Pharmacovigilance Analysis of Posaconazole in the Treatment of Systemic Fungal Infection: Assessing Safety Profiles and Adverse Event Patterns in Real-World Data from FAERS (2018-2022)

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled “Pharmacovigilance Analysis of Posaconazole in the Treatment of Systemic Fungal Infection : Assessing Safety Profiles and Adverse Event Patterns in Real-World Data from FAERS (2018-2022)” submitted by Md. Maruf Parves (19346007) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on June, 2023.

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Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

This study uses FDA Adverse Event Reporting System (FAERS) data to analyse Posaconazole, a second-generation antifungal drug. The goal is to gain insights into Posaconazole's safety profile by analysing clinical adverse occurrences. Data spanning 2018 to 2022 were extracted from FAERS, cleaned, and merged with the MedDRA terminology for adverse event categorization. Using the Reporting Odds Ratio (ROR), the study focuses on comparing the relative odds of specific adverse events associated with Posaconazole versus other drugs. Potential associations between Posaconazole and adverse events were identified based on ROR values and 95% confidence intervals. Among the 32,954 reports analyzed, 2,359 distinct adverse events and 727 signals were identified. Notable adverse events with high ROR values included Pseudoaldosteronism, CARD9 deficiency, Microsporum infection, Left-atrial hypertrophy, Acquired apparent mineralocorticoid excess, Donor leukocyte infusion, and SARS-CoV-2 RNA. By using real-world FAERS data, this study provides useful understanding of Posaconazole's safety profile, can help healthcare professionals make informed decisions about its use, and advances pharmacovigilance.

Keywords: Posaconazole; adverse events; drug profiling; FAERS; pharmacovigilance; safety profile.

Dedication

To my esteemed mentors, cherished family, and dear friends, this is dedicated with profound gratitude for your invaluable support and unwavering belief in my endeavors.

Acknowledgement

I would like to begin by expressing my gratitude towards Almighty Allah for providing me with the strength during this whole period; I am indebted and would like to express my sincere gratefulness and gratitude towards Dr. Mesbah Talukder, Professor, School of Pharmacy, Brac University for being a constant guiding spirit throughout my study and for being so supportive, kind and motivating throughout the journey.

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List of Acronyms

FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
EMA	European Medicines Agency
CYP51	Cytochrome P450-dependent 14α-demethylase
IV	Intravenous
OPC	Oropharyngeal Candidiasis
rOPC	Refractory Oropharyngeal Candidiasis
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System Organ Class
HLGT	High-Level Group Term
HLT	High-Level Term
PT	Preferred Term
LLT	Lowest Level Term
ROR	Reporting Odds Ratio
CI	Confidence Interval

Chapter 1

Introduction

Posaconazole is a pharmacological agent belonging to the class of triazole, a second generation antifungal drug and widely utilized in clinical practice for the prevention and treatment of invasive fungal infections, particularly in immunocompromised patients (Hof, 2006). Posaconazole has demonstrated efficacy against a broad range of fungal pathogens, including Aspergillus, Candida, and Zygomycetes species (Hof, 2006; Schiller & Fung, 2007).

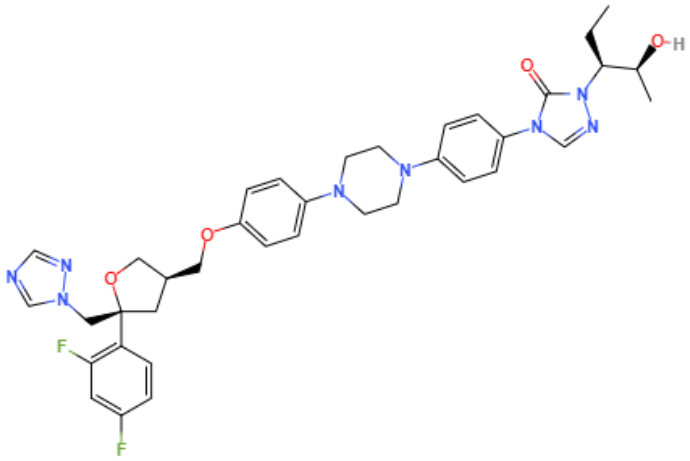

Figure 1.Chemical structure of Posaconazole

Posaconazole, much like other triazole antifungal agents, works by binding to the heme cofactor located on the active site of an enzyme called cytochrome P450 (CYP51)-dependent 14α-demethylase. This specific enzyme plays a crucial role in converting lanosterol to 14α-dimethyl lanosterol as part of the ergosterol biosynthetic pathway, which is essential for the fungal cell membrane. Ergosterol, a vital component of the fungal cell membrane, is significantly affected when 14α-demethylase is inhibited by Posaconazole. Not only does this inhibition led to the depletion of ergosterol, but it also causes the accumulation of toxic

methylated sterol precursors. As a consequence, the integrity and functionality of the fungal cell membrane become disrupted, impeding proper fungal growth (Hof, 2006; Morris, 2009; Schiller & Fung, 2007).

Posaconazole forms stronger hydrophobic bonds with the CYP51 enzyme due to the presence of its long side chain. This enhanced hydrophobic binding capability enables Posaconazole to interact more effectively with the enzyme, resulting in enhanced activity against fungal isolates that have acquired resistance to fluconazole and voriconazole (Morris, 2009).

Posaconazole received its initial approval from the U.S. Food and Drug Administration (FDA) in 2006 as an oral suspension. Subsequently, the delayed-release tablet was approved in 2013, followed by the approval of the intravenous injection in 2014. The increased availability of various types of Posaconazole has given healthcare workers more choices in how they give it to patients (Clark et al., 2015; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., 2006).

Table 1. Posaconazole's (Noxafil®) indication, dose and duration, adopted from package insert (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., 2006).

<table>
<tr><th>Indication</th><th>Dosage form</th><th>Dose</th><th>Duratiom</th></tr>
<tr><td rowspan="5">Prophylaxis of Invasive Aspergillus and Candida Infections</td><td rowspan="2">Noxafil Injection:</td><td>- Loading dose: 300 mg IV twice a day (first day)</td><td rowspan="5">Based on patient recovery from neutropenia or immunosuppression.</td></tr>
<tr><td>- Maintenance dose: 300 mg IV daily</td></tr>
<tr><td rowspan="2">Delayed-Release Tablets:</td><td>- Loading dose: 300 mg (three 100 mg tablets) on the first day</td></tr>
<tr><td>- Maintenance dose: 300 mg (three 100 mg tablets)
once a day from the second day</td></tr>
<tr><td>Oral Suspension:</td><td>200 mg (5 mL) three times a day</td></tr>
</table>

Treatment of Oropharyngeal Candidiasis (OPC)	Oral Suspension:	- Loading dose: 100 mg (2.5 mL) twice daily on the first day Maintenance dose: 100 mg (2.5 mL) once a day	Therapy duration: 13 days
Treatment of OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	Oral Suspension:	Dose: 400 mg (10 mL) twice a day	Duration determined by disease severity and clinical response

In Europe, Posaconazole is only allowed for adults, but the US FDA has approved an oral suspension for patients who are at least 13 years old. Posaconazole can only be used as prescribed off-label for certain cases in patients who are 12 years old or younger. (Accord Healthcare S.L.U., n.d.; Katragkou et al., 2012; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., 2006).

