Impact of regulatory decisions for drug safety surveillance: Interrupted time series analysis

**Version:** 0.2

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**Date:** July 9, 2024

**Acknowledgement:** The analysis is based in part on work from the Observational Health Sciences and Informatics collaborative. OHDSI (<http://ohdsi.org>) is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics.

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# List of abbreviations

ADR Adverse drug reaction

FDA Food and Drug Administration

EMA European Medicines Agency

MFDS Ministry of Food and Drug Safety

OHDSI Observational Health Data Sciences and Informatics

RMP Risk management plan

DUR Drug utilization review

FQ Fluoroquinolone

HES Hydroxy-ethyl starch

JAK inhibitor Janus kinase inhibitor

# Abstract

The growth rate occupies a high portion for chronic diseases, neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease, and disease found new treatments such as targeted therapies and the medication is particular importance to maintain a healthy life by curing and preventing diseases. However, all medications have double-edged sword, and it is essential to monitor adverse drug reaction (ADR) in order to avoid missing and manage fatal events. However, clinical trials are fixed size, duration, design, patient variability, range of exposure and indirect endpoint, which have limitations to identify impact of drug that are slow to develop, rare, or appear only in patients with relating diseases or drugs.

The governance as the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and Ministry of Food and Drug Safety (MFDS) are responsible for collecting and analyzing ADR reports, prompt issuing warnings, and changes the labeling. Medication use assessment has an important role in promoting the rational use of medicines. Prescribing pattern examining study is essential for policymakers and clinicians because it helps they make decisions to improve reasoning medication use at the national level. However, there is few previous studies that explored the prescription pattern for several drugs announced recently regulatory decisions.

In this study, we will conduct systematic study to investigate the monthly prescribing patterns (the number of patients prescribed drugs with safety warning, prescriptions, prescription duration, first prescription, and first prescription, days' supply of the first prescription) on warning drug. We will evaluate the effect of the regulatory decisions for drug safety surveillance on medication use using interrupted time series analysis.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | September 6, 2023 | SJ Kim | Initial draft |
| 0.2 | July 9, 2024 | SJ Kim, SB Kim | Revised statistical methods |

# Rationale and Background

The global expenditure for medicine has grown steadily which the compound annual growth rate is anticipated to be 3–6%, reaching approximately $1.6 trillion excluding COVID-19 vaccines in 2025.1, 2 The growth rate occupies a high portion for chronic diseases, neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease, and disease found new treatments such as targeted therapies and the medication is particular importance to maintain a healthy life by curing and preventing diseases.2, 3

However, all medications have double-edged sword, and it is essential to monitor adverse drug reaction (ADR) in order to avoid missing and manage fatal events.4 Overall incidences were 15.1% in ADR, 6.7% in serious adverse events, and 0.32% in fatal ADR among the hospitalized patients.5 In terms of economic burden, the incremental total healthcare costs for each patient for adverse drug events leading to hospitalization including preventable drug reaction ranged from €702.21 to €40,273.08 in non-hospitalized patients and €940.40 to €7,192.36 in hospitalized patients.6

In addition, clinical trials are fixed size, duration, design, patient variability, range of exposure and indirect endpoint, which have limitations to identify impact of drug that are slow to develop, rare, or appear only in patients with relating diseases or drugs.7 Therefore, ADRs are a more common challenge with a greater burden, and post-marketing drug safety surveillance become major healthcare activity for the patient safety since randomized controlled trials is difficult to comprehensively detect ADRs.4, 7

There are several organizations involved in the post-marketing identification of adverse effects. The World Health Organization-Uppsala Monitoring Center established in 1978 collects, screens and analyzes ADRs and provides data, tools, and training to pharmacovigilance professionals worldwide.8 The governance as the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and Ministry of Food and Drug Safety (MFDS) are responsible for collecting and analyzing ADR reports, prompt issuing warnings, and changes the labeling.9 Medication use assessment has an important role in promoting the rational use of medicines.10 Prescribing pattern examining study is essential for policymakers and clinicians because it helps they make decisions to improve reasoning medication use at the national level.2 However, there is few previous study that explored the prescription pattern for several drugs announced recently regulatory decisions. In this study we will perform to investigate the change of prescribing patterns after the regulatory decisions for drug safety surveillance on warning drugs.

