

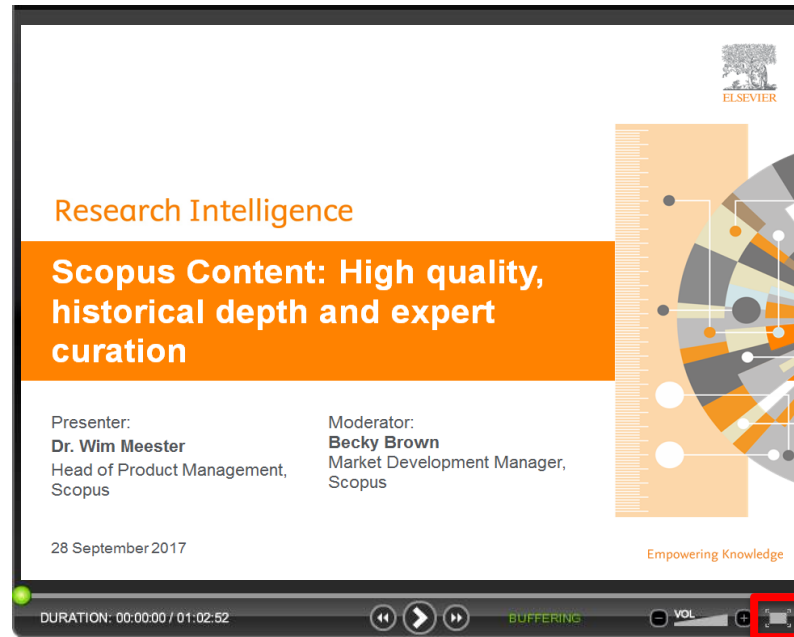
Introduction to PharmaPendium: Leveraging FDA and EMA drug approval data



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We suggest viewing the presentation in full screen



Agenda

- Overview
- Focus on:
 - Content
 - Taxonomies
- Text searching vs extracted information
- Example use cases showing:
 - Types of searching (extracted vs text)
 - Drug safety search
 - FAERS