Although the safety and ability to tolerate Posaconazole have been extensively researched in clinical studies it is important to enhance this understanding with real-life information to get a complete grasp of its safety profile (Wong et al., 2020). The analysis of Pharmacovigilance allows for the study of adverse effects linked to Posaconazole, using big pharmacovigilance databases like the FAERS (FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files | FDA, n.d.). These databases gather information about adverse effects reported after a product has been approved and is available in the market. This helps in finding out possible signs of danger that may have gone unnoticed in carefully monitored clinical trials.

The main goal of this study is to perform a comprehensive drug profiling analysis of Posaconazole. The analysis will be done by examining data from the FAERS database, specifically for the years 2018 to 2022. By examining this large set of data, we will

investigate the safety characteristics of Posaconazole and gather information about the negative occurrences recorded in actual medical practice.

the main objective of this research is to provide a comprehensive overview of the negative impacts connected to Posaconazole, including information about how frequently they happen, how severe they are, and distribution by system organ class (SOC). By observing the medication in this manner, we can discover potential safety concerns and gain more knowledge about the adverse outcomes that may occur to individuals who consume Posaconazole.

Furthermore, this study will provide demographic details about the patients who encountered adverse events such as their age, sex etc. This information will help us find possible reasons for negative results and better understand patients who might be at risk.

In addition, the study will examine the temporal patterns of Posaconazole-related negative effects to find any patterns or shifts in how often they are reported over time. This research will contribute to our knowledge of Posaconazole's safety over a long period of time and assist in identifying any new safety issues that may arise.

In general, this thesis aims to give a complete drug profiling analysis of Posaconazole using information from FAERS. By studying the negative effects linked to Posaconazole in actual medical practice, we aim to enhance our knowledge of its safety record and make a valuable contribution to the field of drug safety monitoring. The results of this research will help doctors and nurses make wise choices about using Posaconazole, which will enhance patient safety.

Chapter 2

Materials and Methods

2.1. Data Source

2.1.1. FAERS Data

The FAERS database is a very important tool for gathering and studying information on adverse drug reactions and medication errors. The Food and Drug Administration (FDA) of the United States runs and relies on voluntary reporting from healthcare providers, individuals, and manufacturers These reports include many different unfavorable events, like adverse effects, medication errors, problems with product quality, and other concerns about safety.

The FAERS data is published every three months in seven separate documents, each with a specific purpose. These papers include:

Patient Demographic Information Form (DEMO): This document has the basic details of patients Demographic, who have experienced negative events which have been reported.

Drug/Biological Information Form (DRUG): This document gives details about the medicines or therapeutic products involved in adverse reactions, such as their name, strength, route of administration, and other important details.

The Adverse Reaction Form (REAC): includes in-depth information about adverse reactions that have been reported, including their explanation, seriousness, result, and any other relevant details.

Clinical Outcome Form (OUTC): It gives details about the clinical results of reported harmful incidents, such as whether the patient got better, had ongoing issues, or faced deadly outcomes.

Report Sources From (RPSR): This document contains records of adverse event reports, whether they came from a healthcare professional, consumer, or manufacturer.

Drug Therapy Start and End Date Form (THER): This form has details about when the drug therapy relating to the Adverse Reaction began and ended.

Use/Diagnosis Indication Form (INDI): This document includes details about the particular purpose or reason for which the medication was given or recommended.

The "primaryid" acts as an exclusive identifier for each record in the FAERS database. It functions as the main identifier that facilitates the connection and retrieval of data in all subordinate files.

In the previously mentioned examination, data from the FAERS database for the period between 2018 and 2022 (first quarter of 2018 to fourth quarter of 2022) was obtained. The information was given in zip files encoded in two formats, ASCII and XML. The information was analyzed using ASCII format data. After downloading and extracting the .zip file, we acquired seven .txt files containing the mentioned data. The document was subsequently introduced into statistical analysis software.

It is essential to acknowledge the limitations of the FAERS database. The data in the reports may lack necessary details, have mistaken or repetitions, and could be influenced by the tendency to underestimate or present distorted information. Furthermore, it is imperative to highlight that the database by itself does not establish a cause-and-effect relationship between a medication and a negative occurrence. However, in spite of these constraints, the FAERS database continues to be a valuable asset for recognizing potential safety indications and facilitating additional investigation and observation of medication safety.

2.1.2. Standardized Medical Terminology: Preferred Terms and System Organ Class

Adverse events in the FAERS database are recorded and sorted according to the Preferred Term (PT) framework that aligns with the hierarchical levels of the Medical Dictionary for Regulatory Activities (MedDRA) terminology. MedDRA is a standardized medical terminology created by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The MedDRA structure comprises multiple levels with the topmost and most comprehensive tier referred to as the System Organ Class (SOC). The SOC is further segmented into High-Level Group Words (HLGT), High-Level Words (HLT), Preferred Words (PT), and ultimately, the most detailed level known as Lowest Level Words (LLT). The PT intensity is employed in FAERS to communicate negative occurrences.

In order to link the relevant System Organ Class (SOC) with every Preferred Term (PT), the data is obtained from the MedDRA portal. In this instance, the data was acquired using MedDRA version 26.0. The acquired information consists of a grand total of 25,916 PTs and their respective associations with 27 SOC categories (English | MedDRA, n.d.).

This mapping between PT and SOC allows for the categorization and analysis of adverse events based on the specific organ system or physiological function affected. It provides a structured and standardized approach to organizing and understanding the reported adverse events within the FAERS database.

2.2. Deduplication of data

Following the suggestions of the FDA, a deduplication method was employed to ensure the reliability and credibility of the information utilized in this research. The deduplication procedure comprised of two stages to eradicate duplicate instances and keep the most pertinent and current data.