# Study Objectives

## Hypothesis

This study’s hypothesis is:

Regulatory decisions on drug safety surveillance will impact the decisions of healthcare professionals. However, prescribing patterns will vary depending on the drugs and over time.

**Table 1**. List of drug exposures and information about safety issues from 2018 to 2021

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Regulatory actions** | **Drug** | **Date of regulatory decisions (FDA)** | **Date of regulatory decisions (MFDS)** | **Adverse drug reaction** |
| Announcement of safety alert | Fluoroquinolones (FQs) | 2018.07.10,  2018.12.20 | 2018.07.13,  2018.12.21 | Serious low blood sugar levels and mental health side effects  Aortic aneurysm and dissection |
| Febuxostat | 2019.02.21 | 2019.02.25 | Death |
| Ranitidine | 2019.09.13 | 2019.09.26 | Cancer (Excessive amounts of N-Nitrosodimethylamine) |
| Nizatidine | - | 2019.11.22 | Cancer (Excessive amounts of N-Nitrosodimethylamine) |
| Lorcaserin | 2020.01.14 | 2020.01.16 | Cancer |
| Hydroxyethyl Starch (HES) | 2021.07.07 | 2021.07.08 | Death, acute kidney injury and excess bleeding |
| Janus kinase inhibitors (JAK inhibitors) | 2021.09.01 | 2021.09.03 | Serious heart-related events, cancer, blood clots and death |
| Announcement of guide for drug safety | Phentermine, phendimetrazine, diethylpropion, mazindol, lorcaserin | - | 2018.01.15 | Overuse and misuse of psychotropic drugs |
| Notice on submission of risk management plan (RMP) | Phentermine, phendimetrazine, diethylpropion, mazindol | - | 2021.08.26 | Overuse and misuse of psychotropic drugs |
| Computerization to drug utilization review (DUR) system | Mirtazapine | - | 2016.12.30 | Drug-age conflict for younger than age 18 years (Contraindicated Drugs) |
| L-carbocisteine | 2017.11.06 | Drug-age conflict for younger than age 24 months (Contraindicated Drugs) |
| Tramadol | 2019.05.22 | Drug-age conflict for younger than age 12 years (Contraindicated Drugs) |
| Haloperidol | 2018.08.31 | Geriatric precaution (aged ≥ 65 years, drugs to be used with caution) |
| Chlorpheniramine | 2020.09.24 |
| Dimenhydrinate | 2020.09.24 |
| Hydroxyzine | 2020.09.24 |
| Oxybutynin | 2020.09.24 |
| Propiverine | 2020.09.24 |
| Solifenacin | 2020.09.24 |

## Objectives

* The overall goal of this protocols is conducting systematic study to investigate the monthly prescribing patterns (the number of patients prescribed drugs with safety warning, prescriptions, prescription duration, first prescription, and days' supply of the first prescription) before and after the regulatory decisions for drug safety surveillance on warning drug.
* We will also evaluate the effect of the regulatory decisions for drug safety surveillance on medication use using interrupted time series analysis.

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational, cross-sectional study. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘cross-sectional study’ one cohort is selected, and from these individuals, we calculate the occurrence of the events of interest at only one point in time. Interrupted time series analysis will be used to identify changes in patients and prescriptions patterns. We will use segmented regression models for the interrupted time series to quantify changes in level and slope of medication use over time.

## Study population

The target group is patients who used warning drugs (systemic FQs, febuxostat, ranitidine, nizatidine, phentermine, phendimetrazine, diethylpropion, mazindol, lorcaserin, HES, JAK inhibitors, mirtazapine, L-carbocisteine, tramadol, haloperidol, chlorpheniramine, dimenhydrinate, hydroxyzine, oxybutynin, propiverine and solifenacin) from January 1, 2006 to December 31, 2022 (Based on Korean 7 CDM databases included in the study).

### Inclusion criteria

All subjects in the database will be included who meet the following criteria:

* Users with warning drugs at least once from January 1, 2006 to December 31, 2022

The end of on-treatment duration is defined as the end of the exposure of the drug of interest.

