, Scarino ML. Heavy metal toxicity following apical and basolateral exposure in the human intestinal cell line Caco-2. Toxicol Vitr [Internet]. 1996;10(1):27–36. Available from: https://www.sciencedirect.com/science/article/pii/0887233395000976
13. He W, Feng Y, Li X, Wei Y, Yang X. Availability and toxicity of Fe(II) and Fe(III) in Caco-2 cells. J Zhejiang Univ Sci B [Internet]. 2008 Sep;9(9):707–12. Available from: https://pubmed.ncbi.nlm.nih.gov/18763303
14. Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J. Body iron metabolism and pathophysiology of iron overload. Int J Hematol. 2008;88(1):7–15.
15. McKie AT, Latunde-Dada GO, Miret S, McGregor JA, Anderson GJ, Vulpe CD, et al. Molecular evidence for the role of a ferric reductase in iron transport. Portland Press Ltd.; 2002.
16. Trinder D, Fox C, Vautier G, Olynyk JK. Molecular pathogenesis of iron overload. Gut. 2002;51(2):290–5.
17. West A-R, Oates P-S. Mechanisms of heme iron absorption: Current questions and controversies. World J Gastroenterol. 2008 Jul 14;14:4101–10.
18. Sargent PJ, Farnaud S, Evans RW. Structure/function overview of proteins involved in iron storage and transport. Curr Med Chem. 2005;12(23):2683–93.
19. Cabantchik ZI, Breuer W, Zanninelli G, Cianciulli P. LPI-labile plasma iron in iron overload. Best Pract Res Clin Haematol. 2005;18(2):277–87.
20. Andrews NC. Disorders of iron metabolism. N Engl J Med. 1999;341(26):1986–95.
21. Bozza MT, Jeney V. Pro-inflammatory Actions of Heme and Other Hemoglobin-Derived DAMPs [Internet]. Vol. 11, Frontiers in Immunology . 2020. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.01323
22. Anderson GJ, Frazer DM. Current understanding of iron homeostasis. Am J Clin Nutr [Internet]. 2017/10/25. 2017 Dec;106(Suppl 6):1559S-1566S. Available from: https://pubmed.ncbi.nlm.nih.gov/29070551
23. Angelucci E, Brittenham GM, Mclaren CE, Ripalti M, Baronciani D, Giardini C, et al. Hepatic iron concentration and total body iron stores in thalassemia major.

N Engl J Med. 2000;343(5):327–31.

24. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood, J Am Soc Hematol. 1997;89(3):739–61.
25. Liuzzi JP, Aydemir F, Nam H, Knutson MD, Cousins RJ. Zip14 (Slc39a14) mediates non-transferrin-bound iron uptake into cells. Proc Natl Acad Sci. 2006;103(37):13612–7.
26. Schranzhofer M, Schifrer M, Cabrera JA, Kopp S, Chiba P, Beug H, et al. Remodeling the regulation of iron metabolism during erythroid differentiation to ensure efficient heme biosynthesis. Blood. 2006;107(10):4159–67.
27. Fleming MD. The genetics of inherited sideroblastic anemias. In: Seminars in hematology. Elsevier; 2002. p. 270–81.
28. Farid Y, Bowman NS, Lecat P. Biochemistry, hemoglobin synthesis. 2019;
29. Marengo-Rowe AJ. Structure-function relations of human hemoglobins. Proc (Bayl Univ Med Cent) [Internet]. 2006 Jul;19(3):239–45. Available from: https://pubmed.ncbi.nlm.nih.gov/17252042
30. Bayraktar UD, Bayraktar S. Treatment of iron deficiency anemia associated with gastrointestinal tract diseases. World J Gastroenterol WJG. 2010;16(22):2720.
31. Hemoglobin test [Internet]. Available from: https://www.mayoclinic.org/tests-procedures/hemoglobin-test/about/pac-20385075#:~:text=For a hemoglobin test%2C a,to a lab for analysis.
32. Anemia [Internet]. Available from: https://www.hematology.org/education/patients/anemia
33. Sickle cell anemia [Internet]. Available from: https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876
34. Thalassemia [Internet]. Available from: https://www.mayoclinic.org/diseases-conditions/thalassemia/symptoms-causes/syc-20354995
35. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis [Internet]. 2010 May 21;5:11. Available from: https://pubmed.ncbi.nlm.nih.gov/20492708
36. Beta thalassemia [Internet]. Available from: https://medlineplus.gov/genetics/condition/beta-thalassemia/