Analyzing instances with the same CASEIDs, which serve as distinct identifiers for FAERS cases, was the first phase. The latest FDA_DT, which shows the date the case was received by the FDA, was selected. When both the CASEID and FDA_DT were the same, the PRIMARYID, a distinct identifier for FAERS reports, was chosen based on the bigger value. This procedure was designed to protect the latest and pertinent data that is specific to each case (Chai et al., 2022; Liao et al., 2021).

The second phase of the deduplication process involved detecting duplicate cases by examining the existence of multiple matching identifiers. Situations with the same patient age, occurrence date, and patient weight, for example, were considered as duplicates In order to preserve the accuracy and prevent unnecessary repetition of data, one instance of these duplicated cases was eliminated from the entire dataset (Hu et al., 2020; Zhou et al., 2022).

2.3. Data Cleaning and Dataset Processing

The data extraction process involved extracting .txt files from an encoded ASCII Zip file, encompassing a five-year dataset. The individual files included the Patient Demographic Information Form (DEMO.txt), Drug/Biological Information Form (DRUG.txt), Adverse Reaction Form (REAC.txt), Clinical Outcome Form (OUTC.txt), and Reporting Source Form (RPSR.txt). Each of these files was combined individually and loaded into statistical software for subsequent analysis.

To ensure data quality and eliminate duplicate entries, the deduplication process focused on the demographic data. By applying deduplication criteria, duplicate entries within the demographic data were identified and removed. Once the deduplication was complete, all the combined files were merged using the unique identifier Primaryid, creating a consolidated dataset.

In order to enhance the analysis and improve understanding of adverse events, the MedDRA standardized terminology, specifically the System Organ Class (SOC), was incorporated into the merged dataset. This was achieved by mapping the Preferred Term (PT) to the corresponding SOC using MedDRA standards.

Furthermore, a separate dataset was filtered out from the merged dataset specifically for the drug Posaconazole. This filtration process involved searching for entries that included the keyword "Posacona" in both the drug name and active ingredient (prod_ai) fields. By filtering based on this criterion, a subset of data specifically related to Posaconazole was isolated for further analysis.

Using these two datasets, subsequent statistical analysis was conducted to explore and analyze the relevant patterns, trends, and associations related to adverse events associated with Posaconazole.

(Figure 2) below visually summarizes these sequential steps, providing a clear overview of the data cleaning and dataset creation process.

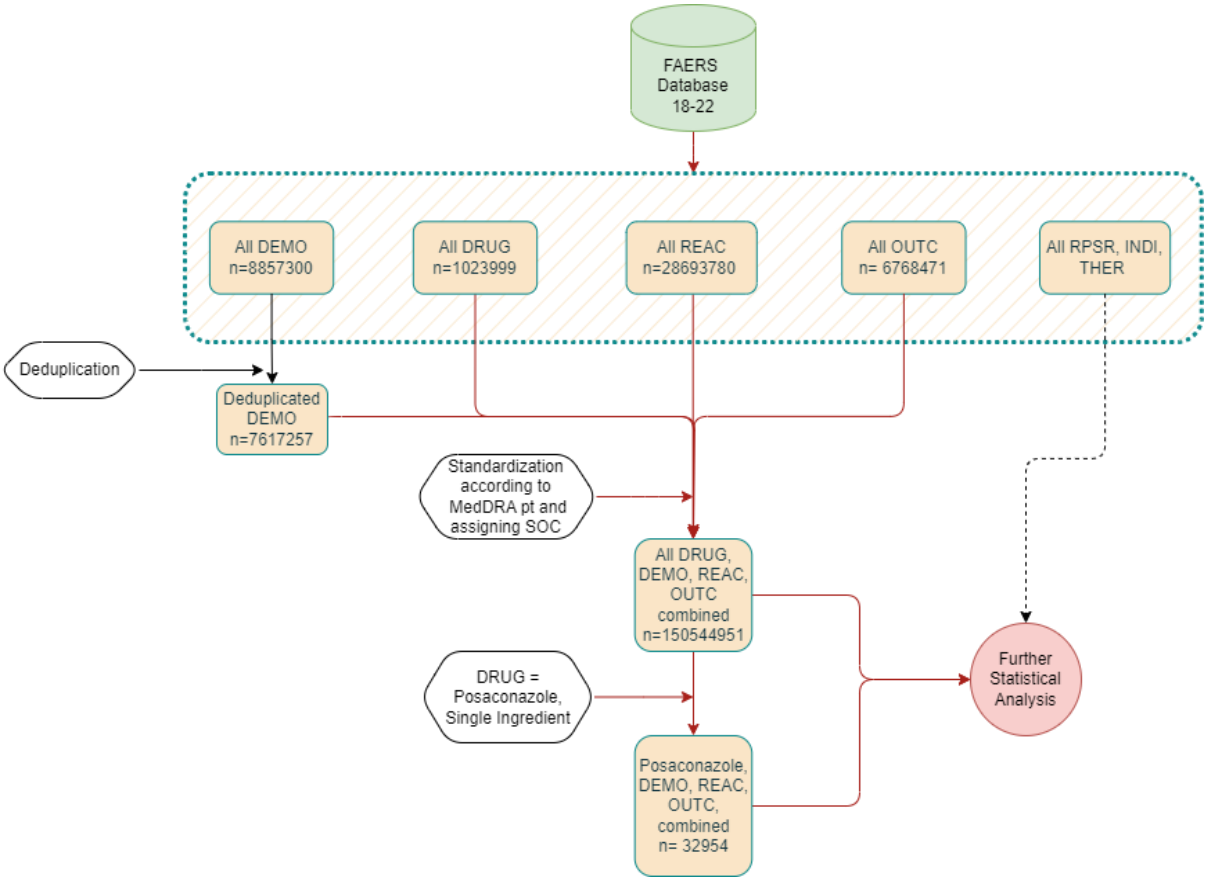

Figure 2. Major Steps in FAERS data processing.

2.4. Statistical Analysis

Examining the relative odds of specific adverse event reports associated with Posaconazole versus other drugs in the same Adverse event (AE), coded as PT, was the focus of this study's analysis. This evaluation relied heavily on the Reporting Odds Ratio as its primary statistical metric (ROR).

To determine the relationship between drugs and adverse reactions, a contingency table with the structure outlined in (Table 2) was constructed. This table provided a comprehensive overview of drug-adverse reaction combinations and served as the foundation for subsequent statistical analyses and investigations into disproportional relationships.