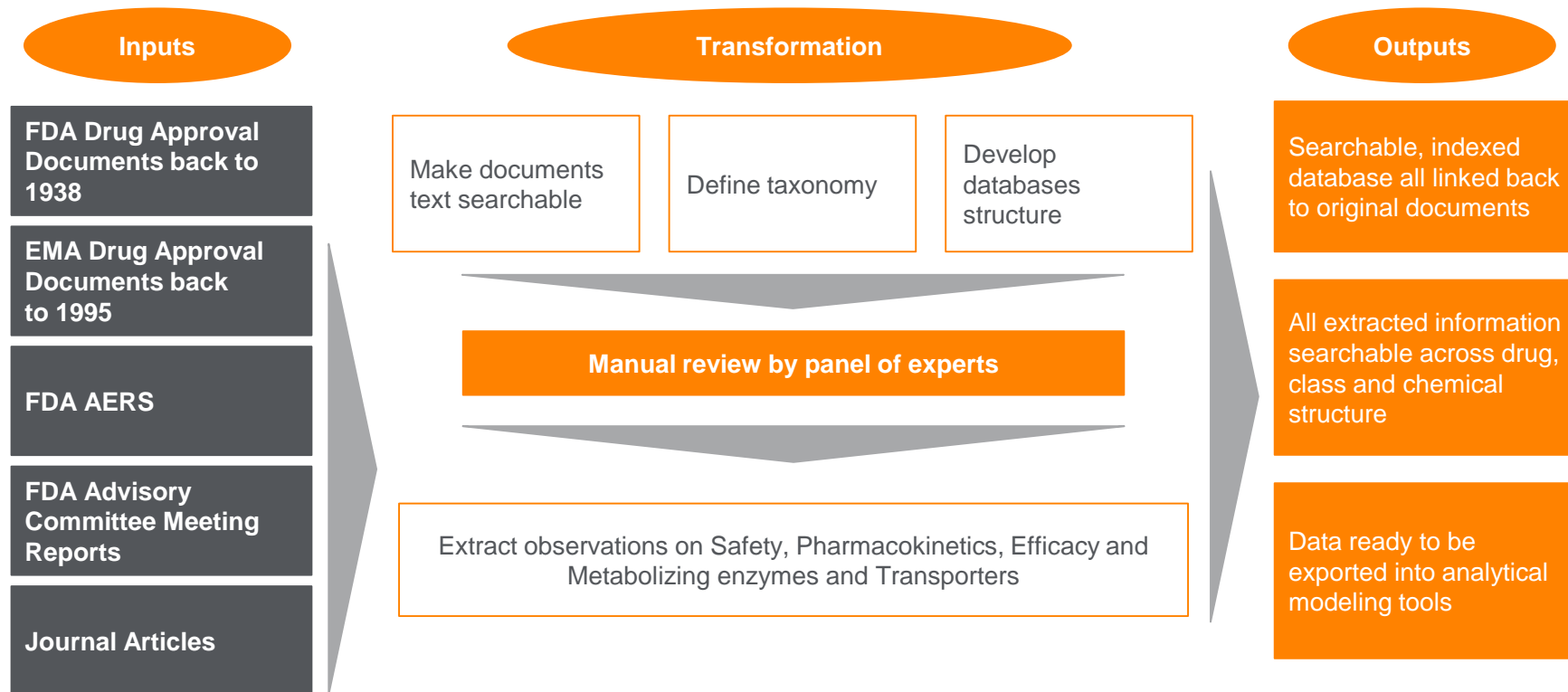
Critical decision-support



- ✓ Leverage past drug approvals to inform bottleneck issues
- ✓ Design studies that provide the most meaningful data
- ✓ Reduce unnecessary preclinical and clinical costs by comparing your drug to successful ones
- ✓ Rapidly evaluate potential DDI risks

PharmaPendium

Our Process and Industry's challenge – making regulatory documents accessible



A critical decision-support tool

searchable FDA/EMA Drug Approval Docs, extracted data, expert taxonomies and prediction tools

Text searchable Content

FDA approval packages (1938 – now)

EMA approval packages (1995 – now)

FDA Advisory Committee Meetings

DESI (Drug Efficacy Study Implement'n)

Meyler's, Mosby's

FAERS (FDA Adverse Event Reporting System)

Summary Table and Visualization Analysis

Content

Manually
extracted
data

Taxonomies/
Search
Strategies

Preclinical AND Clinical

Drug Safety data

Pharmacokinetic data

Met. Enzymes and Transporters data

Efficacy data

Activity data

Prediction Tools

DDI Risk Calculator

Drugs/Drug Classes

Targets/Target Classes

MedDRA (Adverse Events)

Indications

Chemical Structures/Substructure

Species

Concomitants (*coming soon!*)

Endpoints

.....and more!

Our users report that PharmaPendium *supports confident decision-making and informs product positioning*

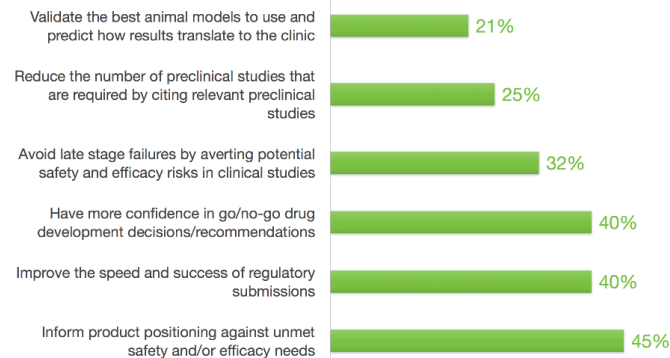
Why is that critical?

72% of surveyed research organizations agree that PharmaPendium provides important **insights that impact the success of a project.**

ELSEVIER PHARMAPENDIUM CUSTOMER RESEARCH

Users report improved speed, success, and confidence with PharmaPendium

PharmaPendium helps me support the following business objectives for my company:



Source: TechValidate survey of 110 users of Elsevier PharmaPendium

ELSEVIER

TechValidate

Validated

Published: Jun. 28, 2017 TVID: B58-B5C-D77

How PharmaPendium supports phases along the Drug Development pipeline



R&D Phase	Information in PharmaPendium helps you to:
Preclinical	<ul style="list-style-type: none">• Determine Drug Safety assessments on lead candidates• Anticipate drug-drug interactions and other adverse events• Optimize <i>in vivo</i> / <i>in vitro</i> study designs, select and prioritize leads• Increase chances of successful submissions to regulatory authorities based on past precedents• Leverage drug precedents to help translate preclinical data into human effects / outcomes
Clinical	<ul style="list-style-type: none">• Examine on- and off-target effects to predict adverse events• Examine drug approval packages to inform clinical study designs (population, indications, endpoints, etc)
Post-launch	<ul style="list-style-type: none">• Leverage lessons learned to:<ul style="list-style-type: none">• Develop risk management and strategic programs,• Improve clinical trial design• Monitor AERS reports for to identify post marketing safety concerns

How can PharmaPendium be used?