### Subgroups

* First prescription among warning drug users

## Intervention

The definition of intervention is regulatory decisions for drug safety surveillance. The starting point of the intervention (intervention date) was defined to the next month to dates of regulatory action.

## Outcomes

#### Primary outcome

* Patients prescribed drugs with regulatory decisions
* Prescriptions for drugs with regulatory decisions
* Prescription duration for drugs with regulatory decisions

#### Secondary outcome

* First prescription for drugs with regulatory decisions
* Days' supply of the first prescription for drugs with regulatory decisions

# Data Analysis Plan

## Calculation of monthly number

**Primary analysis**

* Number of patients: We count the number of patients who were prescribed the target drug on the regulatory decisions relevant to safety alert, guide for drug safety, risk management plan and DUR for medicines by calendar date of each database.
* Number of prescriptions: We count the number of prescriptions for target drug by calendar date of each database.
* Prescription duration: We extract total prescription amount of target drug by calendar date of each database.

**Secondary analysis**

After extracting the earliest prescription per patient,

* Number of first prescriptions: The number of prescriptions is calculated by calendar date of each database.
* Days' supply of the first prescription: We extract prescription amount of target drug by calendar date of each database.

## Definition of start and end point

In this study, we identify the total collectable periods of the included databases.

**Start point**

* The latest between the analyzable start dates or the first marketing dates of each drug.

**End point**

* End point is defined as the latest end available date for analysis which can be observed at least 365 days after the intervention date.

## Investigation of monthly prescribing patterns

Monthly prescribing patterns (the number of patients prescribed drugs with safety warning, prescriptions, prescription duration, first prescription, and days' supply of the first prescription) will be obtained by sum of the frequencies calculated from each database drug between start point and end point.

### Statistical model for interrupted time series analysis

Interrupted time series analysis will be conducted to identify changes in patients and prescriptions patterns before and after the regulatory decisions for drug safety surveillance on warning drug. Interrupted time series analysis is known for robust methods because it can control by longitudinally tracking the events pre-post intervention.11

We will use segmented linear regression models for interrupted time series analysis. In the regression models, we will include time as a continuous variable to indicate baseline slope, a binary indicator variable indicating before or after the exposure to measure the level change, and the continuous variable that counted the number of months after the exposure to measure the changes in the slope. Additionally, we will include a month variable to adjust for seasonality.

To test for first-order autocorrelation in the model, we will examine the Durbin-Watson statistic. If first-order autocorrelation detect, we will use Prais-Winsten generalized least squares regression.11 Otherwise, we will use ordinary least squares regression with Newey-West standard errors to account for potential autocorrelation.12 A two-tailed value of P < 0.05 will be considered statistically significant.

## Analyses to perform

The following analyses will be performed:

* 19 target drugs: systemic FQs, febuxostat, ranitidine, nizatidine, lorcaserin, psychotropic drugs, psychotropic drugs without lorcaserin, HES, JAK inhibitors, mirtazapine, L-carbocisteine, tramadol, haloperidol, chlorpheniramine, dimenhydrinate, hydroxyzine, oxybutynin, propiverine and solifenacin
* 5 outcomes: the number of patients prescribed drugs with safety warning, prescriptions, prescription duration, first prescription, and first prescription, days' supply of the first prescription
* 1 model: segmented regression model

The total number of analyses is 95 (19 target drugs x 5 outcomes x 1 model) in each database.

## Output

A plot showing monthly prescribing patterns by calendar date will be provided. The final outcome model will be summarized by providing the pre-intervention slope, level change and slope change with 95% confidence interval.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>.

## Quality control

We will evaluate the impact of regulatory decisions by

* Interrupted time series analysis to control small number of events pre- and post-intervention through longitudinally tracking the outcome before and after an intervention.
* Durbin-Watson statistic to test the existence of first-order autocorrelation. Newey-West standard errors to account for potential autocorrelation in the model.