Table 2. Two–by–two contingency table and formula for ROR calculation with 95% CI

	Suspected pt	**All other pt**
Posaconazole	**a**	**b**
All other drug	**c**	**d**

$$\textbf{\textit{Reporting Odd Ratio (ROR)}} = \frac{a/c}{b/d}$$

$$\textbf{\textit{95\% Confidence interval (CI)}} = e^{\ln(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

For each drug-adverse event pair in the dataset, a simplified proportional analysis table was generated to facilitate analysis by researchers unfamiliar with large databases. This table emphasized the ROR and its associated 95% confidence interval (CI) as the primary data-mining tools for assessing associations between drugs and adverse events.

The Relative Reporting Odds Ratio (ROR) was employed to assess the likelihood of Posaconazole being associated with particular adverse events compared to other drugs. A higher ROR value indicated a stronger relationship between the drug and the specific adverse event under investigation. The utilization of the 95% confidence interval (CI) provided valuable information regarding the precision and uncertainty associated with the estimated ROR. By applying a statistical threshold whereby, the lower limit of the 95% CI exceeded 1, and at least three reports were available, signals were detected in the analysis, suggesting a potential association between Posaconazole and the adverse events of interest (Reynolds et al., 2016).

Statistical analysis and data visualization were performed using R studio software (R 4.2.1) and Microsoft Excel 2021.

Chapter 3

Results

3.1. Descriptive analysis

From a total of 150,544,951 reports detected in the FAERS database from 2018 to 2022, 32,954 reports were filtered for Posaconazole form 7165 unique case Id. Among these cases, a total of 2,359 different adverse events were reported in relation to Posaconazole. Out of these adverse events, 727 signals were identified based on the statistical analysis.

The following list presents the top 10 adverse events identified in (Table 3), which indicate significant signals based on their high Reporting Odds Ratio (ROR) values:

Table 3. Top 10 Adverse event based on ROR

pt	Case	ROR	Lower_CI	Upper_CI
Pseudoaldosteronism	92	1942.28	1521.99	2478.63
CARD9 deficiency	4	916.25	313.17	2680.67
Microsporum infection	8	581.74	278.77	1214
Left atrial hypertrophy	15	572.65	334.79	979.51
Acquired apparent mineralocorticoid excess	11	524.93	281.29	979.63
Donor leukocyte infusion	4	469.87	167.91	1314.86
SARS-CoV-2 RNA	4	458.12	163.91	1280.46
Lymphadenitis fungal	3	443.35	135.54	1450.19
Burkholderia cepacia complex sepsis	3	416.48	127.73	1357.98
Pseudohypoaldosteronism	9	408.23	206.44	807.26

Pseudoaldosteronism: 1942.28 (1521.99-2478.63), CARD9 deficiency: 916.25 (313.17-2680.67), Microsporum infection: 581.74 (278.77-1214.00), Left atrial hypertrophy: 572.65 (334.79-979.51), Acquired apparent mineralocorticoid excess: 524.93 (281.29-979.63), Donor leukocyte infusion: 469.87 (167.91-1314.86). SARS-CoV-2 RNA: 458.12 (163.91-1280.46), Lymphadenitis fungal: 443.35 (135.54-1450.19), Burkholderia cepacia complex sepsis: 416.48 (127.73-1357.98), Pseudohypoaldosteronism: 408.23 (206.44-807.26)

The following list presents the top 10 adverse events identified in (Table 4), which indicate significant signals based on their high case counts:

Table 4. Top 10 Adverse event based on case count.

pt	Case	ROR	Lower_CI	Upper_CI
Off label use	1002	2.04	1.92	2.17
Drug ineffective	823	1.44	1.35	1.54
Febrile neutropenia	702	13.42	12.47	14.46
Product use in unapproved indication	604	3.92	3.62	4.25
Pyrexia	557	2.72	2.5	2.95
Death	502	1.95	1.79	2.13
Pneumonia	440	2.26	2.06	2.48
Neutropenia	433	5.42	4.94	5.96
Drug interaction	423	4.75	4.32	5.22
Thrombocytopenia	289	4.52	4.03	5.08

Off label use had 1002 cases with a Reporting Odds Ratio (ROR) of 2.04 (1.92-2.17). Drug ineffective had 823 cases with an ROR of 1.44 (1.35-1.54). Febrile neutropenia had 702 cases with a significantly higher ROR of 13.42 (12.47-14.46). Product use in unapproved indication had 604 cases with an ROR of 3.92 (3.62-4.25). Pyrexia had 557 cases with an ROR of 2.72 (2.5-2.95). Death had 502 cases with an ROR of 1.95 (1.79-2.13). Pneumonia had 440 cases with an ROR of 2.26 (2.06-2.48). Neutropenia had 433 cases with an ROR of 5.42 (4.94-5.96). Drug interaction had 423 cases with an ROR of 4.75 (4.32-5.22). Thrombocytopenia had 289 cases with an ROR of 4.52 (4.03-5.08).

These adverse events showed significant associations with posaconazole based on their respective ROR values and the corresponding 95% confidence intervals.

3.2. Signal Strength by System Organ Class

Eight signals were identified after grouping the adverse events by System Organ Class (SOC) among 27 (Table 5). These signals (Figure 3) include the following

Table 5. Signal strength of AEs of Posaconazole at the System Organ Class (SOC) level.

SOC	Posa_count	ALL_except_posa_count	ROR	Lower_CI	Upper_CI
Blood and lymphatic system disorders	2384	2804951	3.89	3.74	4.05
Cardiac disorders	864	3181950	1.24	1.16	1.33
Congenital, familial and genetic disorders	106	344209	1.41	1.17	1.71
Ear and labyrinth disorders	34	552145	0.28	0.2	0.39
Endocrine disorders	239	459170	2.38	2.1	2.71
Eye disorders	457	2179470	0.96	0.88	1.05
Gastrointestinal disorders	2047	13006512	0.72	0.69	0.75
General disorders and administration site conditions	4951	24089465	0.94	0.92	0.97
Hepatobiliary disorders	812	1292845	2.88	2.69	3.08
Immune system disorders	806	1975445	1.87	1.74	2
Infections and infestations	5889	9524992	2.83	2.76	2.91
Injury, poisoning and procedural complications	2818	14335654	0.9	0.87	0.93
Investigations	2353	10976375	0.98	0.94	1.02
Metabolism and nutrition disorders	1037	3297665	1.44	1.36	1.53
Musculoskeletal and connective tissue disorders	752	10936758	0.32	0.29	0.34
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	726	4337139	0.77	0.71	0.82
Nervous system disorders	1579	10424266	0.69	0.66	0.73
Pregnancy, puerperium and perinatal conditions	0	391599	0	0	
Product issues	61	1019182	0.27	0.21	0.35
Psychiatric disorders	459	7422894	0.28	0.26	0.31
Renal and urinary disorders	920	4860652	0.87	0.81	0.93
Reproductive system and breast disorders	31	657241	0.22	0.15	0.31
Respiratory, thoracic and mediastinal disorders	1582	7599026	0.95	0.91	1
Skin and subcutaneous tissue disorders	815	8641064	0.43	0.4	0.46
Social circumstances	20	808007	0.11	0.07	0.18
Surgical and medical procedures	280	1530891	0.84	0.75	0.94
Vascular disorders	642	2992051	0.98	0.91	1.06