37. Clinic C. Beta Thalassemia [Internet]. Available from: https://my.clevelandclinic.org/health/diseases/23574-beta-thalassemia
38. Holstege CP. Pediatric Iron Toxicity Medication. Available from: https://emedicine.medscape.com/article/1011689-medication#:~:text=The oral chelating agent deferasirox,from non–transfusion-dependent thalassemia
39. Myelodysplastic syndromes [Internet]. Available from: https://www.mayoclinic.org/diseases-conditions/myelodysplastic-syndrome/symptoms-causes/syc-20366977
40. Supportive Therapy for Myelodysplastic Syndromes [Internet]. Available from: https://www.cancer.org/cancer/myelodysplastic-syndrome/treating/supportive-therapy.html
41. Fleming RE, Sly WS. Mechanisms of Iron Accumulation in Hereditary Hemochromatosis. Annu Rev Physiol [Internet]. 2002 Mar 1;64(1):663–80. Available from: https://doi.org/10.1146/annurev.physiol.64.081501.155838
42. Crownover B, Covey C. Hereditary hemochromatosis. Am Fam Physician. 2013 Feb 1;87:183–90.
43. Hemochromatosis: Symptoms, Treatment, and Long-Term Outlook [Internet]. Available from: https://1md.org/health-guide/heart/disorders/hemochromatosis
44. Hemochromatosis (Iron Overload) [Internet]. Available from: https://my.clevelandclinic.org/health/diseases/14971-hemochromatosis-iron-overload
45. Hemochromatosis [Internet]. Available from: https://www.mayoclinic.org/diseases-conditions/hemochromatosis/diagnosis-treatment/drc-20351448
46. Kim KH, Oh KY. Clinical applications of therapeutic phlebotomy. J Blood Med [Internet]. 2016 Jul 18;7:139–44. Available from: https://pubmed.ncbi.nlm.nih.gov/27486346
47. Bring P, Partovi N, Ford J-AE, Yoshida EM. Iron Overload Disorders: Treatment Options for Patients Refractory to or Intolerant of Phlebotomy. Pharmacother J Hum Pharmacol Drug Ther [Internet]. 2008 Mar 1;28(3):331–42. Available from: https://doi.org/10.1592/phco.28.3.331

48. Yetişkinde Demir Eksikliği Anemisi (DEA) Tanı ve Tedavi Kılavuzu [Internet]. 2011. Available from: https://www.thd.org.tr/thddata/userfiles/file/demir eks 26_04_2011%5B1%5D.pdf
49. Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of Iron Deficiency Anemia. Gastroenterol Hepatol (N Y) [Internet]. 2015 Apr;11(4):241–50. Available from: https://pubmed.ncbi.nlm.nih.gov/27099596
50. Baird-Gunning J, Bromley J. Correcting iron deficiency. Aust Prescr [Internet]. 2016/12/05. 2016 Dec;39(6):193–9. Available from: https://pubmed.ncbi.nlm.nih.gov/27990046
51. Michael Auerbach, MD F. Treatment of iron deficiency anemia in adults [Internet]. Available from: https://www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults
52. CALCULATION OF THE TOTAL IRON DEFICIT – ALTERNATIVE EQUATION [Internet]. Available from: https://globalrph.com/medcalcs/calculation-of-the-total-iron-deficit-alternative-equation/
53. Long B, Koyfman A. Red Blood Cell Transfusion in the Emergency Department. J Emerg Med [Internet]. 2016 Aug 1;51(2):120–30. Available from: https://doi.org/10.1016/j.jemermed.2016.04.010
54. Coad J, Conlon C. Iron deficiency in women: assessment, causes and consequences. Curr Opin Clin Nutr Metab Care [Internet]. 2011;14(6). Available from: https://journals.lww.com/co-clinicalnutrition/Fulltext/2011/11000/Iron_deficiency_in_women__assessment,_causes_and.17.aspx
55. Milman NT. Dietary Iron Intake in Women of Reproductive Age in Europe: A Review of 49 Studies from 29 Countries in the Period 1993-2015. J Nutr Metab [Internet]. 2019 Jun 13;2019:7631306. Available from: https://pubmed.ncbi.nlm.nih.gov/31312532
56. Birliği TE. TEB RP [Internet]. Available from: https://www.tebrp.com/
57. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr [Internet]. 2000 Jul 1;72(1):257S-264S. Available from:

https://doi.org/10.1093/ajcn/72.1.257S
58. IRON [Internet]. Available from: https://www.webmd.com/vitamins/ai/ingredientmono-912/iron
59. Dietary Iron and Iron Supplements [Internet]. Available from: https://www.webmd.com/diet/supplement-guide-iron#1
60. Liebelt LE. Acute iron poisoning [Internet]. UpToDate. 2020. Available from: https://www.uptodate.com/contents/acute-iron-poisoning
61. MedlinePlus. Taking iron supplements [Internet]. Available from: https://medlineplus.gov/ency/article/007478.htm
62. Yuen H, Becker W. Iron Toxicity [Internet]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK459224/
63. Iron Reduction: Chelation Therapy [Internet]. Available from: https://irondisorders.org/chelation-therapy/
64. Iron Chelating Agents [Internet]. Available from: https://go.drugbank.com/categories/DBCAT001107
65. Deferasirox [Internet]. Available from: https://go.drugbank.com/drugs/DB01609
66. EXJADE® (deferasirox) [Internet]. 2007. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021882s002lbl.pdf
67. Deferiprone [Internet]. Available from: https://go.drugbank.com/drugs/DB08826
68. Deferoxamine [Internet]. Available from: https://go.drugbank.com/drugs/DB00746
69. Aydınok Y, Oymak Y, Atabay B, Aydoğan G, Yesilipek A, Ünal S, et al. A National Registry of Thalassemia in Turkey: Demographic and Disease Characteristics of Patients, Achievements, and Challenges in Prevention. Turkish J Hematol [Internet]. 2018;35(1):12–8. Available from: https://dx.doi.org/10.4274/tjh.2017.0039
70. BLAKE DR, WINYARD P, LUNEC J, WILLIAMS A, GOOD PA, CREWES SJ, et al. Cerebral and Ocular Toxicity Induced by Desferrioxamine. QJM An Int J Med [Internet]. 1985 Jul 1;56(1):345–55. Available from: https://doi.org/10.1093/oxfordjournals.qjmed.a067880

71. Vichinsky E. Oral Iron Chelators and the Treatment of Iron Overload in Pediatric Patients With Chronic Anemia. Pediatrics [Internet]. 2008 Jun 1;121(6):1253 LP – 1256. Available from: http://pediatrics.aappublications.org/content/121/6/1253.abstract
72. Algren DA. Review of oral iron chelators (deferiprone and deferasirox) for the treatment of iron overload in pediatric patients. World Heal Organ [on line]. 2010;1–22.
73. Ila HB, Topaktas M, Arslan M, Büyükleyla M. Signs of deferasirox genotoxicity. Cytotechnology [Internet]. 2013/07/26. 2014 Aug;66(4):647–54. Available from: https://pubmed.ncbi.nlm.nih.gov/23887830
74. Weatherall DJ, Clegg JB. The thalassaemia syndromes. John Wiley & Sons; 2008.
75. Thein SL. The molecular basis of β-thalassemia. Cold Spring Harb Perspect Med. 2013;3(5):a011700.
76. Cao A, Kan YW. The prevention of thalassemia. Cold Spring Harb Perspect Med. 2013;3(2):a011775.
77. Kountouris P, Lederer CW, Fanis P, Feleki X, Old J, Kleanthous M. IthaGenes: An Interactive Database for Haemoglobin Variations and Epidemiology. PLoS One [Internet]. 2014 Jul 24;9(7):e103020. Available from: https://doi.org/10.1371/journal.pone.0103020
78. Ladis V, Karagiorga-Lagana M, Tsatra I, Chouliaras G. Thirty-year experience in preventing haemoglobinopathies in G reece: achievements and potentials for optimisation. Eur J Haematol. 2013;90(4):313–22.
79. Williams TN, Weatherall DJ. World distribution, population genetics, and health burden of the hemoglobinopathies. Cold Spring Harb Perspect Med. 2012;2(9):a011692.
80. Türk Hematoloji Derneği. AKDENİZ ANEMİSİ (BETA TALASEMİ) TAŞIYICILIĞI VE HASTALIĞI [Internet]. Available from: http://www.thd.org.tr/thd_halk/?sayfa=akdeniz_anemisi
81. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, et al. 2018 Annual Report of the American Association of Poison Control Centers’

National Poison Data System (NPDS): 36th Annual Report. Clin Toxicol. 2019;57(12):1220–413.