Example User Questions:

Can I find safety, efficacy and DMPK data to support my analysis of in vitro and in vivo test results?

Can I compare my drug to approved drugs to help optimize my drug safety analyses and trial design?

How can I assess PK parameters and potential drug-drug interaction risks for my drug candidate?

What support can I get for making my case to the regulatory authorities?

What are the efficacy benchmarks that must be met to compete?

Which primary endpoints were used during Phase III clinical trials for similar drugs?

Can I cite a previously-run experiment from a similar drug?

Possible use cases:



Prioritize drug candidates

Assess small and large molecule drug safety



Anticipate and mitigate risk

Answer which drug candidate to progress



Content and value is continually growing

Source Documents

2.4M+

pages of FDA
approval
documents

215K+

pages of EMA
approval
documents

10.4M+

FDA AERS
reports

690K+

Pages from FDA
Advisory
Committee
Meetings

Extracted Data

4527

Drugs indexed
& fully
searchable

1.64M+

PK data lines

315K+

Metabolizing
enzyme and
transporter data
lines

1.78M+

safety data lines

2.71M+

efficacy data
lines

115K

activity data lines

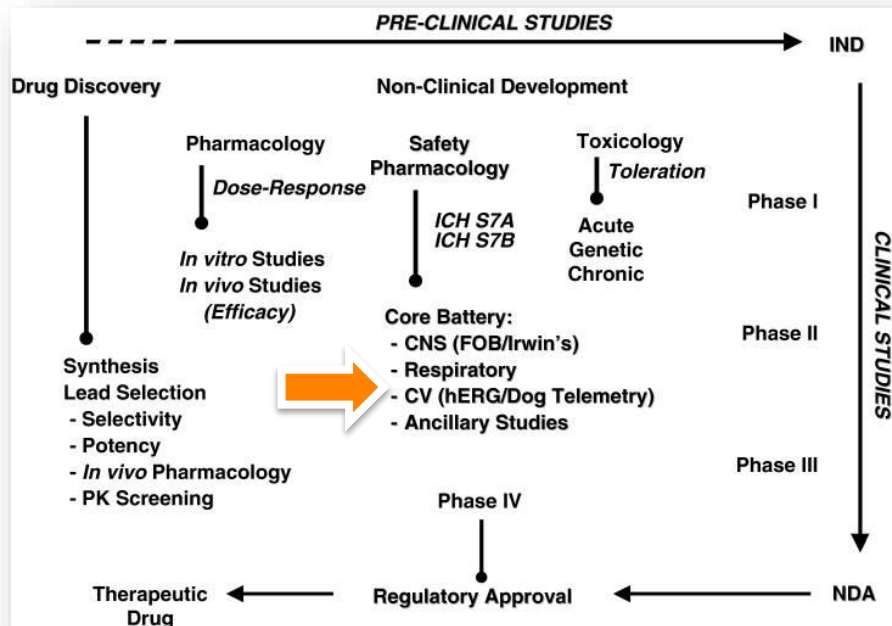
Information is organised around unique taxonomies

- Adverse effects taxonomy
 - Taxonomy contains MedDRA preferred terms and synonyms linked to MedDRA preferred terms
- Targets taxonomy
 - Target information and the relationship between targets and drugs comes from xPharm, drug labels and FDA Approval Packages
- Endpoint taxonomy
 - Developed in-house
- Indications taxonomy
 - Based on MedDRA with additional indications from Mosby's
- Drug names
 - FDA generic drug names are the main PharmaPendium drug name
 - European drug names are taken primarily from Meyler's
 - Synonyms are linked to the main drug name
 - Excerpted PK, MET and efficacy data based on defined thesauri/parameters

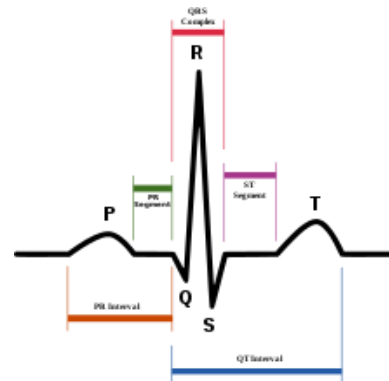
$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{-(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

Demo

Safety pharmacology – QT prolongation studies



QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like **torsades de pointes** and a **risk factor for sudden death**.