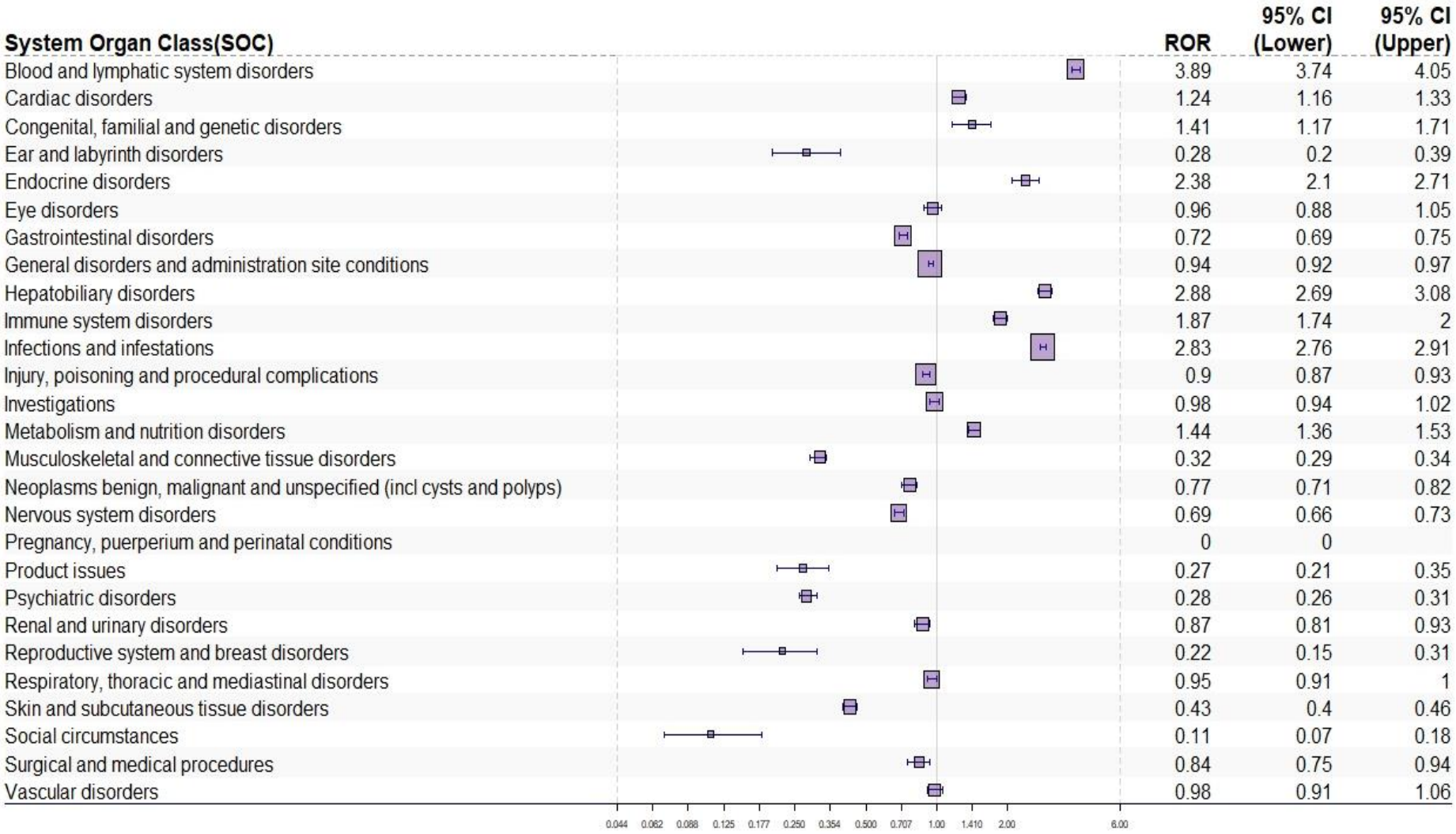

Figure 3. Forest plot of Posaconazole's AEs at the System Organ Class (SOC) level.

1. Blood and lymphatic system disorders showed a signal with a Relative Odds Ratio (ROR) of 3.89 (95% CI: 3.74 - 4.05).

2. Cardiac disorders exhibited a signal with an ROR of 1.24 (95% CI: 1.16 - 1.33).

3. Congenital, familial, and genetic disorders displayed a signal with an ROR of 1.41 (95% CI: 1.17 - 1.71),

4. Endocrine disorders demonstrated a signal with an ROR of 2.38 (95% CI: 2.10 - 2.71),

5. Hepatobiliary disorders showed a signal with an ROR of 2.88 (95% CI: 2.69 - 3.08),

6. Immune system disorders exhibited a signal with an ROR of 1.87 (95% CI: 1.74 - 2.00),

7. Infections and infestations displayed a signal with an ROR of 2.83 (95% CI: 2.76 - 2.91),

8. Metabolism and nutrition disorders demonstrated a signal with an ROR of 1.44 (95% CI: 1.36 - 1.53).

Out of the 27 System Organ Classes (SOC) analyzed, signals were not found for 18 SOC categories. Additionally, there was no response found for the SOC category "Pregnancy, puerperium, and perinatal conditions.

To provide a clearer visual representation, a forest plot has been included for better visualization of these signals.

3.3. Demographics

Within 7165 unique cases, the age range ≤17 includes 586 individuals, constituting approximately 8.18% of the total population. The age range 18-64 has the highest count, with 3111 individuals, accounting for about 43.42% of the total population. The age range 65-84 comprises 1677 individuals, representing approximately 23.41% of the total population. The age range 85< consists of 93 individuals, making up around 1.30% of the total population.

There are 1698 instances where age information is missing, accounting for approximately 23.70% of the total population (Table 6), The data is illustrated in a bar chart in (Figure 4).

Table 6. Age distribution of patients Posaconazole related AEs.