## Strengths and Limitations of the Research Methods

Strength

* The common data model use standard vocabularies ensuring portability of phenotypes and interoperability. The use of a federated study model will ensure no movement of patient-level data from institutions participating in this analysis. This is critically important to ensure the protection of patient privacy in the secondary use of routinely collected patient data.
* Interrupted time series analysis is known for robust methods because it can control by longitudinally tracking the events pre-post intervention.
* To obtain robust and unbiased estimators using segmented regression model, we will adjust the seasonality and autocorrelation in the time-series. By including month variable as independent variable in the segmentation model, we will adjust the seasonality. Also, we will test autocorrelation of error terms and adjust the autocorrelation by using Prais-Winsten generalized least squares regression or Newey-West standard errors.

Limitations

* Medication records indicate that an individual was prescribed or dispensed a particular drug, but this does not necessarily mean that an individual took the drug as originally prescribed or dispensed.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

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10 Bilal AI, Osman ED, Mulugeta A. Assessment of medicines use pattern using World Health Organization’s prescribing, patient care and health facility indicators in selected health facilities in eastern Ethiopia. BMC health services research. 2016;16:1-8.

11 Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of Public Health Interventions: A tutorial. International Journal of Epidemiology. 2017;46.1: 348-355.

12 Newey WK, West KD. A simple, positive semi-definite, heteroskedasticity and autocorrelation consistent covariance matrix. Econometrica 1987;55:703.