Since 2005, the FDA and EMA have required that **nearly all new molecular entities be evaluated in a Thorough QT (TQT) study** to determine a drug's effect on the QT interval.

What effects on QT prolongation have been observed in drugs that act on the same target?

The screenshot displays the DrugTarget database interface. On the left, a navigation menu highlights 'Targets'. The main content area shows a hierarchical tree of targets, with 'Cyclin-dependent kinase (CDK) 4 and 6' selected. To the right, a panel provides details for this target, including a list of drugs where it is the primary target (Palbociclib and Ribociclib) and links to various data sources. An orange arrow points to the 'View Drug Safety Data' link. Below this, a table titled 'Adverse Effects / Toxicity (for drugs that interact with this target)*:' shows the number of drugs associated with specific adverse effects, categorized by preclinical and clinical data.

Browse ▾ Search ▾ My tools new

Drugs

Adverse Effects/Toxicity

Targets

Indications

Find adverse effect/toxicity data across pre

Browse targets

🔍 cyclin-dependent kinase 4 (CDK4) ✕

- By SuperFamily
 - Enzymes
 - Transferases
 - Transferases Transferring Phosphorus-Contai...
 - Kinases
 - Cyclin-dependent kinases (CDK)
 - Cyclin-dependent kinase 4 (CDK4)
 - Tyrosine Kinases
 - **Cyclin-dependent kinase (CDK)...**

Browse targets - By SuperFamily > Enzymes > Transferases > Transferases Transferring Phosphorus-Containing Kinases > Tyrosine Kinases

Cyclin-dependent kinase (CDK) 4 and 6

Drugs where target is **primary:** Palbociclib ⁽¹⁾
Ribociclib ⁽¹⁾

(1) Drug/Target association is from FDA approval packages

Biology data: View Pharmacokinetic Data
for drugs where this is the primary target: View Metabolizing Enz. & Trans. Data
View Drug Safety Data
View FAERS Data
View Efficacy Data

Adverse Effects / Toxicity (for drugs that interact with this target)*:

[View by area affected](#) [View by name](#)

	Preclinical Data view all 671	Clinical Data view all 1365
+ Blood and lymphatic system d...	35	212
+ Cardiac disorders	1	10
+ Congenital, familial and geneti...	47	no data
+ Ear and labyrinth disorders	no data	no data
+ Endocrine disorders	3	no data

First, look at preclinical data

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Browse ▾ Search ▾ My tools ^{new}

Safety data search results 671 records from Safety data: Palbociclib (437) OR Ribociclib (234)

Refine search results:

Apply Clear All

Adverse Effects / Toxicity

Preclinical Data Clinical Data Post-Marketing Reports (AERS)

Safety data search results 1 records from Safety data: Palbociclib (0) OR Ribociclib (1) AND [Electrocardiogram QT corrected interval prolonged (1)]

Preclinical Data Clinical Data Post-Marketing Reports (AERS) All Data Preclinical and clinical data

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
1	Ribociclib	Electrocardiogram QT corrected interval prolonged	Dog	20 mg/kg	Single	Oral	FDA approval package document: Approval Package (Page:40) PDF 1644k	2016
5	Palbociclib	Blood alkaline phosphatase increased	Rat					
6	Palbociclib	Oral intake reduced	Rabbit					
6	Palbociclib	Red blood cell count decreased	Dog					


Grouping option optional (OR)






Dose-dependent QT prolongation was seen

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Browse ▾ Search ▾ My tools new IP-authorized 