Age	Case	Percentage (%)
≤17	586	8.178646197
18-64	3111	43.41939986
65-84	1677	23.40544313
85<	93	1.297976274
Missing	1698	23.69853454

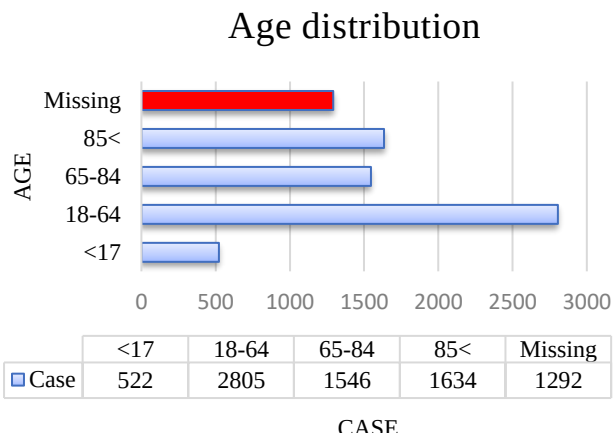

Figure 4. Bar Chart: Age distribution of patients Posaconazole related AEs.

Among the reported cases, 2475 individuals (34.54%) were classified as female, while 3846 individuals (53.68%) were classified as male (Table 7), depicted in (Figure 5) below.

Table 7. The gender distribution of AEs related to Posaconazole.

Gender	Case
Female	2475
Male	3846
Missing or unknown	844

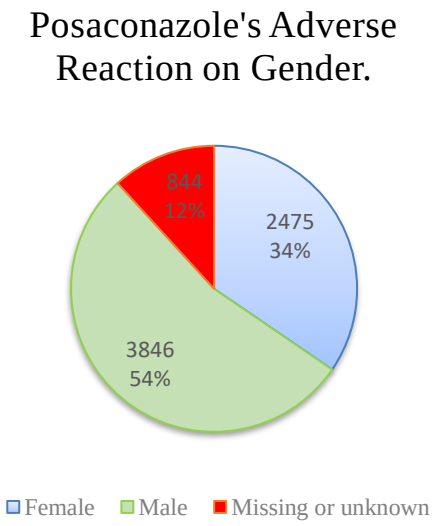

Figure 5. Pie Chart; The gender distribution of AEs related to Posaconazole.

There were also 844 cases where the gender information is either missing or unknown, which constitutes approximately 11.78% of the total population.

3.4. Outcome

Among the analyzed 7,156 unique cases, a total of 58,753 reports were included, covering 7 distinct outcomes. (Table 8) below showcases the distribution of reported outcomes in the pharmacovigilance analysis. The outcome with the highest count is "Other Serious (Important Medical Event)" with 24,151 cases, representing 41.1060% of the total reports. Following closely is "Hospitalization - Initial or Prolonged" with 19,073 cases, accounting for 32.4630% of the reports. "Life-Threatening" is reported in 5,187 cases, making up 8.8285% of the total. Instances of "Disability" were found in 719 cases, contributing 1.2238% to the overall distribution. The outcome "Required Intervention to Prevent Permanent Impairment/Damage" was reported in 23 cases, representing a minimal percentage of 0.0391%. A small number of reports (2 cases) were categorized as "Congenital Anomaly," comprising only 0.0034% of the total.

Lastly, the outcome "Death" was reported in 9,598 cases, accounting for 16.3362% of the reports. This data is depicted in a pie chart (Figure 6) below.

Table 8. Outcomes of AEs related to Posaconazole.

Outcome	Case
Other Serious (Important Medical Event)	24151
Hospitalization - Initial or Prolonged	19073
Death	9598
Life-Threatening	5187
Disability	719
Required Intervention to Prevent Permanent Impairment/Damage	23
Congenital Anomaly	2

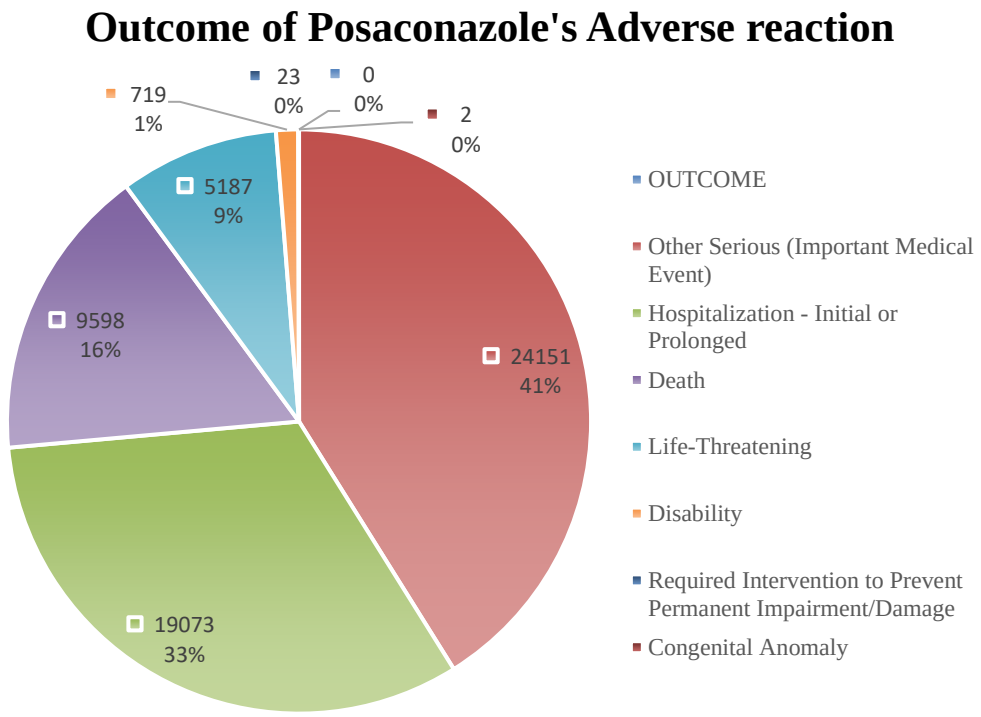

Figure 6. Pie Chart; Outcomes of AEs related to Posaconazole.

The summary of the top 10 reported adverse events and outcomes associated with the use of Posaconazole (Table 9):

Table 9. Top 10 cause of each outcome.