Appendix: Concept Set Definitions

1. Systemic fluoroquinolones

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40161662 | besifloxacin | Drug | RxNorm | NO | YES | NO |
| 42613186 | besifloxacin Ophthalmic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 2909524 | besifloxacin Ophthalmic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 40161667 | besifloxacin Ophthalmic Suspension | Drug | RxNorm | YES | YES | NO |
| 43534863 | besifloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 1797513 | ciprofloxacin | Drug | RxNorm | NO | YES | NO |
| 42479725 | Ciprofloxacin / Dexamethasone Otic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 40028359 | ciprofloxacin / dexamethasone Otic Suspension | Drug | RxNorm | YES | YES | NO |
| 42629035 | ciprofloxacin / fluocinolone Otic Solution | Drug | RxNorm | YES | YES | NO |
| 42965658 | Ciprofloxacin / fluocinolone Topical Solution | Drug | RxNorm Extension | YES | YES | NO |
| 43258666 | Ciprofloxacin / Hydrocortisone Otic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 40028361 | ciprofloxacin / hydrocortisone Otic Suspension | Drug | RxNorm | YES | YES | NO |
| 36269500 | Ciprofloxacin Mucous Membrane Topical Solution | Drug | RxNorm Extension | YES | YES | NO |
| 40028718 | ciprofloxacin Ophthalmic Ointment | Drug | RxNorm | YES | YES | NO |
| 40028720 | ciprofloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 40160496 | ciprofloxacin Otic Solution | Drug | RxNorm | YES | YES | NO |
| 35605255 | ciprofloxacin Otic Suspension | Drug | RxNorm | YES | YES | NO |
| 35857832 | ciprofloxacin Topical Gel | Drug | RxNorm Extension | YES | YES | NO |
| 35857838 | ciprofloxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 43534858 | ciprofloxacin; ophthalmic (fluoroquinolones) | Drug | ATC | YES | YES | NO |
| 21605196 | ciprofloxacin; ophthalmic, otic (antiinfectives) | Drug | ATC | YES | YES | NO |
| 21605161 | ciprofloxacin; otic | Drug | ATC | YES | YES | NO |
| 21603009 | ciprofloxacin; systemic | Drug | ATC | NO | YES | NO |
| 1592954 | delafloxacin | Drug | RxNorm | NO | YES | NO |
| 715911 | delafloxacin; systemic | Drug | ATC | NO | YES | NO |
| 1743222 | enoxacin | Drug | RxNorm | NO | YES | NO |
| 35860696 | enoxacin Ophthalmic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 35860698 | enoxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 21603011 | enoxacin; oral | Drug | ATC | NO | YES | NO |
| 19050750 | fleroxacin | Drug | RxNorm | NO | YES | NO |
| 21603015 | fleroxacin; systemic | Drug | ATC | NO | YES | NO |
| 35197938 | garenoxacin mesilate hydrate | Drug | RxNorm Extension | NO | YES | NO |
| 21603026 | garenoxacin; systemic | Drug | ATC | NO | YES | NO |
| 1789276 | gatifloxacin | Drug | RxNorm | NO | YES | NO |
| 35858962 | gatifloxacin Ophthalmic Gel | Drug | RxNorm Extension | YES | YES | NO |
| 40059607 | gatifloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 43534861 | gatifloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 21603023 | gatifloxacin; systemic | Drug | ATC | NO | YES | NO |
| 1716721 | gemifloxacin | Drug | RxNorm | NO | YES | NO |
| 21603022 | gemifloxacin; oral | Drug | ATC | NO | YES | NO |
| 1747032 | grepafloxacin | Drug | RxNorm | NO | YES | NO |
| 21603018 | grepafloxacin; oral | Drug | ATC | NO | YES | NO |
| 35834909 | lascufloxacin hydrochloride | Drug | RxNorm Extension | NO | YES | NO |
| 947811 | lascufloxacin; oral | Drug | ATC | NO | YES | NO |
| 1742253 | levofloxacin | Drug | RxNorm | NO | YES | NO |
| 35861002 | levofloxacin Ophthalmic Gel | Drug | RxNorm Extension | YES | YES | NO |
| 40001157 | levofloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 35860990 | levofloxacin Otic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 43534860 | levofloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 21603019 | levofloxacin; systemic | Drug | ATC | NO | YES | NO |
| 1707800 | lomefloxacin | Drug | RxNorm | NO | YES | NO |
| 40059318 | lomefloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 35144130 | lomefloxacin Otic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 35862078 | lomefloxacin Topical Gel | Drug | RxNorm Extension | YES | YES | NO |
| 35862084 | lomefloxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 2052955 | lomefloxacin Topical Solution | Drug | RxNorm Extension | YES | YES | NO |
| 43534859 | lomefloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 21603014 | lomefloxacin; systemic | Drug | ATC | NO | YES | NO |
| 1716903 | moxifloxacin | Drug | RxNorm | NO | YES | NO |
| 40057467 | moxifloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 43534862 | moxifloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 21603021 | moxifloxacin; systemic | Drug | ATC | NO | YES | NO |
| 36878831 | nadifloxacin | Drug | RxNorm Extension | NO | YES | NO |
| 43678347 | nadifloxacin Topical Cream | Drug | RxNorm Extension | YES | YES | NO |
| 35154779 | nadifloxacin Topical Lotion | Drug | RxNorm Extension | YES | YES | NO |
| 35141912 | nadifloxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 45893527 | nadifloxacin; topical | Drug | ATC | YES | YES | NO |
| 1721543 | norfloxacin | Drug | RxNorm | NO | YES | NO |
| 40066892 | norfloxacin Ophthalmic Ointment | Drug | RxNorm | YES | YES | NO |
| 40066893 | norfloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 35861725 | norfloxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 43534857 | norfloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 21603013 | norfloxacin; oral | Drug | ATC | NO | YES | NO |
| 923081 | ofloxacin | Drug | RxNorm | NO | YES | NO |
| 43695029 | Ofloxacin Ophthalmic Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 40069651 | ofloxacin Ophthalmic Solution | Drug | RxNorm | YES | YES | NO |
| 40069655 | ofloxacin Otic Solution | Drug | RxNorm | YES | YES | NO |
| 35851383 | ofloxacin Topical Gel | Drug | RxNorm Extension | YES | YES | NO |
| 35851392 | ofloxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 43534856 | ofloxacin; ophthalmic | Drug | ATC | YES | YES | NO |
| 21605162 | ofloxacin; otic | Drug | ATC | YES | YES | NO |
| 21603008 | ofloxacin; systemic | Drug | ATC | NO | YES | NO |
| 35198003 | pazufloxacin mesilate | Drug | RxNorm Extension | NO | YES | NO |
| 35851732 | pazufloxacin mesilate Ophthalmic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 21603025 | pazufloxacin; parenteral | Drug | ATC | NO | YES | NO |
| 19027679 | pefloxacin | Drug | RxNorm | NO | YES | NO |
| 35856292 | pefloxacin Topical Ointment | Drug | RxNorm Extension | YES | YES | NO |
| 21603010 | pefloxacin; systemic | Drug | ATC | NO | YES | NO |
| 35197897 | prulifloxacin | Drug | RxNorm Extension | NO | YES | NO |
| 21603024 | prulifloxacin; oral | Drug | ATC | NO | YES | NO |
| 35198165 | sitafloxacin hydrate | Drug | RxNorm Extension | NO | YES | NO |
| 40256175 | sitafloxacin; oral | Drug | ATC | NO | YES | NO |
| 1733765 | sparfloxacin | Drug | RxNorm | NO | YES | NO |
| 21603016 | sparfloxacin; oral | Drug | ATC | NO | YES | NO |
| 19041153 | temafloxacin | Drug | RxNorm | NO | YES | NO |
| 21603012 | temafloxacin; oral | Drug | ATC | NO | YES | NO |
| 43009030 | tosufloxacin tosylate hydrate | Drug | RxNorm Extension | NO | YES | NO |
| 42961482 | tosufloxacin tosylate hydrate Ophthalmic Solution | Drug | RxNorm Extension | YES | YES | NO |
| 715910 | tosufloxacin; systemic | Drug | ATC | NO | YES | NO |
| 1712549 | trovafloxacin | Drug | RxNorm | NO | YES | NO |
| 21603020 | trovafloxacin; systemic | Drug | ATC | NO | YES | NO |