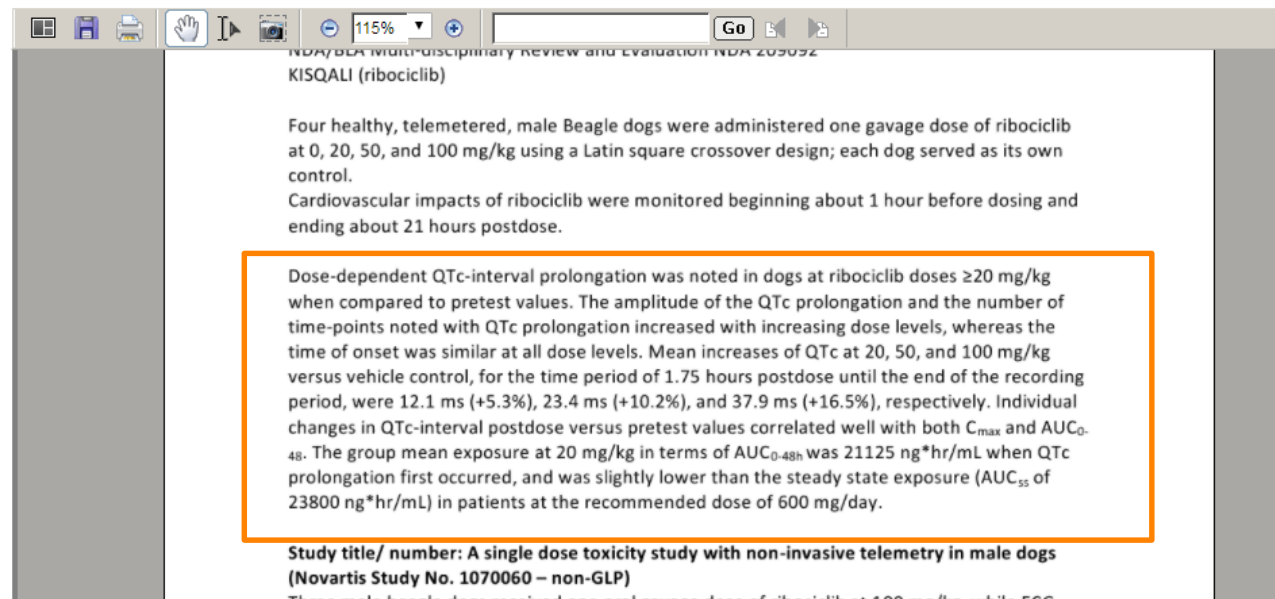
FDA Approval Package

 Search this FDA Package

- + Administrative documents
- + Approval Letter
- Approval Package
 -  [2016-10-04 PDF\(1644k\)](#)
Approval Package 2090...
 -  [2016-10-04 PDF\(2766k\)](#)
Approval Package 20909...
 -  [2016-10-04 PDF\(1681k\)](#)
Approval Package 20909...
 -  [2016-10-04 PDF\(4058k\)](#)
Approval Package 20909...
 -  [2016-10-04 PDF\(2585k\)](#)
Approval Package 20909...
- + Chemistry Review
- + Label
- + Letter
- + Other Important Informatio...

FDA Approval Package - Ribociclib > Approval Package

Approval Package 209092/S-000 Part 01



NDX/DBA Multi-disciplinary Review and Evaluation NDA 209092
KISQALI (ribociclib)

Four healthy, telemetered, male Beagle dogs were administered one gavage dose of ribociclib at 0, 20, 50, and 100 mg/kg using a Latin square crossover design; each dog served as its own control.

Cardiovascular impacts of ribociclib were monitored beginning about 1 hour before dosing and ending about 21 hours postdose.

Dose-dependent QTc-interval prolongation was noted in dogs at ribociclib doses ≥ 20 mg/kg when compared to pretest values. The amplitude of the QTc prolongation and the number of time-points noted with QTc prolongation increased with increasing dose levels, whereas the time of onset was similar at all dose levels. Mean increases of QTc at 20, 50, and 100 mg/kg versus vehicle control, for the time period of 1.75 hours postdose until the end of the recording period, were 12.1 ms (+5.3%), 23.4 ms (+10.2%), and 37.9 ms (+16.5%), respectively. Individual changes in QTc-interval postdose versus pretest values correlated well with both C_{max} and AUC_{0-48h} . The group mean exposure at 20 mg/kg in terms of AUC_{0-48h} was 21125 ng*hr/mL when QTc prolongation first occurred, and was slightly lower than the steady state exposure (AUC_{ss} of 23800 ng*hr/mL) in patients at the recommended dose of 600 mg/day.