Outcome	pt	Case	Group %	Overall %
Congenital Anomaly	Hypotension	1	50.0000	0.0851
	Sepsis	1	50.0000	0.0851
Death	Acute myeloid leukaemia	119	1.2395	0.0021
	Death	494	5.1453	0.0088
	Drug ineffective	346	3.6038	0.0061
	Febrile neutropenia	136	1.4165	0.0024
	Multiple organ dysfunction syndrome	119	1.2395	0.0021
	Off label use	293	3.0518	0.0052
	Pneumonia	182	1.8956	0.0032
	Pyrexia	127	1.3228	0.0023
	Sepsis	136	1.4165	0.0024
	Septic shock	180	1.8748	0.0032
Disability	Acute kidney injury	26	3.6212	0.0062

	Contraindicated product administered	14	1.9499	0.0033
	Diarrhoea	14	1.9499	0.0033
	Dyspnoea	11	1.5320	0.0026
	Labelled drug-drug interaction medication error	14	1.9499	0.0033
	Malaise	17	2.3677	0.0040
	Nausea	21	2.9248	0.0050
	Pneumonia	11	1.5320	0.0026
	Pyrexia	15	2.0891	0.0036
	Vomiting	16	2.2284	0.0038
Hospitalization - Initial or Prolonged	Acute kidney injury	194	1.0178	0.0017
	Diarrhoea	186	0.9759	0.0017
	Drug ineffective	313	1.6422	0.0028
	Febrile neutropenia	511	2.6810	0.0046
	Neutropenia	232	1.2172	0.0021
	Off label use	392	2.0567	0.0035
	Pneumonia	351	1.8416	0.0031
	Pyrexia	397	2.0829	0.0035
	Sepsis	179	0.9391	0.0016
	Thrombocytopenia	179	0.9391	0.0016
Life-Threatening	Device related infection	48	0.9274	0.0016
	Drug ineffective	61	1.1785	0.0020
	Febrile neutropenia	136	2.6275	0.0045
	Hypotension	54	1.0433	0.0018
	Mucormycosis	48	0.9274	0.0016
	Off label use	72	1.3910	0.0024
	Pneumonia	96	1.8547	0.0032
	Pyrexia	113	2.1832	0.0037
	Respiratory failure	55	1.0626	0.0018
	Sepsis	84	1.6229	0.0028
	Septic shock	85	1.6422	0.0028
	Tachycardia	48	0.9274	0.0016
Other Serious (Important Medical Event)	Death	253	1.0464	0.0018
	Diarrhoea	255	1.0546	0.0018
	Drug ineffective	635	2.6262	0.0045
	Drug interaction	281	1.1622	0.0020
	Febrile neutropenia	502	2.0762	0.0035
	Neutropenia	401	1.6585	0.0028
	Off label use	557	2.3037	0.0039
	Pneumonia	309	1.2780	0.0022
	Product use in unapproved indication	311	1.2862	0.0022
	Pyrexia	375	1.5509	0.0026
Required Intervention to Prevent	Abdominal pain	1	4.5455	0.0077

Permanent Impairment/Damage	Acute kidney injury	1	4.5455	0.0077
	Asthenia	3	13.6364	0.0232
	Bronchopulmonary aspergillosis	1	4.5455	0.0077
	Cholangitis acute	1	4.5455	0.0077
	Cholecystitis acute	1	4.5455	0.0077
	Drug-induced liver injury	1	4.5455	0.0077
	Dysuria	2	9.0909	0.0155
	Hepatic enzyme increased	1	4.5455	0.0077
	Hypokalaemia	2	9.0909	0.0155
	Mental disorder	1	4.5455	0.0077
	Mycobacterium avium complex infection	1	4.5455	0.0077
	Pain in extremity	2	9.0909	0.0155
	Peripheral swelling	2	9.0909	0.0155
	Thrombocytosis	1	4.5455	0.0077
	Vomiting	1	4.5455	0.0077

1. Congenital Anomaly: Two cases of hypotension and sepsis were reported in infants with congenital anomalies. These cases accounted for 50% of the congenital anomaly group, with a prevalence of 0.0851% overall.

2. Death: Drug ineffectiveness was the most prevalent cause of Death with 3.6038% in the group of Death as outcomes and 0.0061% overall Outcome reported for posaconazole. Other causes reported for death associated with posaconazole use are death, acute myeloid leukemia, febrile neutropenia, and septic shock.

3. Disability: Acute kidney injury was the most frequently reported cause of disability, associated with the use of posaconazole, accounting for 3.6212% in the group and 0.0062% overall. Other frequently reported adverse events associated are, disability, diarrhea, dyspnea, malaise, nausea, pneumonia, pyrexia, and vomiting.

4. Hospitalization - Initial or Prolonged: The most prevalent cause for Hospitalization was febrile neutropenia, with 2.6810% in the group and 0.0046% overall due to

posaconazole use. Acute kidney injury, diarrhea, drug ineffectiveness, neutropenia, off-label use, pneumonia, pyrexia, sepsis, and thrombocytopenia are some top reported adverse events that lead to hospitalization.

5. Life-Threatening: Several life-threatening events were reported due to adverse events caused by posaconazole use, most frequent of them are device-related infection, drug ineffectiveness, febrile neutropenia, hypotension, mucormycosis, off-label use, pneumonia, pyrexia, respiratory failure, sepsis, septic shock, and tachycardia. Among them febrile neutropenia had the highest prevalence, accounting for 2.6275% in the group and 0.0045% overall.

6. Other Serious (Important Medical Event): Most frequently Reported events included death, diarrhea, drug ineffectiveness, drug interaction, febrile neutropenia, neutropenia, off-label use, pneumonia, product use in unapproved indication, and pyrexia. The most prevalent cause was drug ineffectiveness, accounting for 2.6262% in the group of other Serious (Important Medical Event) and 0.0045% overall Outcome reported.

7. Required Intervention to Prevent Permanent Impairment/Damage: Adverse events requiring intervention to prevent permanent impairment or damage included abdominal pain, acute kidney injury, asthenia, bronchopulmonary aspergillosis, cholangitis acute, cholecystitis acute, drug-induced liver injury, dysuria, hepatic enzyme increased, hypokalemia, mental disorder, Mycobacterium avium complex infection, pain in extremity, peripheral swelling, thrombocytosis, and vomiting.

3.5. Role of drugs

Among 32,954 cases the majority of cases involve drugs classified as Concomitant or Secondary Suspect Drugs, which account for 56% and 29% of the total cases, respectively.

On the other hand, the role codes Interacting and Primary Suspect Drug are reported in a smaller proportion of cases, representing approximately 4% and 11% of the total, respectively.

Table 10. Posaconazole's reported role in AEs.