82. Piccioni MG, Capone C, Vena F, Del Negro V, Schiavi MC, D'Ambrosio V, et al. Use of deferoxamine (DFO) in transfusion-dependent β-thalassemia during pregnancy: A retrospective study. Taiwan J Obstet Gynecol [Internet]. 2020;59(1):120–2. Available from: https://www.sciencedirect.com/science/article/pii/S1028455919302852
83. Deferoxamine Pregnancy and Breastfeeding Warnings [Internet]. Available from: https://www.drugs.com/pregnancy/deferoxamine.html#:~:text=US FDA pregnancy category C,pregnant women despite potential risks.
84. FDA Pregnancy Categories [Internet]. Available from: https://chemm.hhs.gov/pregnancycategories.htm
85. Deferiprone Pregnancy and Breastfeeding Warnings [Internet]. Available from: https://www.drugs.com/pregnancy/deferiprone.html
86. Deferasirox Pregnancy and Breastfeeding Warnings [Internet]. Available from: https://www.drugs.com/pregnancy/deferasirox.html
87. Gabutti V, Piga AG. Results of long-term iron-chelating therapy. Acta Haematol. 1996;95 1:26–36.
88. Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, et al. Survival in Medically Treated Patients with Homozygous β-Thalassemia. N Engl J Med [Internet]. 1994 Sep 1;331(9):574–8. Available from: https://doi.org/10.1056/NEJM199409013310903
89. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, et al. Efficacy of Deferoxamine in Preventing Complications of Iron Overload in Patients with Thalassemia Major. N Engl J Med [Internet]. 1994 Sep 1;331(9):567–73. Available from: https://doi.org/10.1056/NEJM199409013310902
90. Torcharus K, Pankaew T. Health-related quality of life in Thai thalassemic children treated with iron chelation. Southeast Asian J Trop Med Public Heal. 2011;42(4):951.
91. Price G, Patel DA. Drug Bioavailability [Internet]. StatPearls Publishing,

Treasure Island (FL); 2022. Available from: http://europepmc.org/books/NBK557852

92. FDA. What is a Serious Adverse Event? [Internet]. Available from: https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event
93. World Health Organization: Pharmacovigilance [Internet]. Available from: https://www.who.int/teams/regulation-prequalification/pharmacovigilance
94. FDA. CFR - Code of Federal Regulations Title 21 [Internet]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32
95. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255–9.
96. Yartsev A. Classification of adverse drug reactions [Internet]. 2015. Available from: https://derangedphysiology.com/main/cicm-primary-exam/required-reading/variability-drug-response/Chapter 320/classification-adverse-drug-reactions
97. Database of Adverse Event Notifications (DAEN) [Internet]. Available from: https://www.tga.gov.au/database-adverse-event-notifications-daen
98. Eudravigilance - European Database of Suspected Adverse Drug Reaction Reports [Internet]. Available from: http://www.adrreports.eu/en/search.html
99. Center UM. VIGIBASE [Internet]. 2021. Available from: http://www.vigiaccess.org/
100. Center UM. VigiBase: WHO's global database signalling harm and pointing to safer use. Available from: https://who-umc.org/vigibase/vigibase-who-s-global-database/
101. Eudravigilance: European database of suspected adverse drug reaction reports [Internet]. Available from: http://www.adrreports.eu/en/background.html
102. EudraVigilance Operational Plan Milestones 2018 to 2020 [Internet]. 2018. Available from: https://www.ema.europa.eu/en/documents/other/eudravigilance-operational-plan-milestones-2018-2020_en.pdf
103. Authority JH. JADER [Internet]. Available from:

https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html

104. Canadian Health Authority. Canada Vigilance Adverse Reaction Online Database [Internet]. Available from: https://cvp-pcv.hc-sc.gc.ca/arq-rei/index-eng.jsp
105. Authority DH. Interactive Adverse Drug Reaction overviews. Available from: https://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-of-medicines/interactive-adverse-drug-reaction-overviews/Danish
106. Center UM. Quantitative COVID-19 vaccine safety surveillance with VigiLyze in near real-time [Internet]. Available from: https://www.who-umc.org/vigibase/vigilyze/quantitative-covid-19-vaccine-safety-surveillance-with-vigilyze-in-near-real-time/
107. İyi Farmakovijilans Uygulamaları Kılavuzları [Internet]. 2014. Available from: https://www.titck.gov.tr/faaliyetalanlari/ilac/farmakovijilans
108. TITCK. TITCK - Duyurular [Internet]. Available from: https://www.titck.gov.tr/duyuru
109. Türkiye Farmakovijilans Merkezi [Internet]. Available from: https://www.titck.gov.tr/faaliyetalanlari/ilac/farmakovijilans
110. TITCK. İLLERDE YÜRÜTÜLECEK FARMAKOVİJİLANS FAALİYETLERİ İÇİN STANDART ÇALIŞMA YÖNTEMİ ESASLARI [Internet]. Available from: https://titck.gov.tr/storage/Archive/2020/contentFile/LLERDE YÜRÜTÜLECEK FARMAKOVİJİLANS FAALİYETLERİ İÇİN STANDART ÇALIŞMA YÖNTEMİ 28.02.2020_1fa51437-ee1f-4265-a2e8-b914ea126269.pdf
111. WHO. VigiAccess [Internet]. Available from: https://www.vigiaccess.org/
112. EMA. Medicines under additional monitoring [Internet]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring#:~:text=This medicinal product is subject,base is less well developed.
113. TUFAM. İyi Farmakovijilans Uygulamaları (İFU) Kılavuzu Modül II – Ek İzleme [Internet]. Available from: https://www.titck.gov.tr/Dosyalar/Ilac/Farmakovijilans/İFU-Modül II.pdf

114. FERRAPLUS 90- docusate sodium, folic acid, carbonyl iron, cyanocobalamin, and ascorbic acid tablet, film coated Trigen Laboratories, LLC [Internet]. Available from: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=b044e461-0da3-4b7c-ab6e-e1b7792fa94b&type=display
115. Ferriprox - Important Safety Information [Internet]. Available from: https://ferriprox.com/hcp/
116. FDA. Dear Health Care Provider Letters: Improving Communication of Important Safety Information [Internet]. 2017. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dear-health-care-provider-letters-improving-communication-important-safety-information
117. Exjade - Sayın Doktor Mektubu [Internet]. 2009. Available from: https://titck.gov.tr/storage/dynamicModulesAttachment/e9fe0df650370.pdf
118. EMA. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) [Internet]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
119. Risk management plans (RMP) in post-authorisation phase: questions and answers [Internet]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/risk-management-plans-rmp-post-authorisation-phase-questions-answers
120. EMA. Summary of the risk management plan for Exjade (Deferasirox) [Internet]. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/exjade-epar-risk-management-plan-summary_en.pdf
121. TITCK. ▼Deferasiroks İçeren Film Kaplı Tabletler Tedavisine İlişkin Hekimler İçin Önemli Bilgiler Kılavuzu [Internet]. Available from: https://titck.gov.tr/storage/Archive/2021/dynamicModulesAttachment/HekimMateryali_e9d55fcd-f73a-4b45-87e0-9f6c8c2d9a7c.pdf
122. EMA. Part VI: Summary of the risk management plan [Internet]. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/deferiprone-lipomed-

epar-risk-management-plan-summary_en.pdf
123. TITCK. Deferasiroks İçeren Film Kaplı Tabletler ile Tedaviye İlişkin Hasta Kılavuzu [Internet]. Available from: https://titck.gov.tr/storage/Archive/2021/dynamicModulesAttachment/HastaMateryali_0139cfb9-5f97-4ea6-94f9-728f89949684.pdf
124. SIDER 4.1 [Internet]. Available from: http://sideeffects.embl.de/
125. Center UM. What is a signal? [Internet]. Available from: https://www.who-umc.org/research-scientific-development/signal-detection/what-is-a-signal/
126. Ibrahim H, Abdo A, El Kerdawy AM, Eldin AS. Signal Detection in Pharmacovigilance: A Review of Informatics-driven Approaches for the Discovery of Drug-Drug Interaction Signals in Different Data Sources. Artif Intell Life Sci [Internet]. 2021;1:100005. Available from: https://www.sciencedirect.com/science/article/pii/S2667318521000052
127. Montastruc J-L, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of disproportionality analysis for identification of Adverse Drug Reactions in a Pharmacovigilance Database. Br J Clin Pharmacol. 2011 Jun 10;72:905–8.
128. FDA. Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) [Internet]. Available from: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system
129. UMC. Access the leading source of global safety data [Internet]. Available from: https://who-umc.org/vigibase/vigibase-services/
130. UMC. Statistical reasoning and algorithms in pharmacovigilance [Internet]. Available from: https://learning.who-umc.org/visitor_catalog_class/show/34311
131. FDA. Archived Reports | Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) (formerly AERS) [Internet]. Available from: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/archived-reports-potential-signals-serious-risksnew-safety-