Study title/ number: A single dose toxicity study with non-invasive telemetry in male dogs (Novartis Study No. 1070060 – non-GLP)

Three male beagle dogs received one oral gavage dose of ribociclib at 100 mg/kg, while 500

Next, look at clinical studies (keep ECG filter applied)

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Browse ▾ Search ▾ My tools new

IP-authorized

Safety data search results 5 records from Safety data: [Palbociclib (0) OR Ribociclib (5)] AND [Electrocardiogram QT corrected interval prolonged (5)]

Show/hide columns > Show drugs in... > Save > Export >

Preclinical Data Clinical Data Post-Marketing Reports (AERS) All Data preclinical and clinical data

ID	Drug ▾	Adverse Effect / Toxicity ▾	Species ▾	Dose ▾	Dose Type ▾	Route ▾	Source ▾	Year ▾
1	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:17) PDF 4058k	2016
2	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:59) PDF 1681k	2016
3	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	50-1200 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:16) PDF 4058k	2016
4	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/once a day 21 days, then 7 days off	Repeated	Oral	FDA approval package document: Label (Page:5) PDF 767k	2017

Dose dependent QT prolongation plus potential DDI was seen

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Browse ▾ Search ▾ My tools ^{new}

FDA Approval Package

Search this FDA Package

- + Administrative documents
- + Approval Letter
- + Approval Package
- + Chemistry Review
- Label
 - 2017-03-13 PDF(767k)
Label 209092/S-001
- + Letter
- + Other Important Informatio...
- + Review

FDA Approval Package - Ribociclib > Label
Label 209092/S-001

115%

Go

5 WARNINGS AND PRECAUTIONS

5.1 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms (90% CI: 21.6, 24.1)) at the mean steady-state C_{max} following administration at 600 mg once daily dose [see *Clinical Pharmacology* (12.2)]. In Study 1 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncopal occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. On the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation [see *Adverse Reactions* (6)].

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy [see *Dosage and Administration* (2.2)].


Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure,

5 of 17

Further investigation shows more information on the potential DDI

Metabolizing Enz. & Transporters search results

141 records from ME&T data:  Ribociclib (141)

Show/hide columns >

Show drugs in... >

Save 

Ex


Show Filters

Preclinical Data

Clinical Data

All Data

Preclinical and clinical data

ID	 Drug	Parent/Metabolite	Substance Study
1	Ribociclib	Parent	Ribociclib
2	Ribociclib	Parent	Ribociclib
...			
3	Ribociclib	Parent	Ribociclib
4	Ribociclib	Parent	Ribociclib
5	Ribociclib	Parent	Ribociclib

a strong CYP3A4 inhibitor if concomitant with a strong CYP3A inhibitor cannot be avoided.

CYP3A Inducers: Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma AUC of ribociclib by 89%. The concomitant use of strong CYP3A4 inducers with ribociclib should be avoided.

CYP3A Substrates: Coadministration of midazolam (CYP3A4 substrate) with multiple doses of 400 mg ribociclib increased the midazolam exposure by 3.8-fold. Simulations using PBPK models suggested that ribociclib given at dose of 600 mg once daily is expected to increase the midazolam AUC by 5.2-fold. Caution is recommended when ribociclib is administered with CYP3A substrates with a narrow therapeutic index.

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis indicated no DDI between ribociclib and letrozole.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant DDI between ribociclib and anastrozole.

Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant DDI between ribociclib and exemestane.

6.2.3. Outstanding Issues

See all QT interval AEs reported for antineoplastics

The image displays three overlapping screenshots of the PharmaPendium web application interface, demonstrating the search process for QT interval adverse effects.

Left Screenshot: Shows the main navigation menu with options: Drugs, Adverse Effects/Toxicity, Targets, and Indications. The text "Find adverse effect/toxicity data across pre" is partially visible at the bottom.

Middle Screenshot: Titled "Browse effects", it shows a search bar with the text "electrocardiogram". Below the search bar is a list of search results, with "Electrocardiogram QT interval" highlighted in yellow.

Right Screenshot: Titled "PharmaPendium®", it shows the search results for "electrocardiogram QT interval". The results are organized into a tree structure under "Investigations":

- Investigations
 - Cardiac and vascular investigations (excl enzyme tests)
 - ECG investigations
 - Electrocardiogram QT corrected interval
 - Electrocardiogram QT corrected interval prolonged
 - Electrocardiogram QT corrected interval shortened
 - Electrocardiogram QT interval
 - Electrocardiogram QT interval abnormal

A blue arrow points to the "ECG investigations" sub-category.