Role_code	Case
Concomitant	18514
Interacting	1183
Primary Suspect Drug	3502
Secondary Suspect Drug	9696

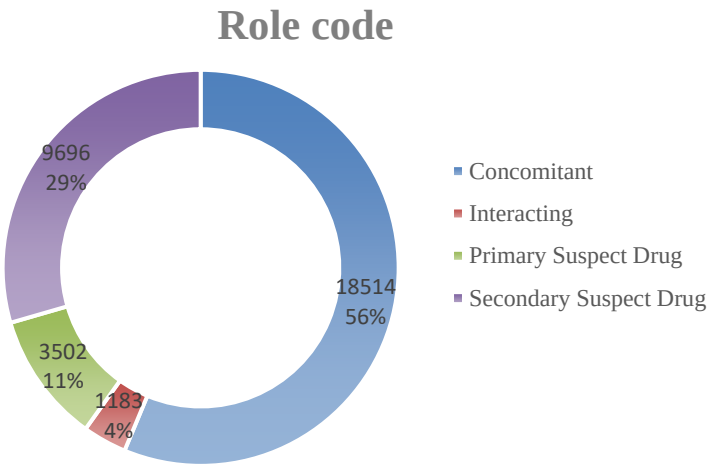

Figure 7. Pie Chart; Posaconazole's reported role in AEs.

These role codes suggest a lesser role or suspicion in adverse events compared to Concomitant and Secondary Suspect Drugs (Table 10). For better data visualization, the information depicted as a pie chart (**Error! Reference source not found.**).

Chapter 4

Discussion

The results of the pharmacovigilance analysis based on the FAERS database from 2018 to 2022 provide valuable insights into the adverse events associated with Posaconazole. From a total of 150,544,951 reports, 32,954 reports were filtered for Posaconazole, representing 7165 unique case IDs. Among these cases, a wide range of adverse events (2359) were reported, highlighting the potential risks and side effects of Posaconazole.

The statistical analysis found 727 signals that showed significant links between Posaconazole and certain side effects. The top 10 adverse effects with the highest ROR values were found, including Pseudoaldosteronism, CARD9 deficiency, Microsporum infection, and others. These adverse events should be closely monitored and considered during the use of Posaconazole, as their occurrence may have important clinical implications.

Based on the System Organ Class (SOC) grouping, further analysis showed that eight signals came from different organ systems. Posaconazole was linked to problems with the blood and lymphatic system, the liver and biliary system, infections and parasites, and other systems. These results show that there may be risks and problems in these areas, which should be carefully watched in Posaconazole patients.

The demographic analysis demonstrated the distribution of the reported instances based on age and sex. The majority of cases fell within the age range of 18 to 64, constituting 43.42% of the entire populace. Out of all the cases, 34.54% included females, whereas 53.68% involved males. The absent or unfamiliar age and gender details indicate a necessity for enhancing data gathering and reporting methods.

The analysis of reported outcomes revealed a diverse range of outcomes associated with Posaconazole. The most common outcome was "Other Serious (Important Medical Event)," followed by "Hospitalization - Initial or Prolonged" and "Death." These findings emphasize the importance of monitoring and managing the potential adverse effects of Posaconazole to ensure patient safety and well-being.

When it came to the role of drugs, Concomitant and Secondary Suspect Drugs were mentioned most often in Posaconazole-related side effects. This shows that they could be a cause of side effects and shows how important it is to look at the safety profiles of all drugs used to treat a patient.

After analyzing the data in this research with the clinical study data found in the FDA's prescribing information for Posaconazole (Noxafil®) (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., 2006) and the European Public Assessment Report (EPAR) published by the EMA for Posaconazole (Posaconazole Accord) (Accord Healthcare S.L.U., n.d.), no notable variations in reporting patterns were identified. This indicates that the consistent reporting of negative events is observed across various sets of data. Furthermore, no significant negative occurrences not previously documented in the aforementioned papers were identified in this thesis. These findings imply that the safety characteristics of Posaconazole remain in line with the details presented in regulatory documents.

Overall, this study shows how important pharmacovigilance analysis is to keep an eye, in order to figure out how safe and effective Posaconazole is for people's health as a whole. The complete look at adverse events, signal strength, demographic information, and medications given at the same time is helpful for healthcare professionals and regulators. By aligning with established regulatory sources, the assessment proves that Posaconazole has a reliable history of being safe in different sets of information. These conclusions can help with making

decisions, figuring out risks, and coming up with ways to lower the risk of harm from using Posaconazole.

Chapter 5

Limitation

It is important to note that this study has some limitations. The analysis is based on data from the FAERS database, which is susceptible to reporting bias (Kvist et al., 2021; Montastruc et al., 2011). Since FAERS relies on spontaneous reporting, different regions may have varying practices for reporting adverse events, leading to potential overreporting or underreporting. Healthcare professionals' awareness of specific adverse events can also influence reporting frequencies and patterns. Furthermore, variations in product label warnings and reporting requirements among countries may contribute to selective reporting, affecting the comparability of safety data (Montastruc et al., 2011).

Another limitation is the challenge of establishing a causal relationship between the reported adverse events and Posaconazole use (Nomura et al., 2015). The available FAERS data lack comprehensive patient information, medication use timelines, and confounder adjustments, making it difficult to assess the timing of events or account for potential confounding factors. Additionally, causality assessment can vary among reporters, and reports may come from different sources, potentially affecting the consistency of assessments. Therefore, the associations and safety signals identified should be interpreted cautiously, considering them as indications of higher-than-expected reporting rather than definitive evidence of causality (Nomura et al., 2015).

Lastly, relying solely on FAERS data may limit the ability to differentiate adverse events directly related to Posaconazole from those influenced by underlying confounding factors (Kvist et al., 2021; Montastruc et al., 2011). Factors like the nature of the treated disease, concurrent medications, or patient characteristics can independently contribute to adverse event occurrence. Although efforts were made to minimize confounding through age-

restricted analyses or subgroup comparisons, the presence of confounding factors cannot be completely ruled out. Thus, additional investigations using alternative data sources are necessary to address this limitation.

Chapter 6

Conclusion

In conclusion, this thesis conducted a drug profiling analysis of Posaconazole using real-world data from the FAERS database. The analysis identified 32,954 reports and 2,359 different adverse events related to Posaconazole, with 727 signals detected. The top 10 adverse events with the highest ROR values included pseudoaldosteronism, CARD9 deficiency, Microsporum infection, left atrial hypertrophy, acquired apparent mineralocorticoid excess, donor leukocyte infusion, SARS-CoV-2 RNA detection, diabetic retinopathy, tubulointerstitial nephritis, and cardiac arrest. The study provided demographic information about patients and found no significant trends in reporting frequency over time. While limitations exist, the findings contribute to our understanding of Posaconazole's safety profile and have implications for healthcare professionals and decision-makers. Further research, including controlled clinical trials, is needed to validate the identified adverse events and ensure patient safety.

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