information-identified-fda-adverse-event

132. EMA. PRAC recommendations on safety signals [Internet]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management/prac-recommendations-safety-signals#list-of-safety-signals-discussed-since-september-2012-section
133. Guidelines for Preparing Core Clinical-Safety Information on Drugs Second Edition – Report of CIOMS Working Groups III and V. Available from: https://cioms.ch/publications/product/guidelines-preparing-core-clinical-safety-information-drugs-second-edition-report-cioms-working-groups-iii-v/#description
134. Questions and Answers on FDA's Adverse Event Reporting System (FAERS) [Internet]. Available from: https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers
135. Center UM. Statistical reasoning and algorithms in pharmacovigilance [Internet]. Available from: https://learning.who-umc.org/visitor_catalog_class/show/34311
136. Hesha J. Duggirala (CVM), Joseph M. Tonning (CDER), Ella Smith (CFSAN) RA, Bright (OITI), John D. Baker (CVM), Robert Ball (CBER), Carlos Bell (CDER) KB, (OCS), Susan J. Bright-Ponte (CVM), Taxiarchis Botsis (CBER), Marc Boyer (CFSAN) K, Burkhart (CDER), G. Steven Condrey (ORA), James J. Chen (NCTR) SC (CFSAN), Ross W. Filice (OCS), Henry Francis (CDER), Hongying Jiang (CDRH) JL, (OITI), David Martin (CBER), Taiye Oladipo (CFSAN), Rene O'Neill (CDRH) LAM, et al. Data Mining at FDA.
137. Stricker BHC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ [Internet]. 2004 Jul 3;329(7456):44–7. Available from: https://pubmed.ncbi.nlm.nih.gov/15231627
138. Hennessy S, Leonard CE, Gagne JJ, Flory JH, Han X, Brensinger CM, et al. Pharmacoepidemiologic Methods for Studying the Health Effects of Drug-Drug Interactions. Clin Pharmacol Ther [Internet]. 2015/11/23. 2016 Jan;99(1):92–100. Available from: https://pubmed.ncbi.nlm.nih.gov/26479278
139. Zink R, Huang Q, Zhang L-Y, Bao W-J. Statistical and graphical approaches for disproportionality analysis of spontaneously-reported adverse events in

pharmacovigilance. Chin J Nat Med. 2013;11:314–20.

140. Bate A, Lindquist M, Edwards I, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. European Journal of Clinical Pharmacology, 54, 315-321. Eur J Clin Pharmacol. 1998 Jul 1;54:315–21.
141. Waller P, Puijenbroek E, Egberts T, Evans S. The reporting odds ratio versus the proportional reporting ratio: “Deuce.” Pharmacoepidemiol Drug Saf. 2004 Aug 1;13:525–6; discussion 527.
142. Confidence Intervals [Internet]. Available from: http://www.stat.yale.edu/Courses/1997-98/101/confint.htm
143. KISA ÜRÜN BİLGİSİ - Exjade [Internet]. Available from: https://titck.gov.tr/storage/Archive/2022/kubKtAttachments/ONAYLIKB_845db8ef-2390-498e-a569-a4f21f4f491b.pdf
144. Kısa Ürün Bilgisi: FERRİPROX 100 mg/ml şurup [Internet]. Available from: https://titck.gov.tr/storage/Archive/2022/kubKtAttachments/FERRPROXKUB_0f76eded-5a53-4628-aea4-5bd9373c2817.pdf
145. Kısa Ürün Bilgileri: DESFERAL 500 mg IM/IV/SC Enjeksiyon İçin Liyofilize Toz İçeren Flakon [Internet]. Available from: https://titck.gov.tr/storage/Archive/2020/kubKtAttachments/kubtemiz_94896572-b3d9-413c-9c21-6cba00de282f.pdf
146. Kısa Ürün Bilgisi: FERRİPROX 500 mg film kaplı tablet [Internet]. Available from: https://titck.gov.tr/storage/Archive/2022/kubKtAttachments/FERRPROX500mgfilmkapltabletKB_a0867835-6434-4654-9b05-c9a52a27f4d0.pdf
147. Kısa Ürün Bilgisi: VEXPERDA 360 mg film kaplı tablet [Internet]. Available from: https://titck.gov.tr/storage/Archive/2021/kubKtAttachments/1_958b750d-24d9-4cc6-b77a-d27a8d7c7f44.pdf
148. KISA ÜRÜN BİLGİSİ - Ferriprox [Internet]. Available from: https://titck.gov.tr/storage/Archive/2022/kubKtAttachments/FERRPROXKUB_0f76eded-5a53-4628-aea4-5bd9373c2817.pdf
149. KISA ÜRÜN BİLGİLERİ - Desferal [Internet]. Available from:

https://titck.gov.tr/storage/Archive/2020/kubKtAttachments/kubtemiz_94896572-b3d9-413c-9c21-6cba00de282f.pdf