2. Febuxostat

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 19017742 | febuxostat | Drug | RxNorm | NO | YES | NO |
| 21604133 | febuxostat; oral | Drug | ATC | NO | YES | NO |

3. Ranitidine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 961047 | ranitidine | Drug | RxNorm | NO | YES | NO |
| 21600083 | ranitidine; systemic | Drug | ATC | NO | YES | NO |

4. Nizatidine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 950696 | nizatidine | Drug | RxNorm | NO | YES | NO |
| 21600085 | nizatidine; systemic | Drug | ATC | NO | YES | NO |

5. Lorcaserin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 43534746 | lorcaserin; oral | Drug | ATC | NO | YES | NO |
| 42873635 | lorcaserin | Drug | RxNorm | NO | YES | NO |

6. Psychotropic drugs without lorcaserin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 725822 | diethylpropion | Drug | RxNorm | NO | YES | NO |
| 21600682 | phentermine; oral | Drug | ATC | NO | YES | NO |
| 735340 | phentermine | Drug | RxNorm | NO | YES | NO |
| 723344 | phendimetrazine | Drug | RxNorm | NO | YES | NO |
| 21600686 | mazindol; oral | Drug | ATC | NO | YES | NO |
| 794229 | mazindol | Drug | RxNorm | NO | YES | NO |
| 21600684 | amfepramone; oral | Drug | ATC | NO | YES | NO |

7. Hydroxyethyl Starch

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 19077117 | hetastarch | Drug | RxNorm | NO | YES | NO |
| 40161354 | pentastarch | Drug | RxNorm | NO | YES | NO |
| 42918540 | 500 ML Hetastarch 60 MG/ML / Sodium Chloride 9 MG/ML Injectable Solution | Drug | RxNorm Extension | NO | YES | NO |
| 42918542 | 500 ML Hetastarch 60 MG/ML / Magnesium Chloride 0.3 MG/ML / Potassium Chloride 0.3 MG/ML / Sodium Acetate Trihydrate 4.63 MG/ML / Sodium Chloride 6 MG/ML Injectable Solution | Drug | RxNorm Extension | NO | YES | NO |
| 42918295 | 500 ML Pentastarch 100 MG/ML Pen Injector | Drug | RxNorm Extension | NO | YES | NO |
| 42918546 | 500 ML calcium chloride, dihydration 0.37 MG/ML / Hetastarch 60 MG/ML / Magnesium Chloride 0.2 MG/ML / malic acid 0.67 MG/ML / Potassium Chloride 0.3 MG/ML / ... Injectable Solution | Drug | RxNorm Extension | NO | YES | NO |
| 42918564 | 500 ML Calcium Chloride 0.37 MG/ML / Glucose 0.92 MG/ML / Hetastarch 60 MG/ML / Lactate 5 MG/ML / Magnesium Chloride 0.09 MG/ML / Potassium Chloride 0.222 MG/ML / ... Injectable Solution | Drug | RxNorm Extension | NO | YES | NO |
| 21601144 | hydroxyethylstarch; parenteral | Drug | ATC | NO | YES | NO |