See all QT interval AEs reported for antineoplastics

PharmaPendium®

Browse ▾ Search ▾ My tools ^{new}

IP-authorized

Browse effects

electrocardiogram QT inter ✕

- Investigations
 - Cardiac and vascular i...
 - **ECG investigations**
 - Electrocardiog...
 - Electrocardiog...
 - Electrocardiog...
 - Electrocardiog...
 - Electrocardiog...

Browse effects - Investigations > Cardiac and vascular investigations (excl enzyme tests)

ECG investigations

+ Anthelmintics	6	6	11
+ Antihemophilic agents	no data	2	48
+ Antihistamines	60	185	1048
+ Antihyperlipidemics	8	15	647
+ Antihypertensives	15	64	152
+ Antihypoglycemics	no data	1	4
+ Antimycobacterials	12	68	101
+ Antineoplastics	254	904	5398
+ Antiparkinson agents	17	111	198
+ Antiprotozoals	12	135	300
+ Antipsoriatics	no data	2	18
+ Antipsychotics	66	677	5540
+ Antipyretics	no data	no data	421
+ Antiseptics, urinary tract	no data	no data	2
+ Antiseptics/disinfectants	no data	1	1

→ 1158 preclinical/clinical records for 118 drugs

PharmaPendium®

Browse ▾ Search ▾ My tools new

Safety data search results

1158 records from Safety data: [ECG Investigations (1158)] AND [Antineoplastics (1158)]

Refine search results:

Apply Clear All

Adverse Effects / Toxicity ▾

Dose Types ▾

Drugs ▾

Routes of Administration ▾

Sources ▾

Species ▾

Years ▾

Preclinical Data Clinical Data Post-Marketing

ID	Drug	Adverse Effect / Toxicity
1	Abarelix	Electrocardiogram QT prolonged
2	Abarelix	Electrocardiogram QT prolonged
3	Abarelix	Electrocardiogram QT prolonged
4	Abarelix	Electrocardiogram QT prolonged

Show drugs in Deselect all

Export All drugs in Excel file (.xls)

Show the filtered drugs in other modules. Based on your filtering.

Selected: 118

- ☒ Abarelix
- ☒ Abemaciclib
- ☒ Abiraterone Acetate
- ☒ Aclarubicin
- ☒ Ado-Trastuzumab Emtansine

- > Show in Pharmacokinetic Data
- > Show in Metabolizing Enz. & Trans. Data
- > Show in FAERS Data
- > Show in Efficacy Data
- > Show in Activity Data

clinical data

Source

FDA approval package Medical/Clinical Re PDF 1629k

FDA approval package Medical/Clinical Re PDF 1629k

FDA approval package Medical/Clinical Re PDF 1629k

FDA approval package Medical/Clinical Re PDF 1629k

What evidence can we look at in PharmaPendium to evaluate a potential DDI signal?

Example

- Routine literature monitoring identified an intracranial hemorrhage in a patient taking theophylline + ciprofloxacin
- What information can PharmaPendium provide to help confirm (or refute) causality?

Was there an increase in post-market reports for this AE and drug combination?

Quick Search

All These Sources



e.g. Coronar* artery disorders

Search >



Include synonyms

Find adverse effect/toxicity data across preclinical, clinical, post-market reports and more



Pharmacokinetic Data



Metabolizing Enz. & Trans. Data



Drug Safety Data



FAERS Data new



Chemistry Search



Efficacy Data




Activity Data



DDI risk calculator

Add drugs to populate the FAERS table

Summary Table and Graphical View ^{new}

- ☒ Select drugs of interest 
- ☐ Select adverse events (AEs) of interest

Start

This new search type enables more advanced queries of FAERS reports.

Options include viewing FAERS reports:

- Based on a group of drugs (applying logic operators AND/OR/NOT)
- With comparative view of drugs in a summary table (e.g., view FAERS reports for a drug versus another drug),
- With a graphical representation of the FAERS reports.
- All types of searches include advanced filtering options (e.g., by reporter occupation, age, gender, etc.)

Watch tutorial for a quick tour!