150. Brody T. Chapter 13 - Coding. In: Brody TBT-FDRP and the PL, editor. Academic Press; 2018. p. 575–607. Available from: https://www.sciencedirect.com/science/article/pii/B9780128146477000130
151. EMA. Exjade SUMMARY OF PRODUCT CHARACTERISTICS [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/exjade-epar-product-information_en.pdf
152. Guarin GE. What is the role of iron chelation therapy in the treatment of transfusion-induced iron overload? [Internet]. 2020. Available from: https://www.medscape.com/answers/1389732-177349/what-is-the-role-of-iron-chelation-therapy-in-the-treatment-of-transfusion-induced-iron-overload
153. Aksel G, Islam MM, Aslan T, Eroglu SE. Prolongation of QT interval due to hydroxychloroquine overdose used in COVID-19 treatment. Turkish J Emerg Med [Internet]. 2020 Jul 18;20(3):149–51. Available from: https://pubmed.ncbi.nlm.nih.gov/32832735
154. Westwood MA, Pennell DJ. 33 - Cardiac Iron Loading and Myocardial T2*. In: Manning WJ, Pennell DJBT-CMR (Third E, editors. Philadelphia: Elsevier; 2019. p. 400-409.e4. Available from: https://www.sciencedirect.com/science/article/pii/B9780323415613000343
155. Simon S, Athanasiov PA, Jain R, Raymond G, Gilhotra JS. Desferrioxamine-related ocular toxicity: a case report. Indian J Ophthalmol [Internet]. 2012 Jul;60(4):315–7. Available from: https://pubmed.ncbi.nlm.nih.gov/22824603
156. Nicola M, Barteselli G, Dell'Arti L, Ratiglia R, Viola F. Functional and Structural Abnormalities in Deferoxamine Retinopathy: A Review of the Literature. Biomed Res Int. 2014 Nov 20;2015.
157. Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk β-thalassemia. Blood, J Am Soc Hematol. 2000;95(4):1229–36.
158. Wu C-H, Yang C-P, Lai C-C, Wu W-C, Chen Y-H. Deferoxamine retinopathy: spectral domain-optical coherence tomography findings. BMC Ophthalmol

[Internet]. 2014;14(1):88. Available from: https://doi.org/10.1186/1471-2415-14-88

159. Piga AG, Luzzatto L, Capalbo P, Gambotto S, Tricta F, Gabutti V. High-dose desferrioxamine as a cause of growth failure in thalassemic patients. 1988;
160. Davies S, Hungerford JL, Arden GB, Marcus RE, Miller MH, Huehns ER. OCULAR TOXICITY OF HIGH-DOSE INTRAVENOUS DESFERRIOXAMINE. Lancet [Internet]. 1983;322(8343):181–4. Available from: http://www.sciencedirect.com/science/article/pii/S0140673683901708
161. Hospital BC. Iron Chelation [Internet]. Available from: https://www.childrenshospital.org/conditions-and-treatments/treatments/iron-chelation-therapy#:~:text=There are two iron chelators,dispersible or film-coated tablet
162. Gattepaille LM, Hedfors Vidlin S, Bergvall T, Pierce CE, Ellenius J. Prospective Evaluation of Adverse Event Recognition Systems in Twitter: Results from the Web-RADR Project. Drug Saf [Internet]. 2020;43(8):797–808. Available from: https://doi.org/10.1007/s40264-020-00942-3
163. TITCK. Ek İzlemeye Tabi İlaçlar Listesi [Internet]. 2022. Available from: https://www.titck.gov.tr/dinamikmodul/57
164. FDA. Drugs@FDA: FDA-Approved Drugs [Internet]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016267
165. FDA. Drugs@FDA: FDA-Approved Drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=021882
166. Kyriakou A, Savva S, Savvides I, Pangalou E, Ioannou Y, Christou S, et al. Gender differences in the prevalence and severity of bone disease in Thalassaemia. Pediatr Endocrinol Rev. 2008 Nov 1;6 Suppl 1:116–22.
167. Wang F, Ni J, Wu L, Wang Y, He B, Yu D. Gender disparity in the survival of patients with primary myelodysplastic syndrome. J Cancer [Internet]. 2019 Jan 30;10(5):1325–32. Available from: https://pubmed.ncbi.nlm.nih.gov/30854142
168. TITCK. Ruhsatlı Ürünler Listesi [Internet]. Available from:

https://www.titck.gov.tr/dinamikmodul/85
169. FDA. Recalls, Market Withdrawals, & Safety Alerts [Internet]. Available from: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts
170. EMA. Product defects and recalls [Internet]. Available from: https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/compliance/product-defects-recalls
171. Ferriprox - SUMMARY OF THE RISK MANAGEMENT PLAN [Internet]. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/ferriprox-epar-risk-management-plan-summary_en.pdf
172. Dear Healthcare Professional Letter - Exjade [Internet]. 2009. Available from: file:///C:/Users/BArda/Downloads/Exjade DHCP_E_2009_Nov.pdf
173. Dear Healthcare Professional Letter - Jadenu [Internet]. Available from: file:///C:/Users/BArda/Downloads/jadenu_dhcp_2016_e (1).pdf
174. Gad SC. Routes in toxicology: An overview. J Am Coll Toxicol. 1994;13(1):34–9.
175. Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in pharmacovigilance. Expert Opin Drug Saf [Internet]. 2005 Sep 1;4(5):929–48. Available from: https://doi.org/10.1517/14740338.4.5.929
176. T.C. Sağlık Bakanlığı. e-nabız [Internet]. Available from: https://enabiz.gov.tr/
177. EMA. Glossary of regulatory terms [Internet]. Available from: https://www.ema.europa.eu/en/about-us/about-website/glossary
178. MSSO. MedDRA® TERM SELECTION: POINTS TO CONSIDER [Internet]. Available from: https://mssotools.com/mssoweb/PTC/ts_ptc_r414.html

7. CURRICULUM VITAE

Kişisel Bilgiler

Adı	Burcu Eda	**Soyadı**	Arda
Doğum Yeri		**Doğum Tarihi**	
Uyruğu		**TC Kimlik No**	
E-mail			

Öğrenim Durumu

Derece	Alan	Mezun Olduğu Kurumun Adı	Mezuniyet Yılı
Doktora	Farmasötik Toksikoloji	**Yeditepe Üniversitesi**	2022
Lisans	Eczacılık Fakültesi	**Yeditepe Üniversitesi**	2016
Lise	Fen Bilimleri	**Sainte Pulchérie Fransız Lisesi**	2011

Bildiği Yabancı Dilleri	**Yabancı Dil Sınav Notu (#)**
İngilizce	C1
Fransızca	B2

Başarılmış birden fazla sınav varsa(KPDS, ÜDS, TOEFL; EELTS vs), tüm sonuçlar yazılmalıdır

İş Deneyimi (Sondan geçmişe doğru sıralayın)

Görevi	Kurum	**Süre (Yıl - Yıl)**
Farmakovijilans Proje Lideri	Excelya Medikal Araştırma ve Danışmaklık	2019-halen
Farmakovijilans Yetkilisi	Zeincro Medikal Araştırma ve Danışmanlık	2017-2019

Bilgisayar Bilgisi

Program	**Kullanma becerisi**
Microsoft Office	Çok iyi
Mendeley	İyi

*****Çok iyi, iyi, orta, zayıf olarak değerlendirin

Diğer (Görev Aldığı Projeler/Sertifikaları/Ödülleri)

Doktora Bursu, Yeditepe Üniversitesi, Ağustos 2017

Bilimsel Çalışmaları

SCI, SSCI, AHCI indekslerine giren dergilerde yayınlanan makaleler

-

-

Diğer dergilerde yayınlanan makaleler

Özal, G. , İnceoğlu, B. , Süzgeç, S. , Duran, N. H. , Topaloğlu, G. , Arda, B. & Gulhan, A. (2021). Pharmacovigilance Activities in the Treatment of COVID-19. Hacettepe University Journal of the Faculty of Pharmacy, 41 (2), 93-101. DOI: 10.52794/hujpharm.903721

Uluslararası bilimsel toplantılarda sunulan ve bildiri kitabında (*Proceedings*) basılan bildiriler

-

Hakemli konferans/sempozyumların bildiri kitaplarında yer alan yayınlar

-

Diğer (Görev Aldığı Projeler/Sertifikaları/Ödülleri)

Doktora Bursu, Yeditepe Üniversitesi, Ağustos 2017