8. Janus kinase inhibitors

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 43534821 | tofacitinib; oral | Drug | ATC | NO | YES | NO |
| 42904205 | tofacitinib | Drug | RxNorm | NO | YES | NO |
| 1123897 | baricitinib; oral | Drug | ATC | NO | YES | NO |
| 1510627 | baricitinib | Drug | RxNorm | NO | YES | NO |
| 1361580 | upadacitinib | Drug | RxNorm | NO | YES | NO |
| 715836 | upadacitinib; oral | Drug | ATC | NO | YES | NO |
| 43534821 | tofacitinib; oral | Drug | ATC | NO | YES | NO |

9. Mirtazapine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40065512 | mirtazapine Disintegrating Oral Tablet | Drug | RxNorm | NO | YES | NO |
| 40065515 | mirtazapine Oral Tablet | Drug | RxNorm | NO | YES | NO |

10. L-carbocisteine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40021844 | carbocysteine Oral Capsule | Drug | RxNorm | NO | YES | NO |
| 42947974 | Carbocysteine Oral Suspension | Drug | RxNorm Extension | NO | YES | NO |

11. Tramadol

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40089949 | tramadol Extended Release Oral Capsule | Drug | RxNorm | NO | YES | NO |
| 40089957 | tramadol Oral Capsule | Drug | RxNorm | NO | YES | NO |
| 40089951 | tramadol Extended Release Oral Tablet | Drug | RxNorm | NO | YES | NO |
| 37593169 | Tramadol Delayed Release Oral Tablet | Drug | RxNorm Extension | NO | YES | NO |
| 43173829 | Tramadol Effervescent Oral Tablet | Drug | RxNorm Extension | NO | YES | NO |
| 40089954 | tramadol Injectable Solution | Drug | RxNorm | NO | YES | NO |
| 36894467 | Tramadol Injection | Drug | RxNorm Extension | NO | YES | NO |

12. Haloperidol

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40046616 | haloperidol Oral Tablet | Drug | RxNorm | NO | YES | NO |
| 40046606 | haloperidol Injectable Solution | Drug | RxNorm | NO | YES | NO |
| 35603237 | haloperidol Injection | Drug | RxNorm | NO | YES | NO |

13. Chlorpheniramine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40023993 | chlorpheniramine Oral Tablet | Drug | RxNorm | NO | YES | NO |
| 40023990 | chlorpheniramine Oral Capsule | Drug | RxNorm | NO | YES | NO |
| 36885613 | Chlorpheniramine Oral Granules | Drug | RxNorm Extension | NO | YES | NO |
| 40023991 | chlorpheniramine Oral Solution | Drug | RxNorm | NO | YES | NO |
| 40023992 | chlorpheniramine Oral Suspension | Drug | RxNorm | NO | YES | NO |
| 40023987 | chlorpheniramine Injectable Solution | Drug | RxNorm | NO | YES | NO |

14. Dimenhydrinate

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40036299 | dimenhydrinate Oral Tablet | Drug | RxNorm | NO | YES | NO |
| 40036296 | dimenhydrinate Oral Solution | Drug | RxNorm | NO | YES | NO |
| 42481557 | Dimenhydrinate Oral Suspension | Drug | RxNorm Extension | NO | YES | NO |
| 40036285 | dimenhydrinate Chewable Tablet | Drug | RxNorm | NO | YES | NO |

15. Hydroxyzine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40051980 | hydroxyzine Oral Suspension | Drug | RxNorm | NO | YES | NO |
| 40051982 | hydroxyzine Oral Tablet | Drug | RxNorm | NO | YES | NO |

16. Oxybutynin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40102617 | oxybutynin Oral Tablet | Drug | RxNorm | NO | YES | NO |

17. Propiverine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 40102657 | propiverine Oral Tablet | Drug | RxNorm | NO | YES | NO |

18. Solifenacin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 42967863 | Solifenacin Disintegrating Oral Tablet | Drug | RxNorm Extension | NO | YES | NO |
| 40083654 | solifenacin Oral Tablet | Drug | RxNorm | NO | YES | NO |