PharmaPendium®

Browse

Summary Table with Adverse Effects Tree (FAERS data)

View as [Table](#) [Graph](#)

Compare Filters



View AEs by [by area af](#)

Summary Table with Adverse Effects Tree

Add Drugs

- + Blood and lymphatic system disorders
- + Cardiac disorders
- + Congenital, familial and genetic disorders
- + Ear and labyrinth disorders
- + Endocrine disorders
- + Eye disorders
- + Gastrointestinal disorders
- + General disorders and administration site conditions
- + Hepatobiliary disorders
- + Immune system disorders
- + Infections and infestations
- + Injury, poisoning and procedural complications
- + Investigations
- + Metabolism and nutrition disorders
- + Musculoskeletal and connective tissue disorders

First, add drugs individually

Add Drugs

×

by name or class by primary target or target class by indication

- Ephedrine Sulfate; Hydroxyzine Hydrochloride; Theophylline [Add](#)
- Ephedrine Sulfate; Phenobarbital; Theophylline [Add](#)
- Guaifenesin; Theophylline [Add](#)
- Theophylline** [Add](#)
- Diuretics [Add](#)
 - Diuretics, other [Add](#)
 - Mersalyl Sodium; Theophylline [Add](#)
- Expectorants [Add](#)
 - Guaifenesin; Theophylline [Add](#)

Logic operators ☐ Do not activate logic operators

Each element from the following selection will be added as separate column:

[Any role](#) ▼

[Add column\(s\)](#) [Back](#)

Then, add drugs in a group

Add Drugs

by name or class by primary target or target class by indication

- Ephedrine Sulfate; Hydroxyzine Hydrochloride; Theophylline [Add](#)
- Ephedrine Sulfate; Phenobarbital; Theophylline [Add](#)
- Guaifenesin; Theophylline [Add](#)
- Theophylline [Add](#)
- Diuretics [Add](#)
 - Diuretics, other [Add](#)
 - Mersalyl Sodium; Theophylline [Add](#)
- Expectorants [Add](#)

[Add group](#) [Back](#)

Logic operators ☐ Activate logic operators [Add OR](#) [Add NOT](#)

All of the following drugs will be added as a single column:

You are adding here (all elements work via AND logical operator)

× Ciprofloxacin Hydrochloride	Any role ▾
× Theophylline	Any role ▾

Even looking at total cases, there seems to be a peak – next convert to percent of total cases

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Browse Search My tools

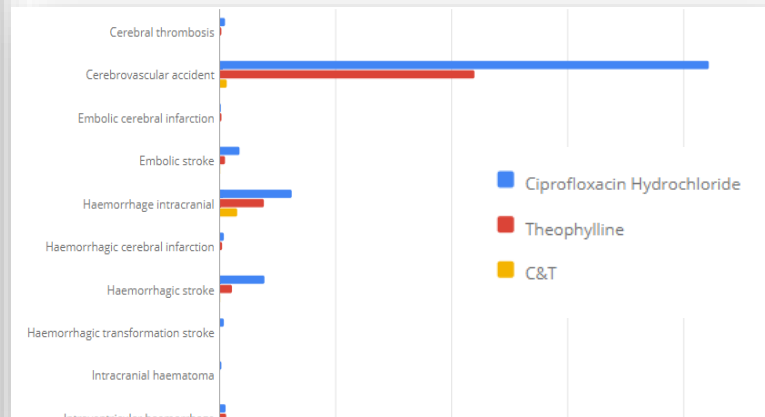
Summary Table with Adverse Effects Tree (FAERS data)

View as **Table** **Graph** Compare Filters View AEs by by area affected Export Save

Summary Table with Adverse Effects Tree	Ciprofloxacin ...	Theophylline	C&T
Total	77575	26948	672
+ Blood and lymphatic system disorders	11031	2303	125
+ Cardiac disorders	9591	4824	160
+ Congenital, familial and genetic disorders	934	231	5
+ Ear and labyrinth disorders	2666	393	33
+ Endocrine disorders	1229	397	19
+ Eye disorders	5581	1292	44
+ Gastrointestinal disorders	20913	6030	217
+ General disorders and administration site conditions	31616	10966	309
+ Hepatobiliary disorders	6551	1476	80
+ Immune system disorders	6298	1216	38
+ Infections and infestations	20459	5793	265
+ Injury, poisoning and procedural complications	4056	2773	69
+ Investigations	17371	6983	204
+ Metabolism and nutrition disorders	9323	3275	128
+ Musculoskeletal and connective tissue disorders	17335	3561	115
+ Neoplasms benign, malignant and unspecified (incl. dysplasia)	5118	1286	57

Drill down into the graph view:

- 1) Nervous system disorders
- 2) Central nervous system vascular disorders
- 3) Central nervous system haemorrhages and cerebrovascular accidents



Export data, expand the relevant part of the AE taxonomy and copy the rows of data

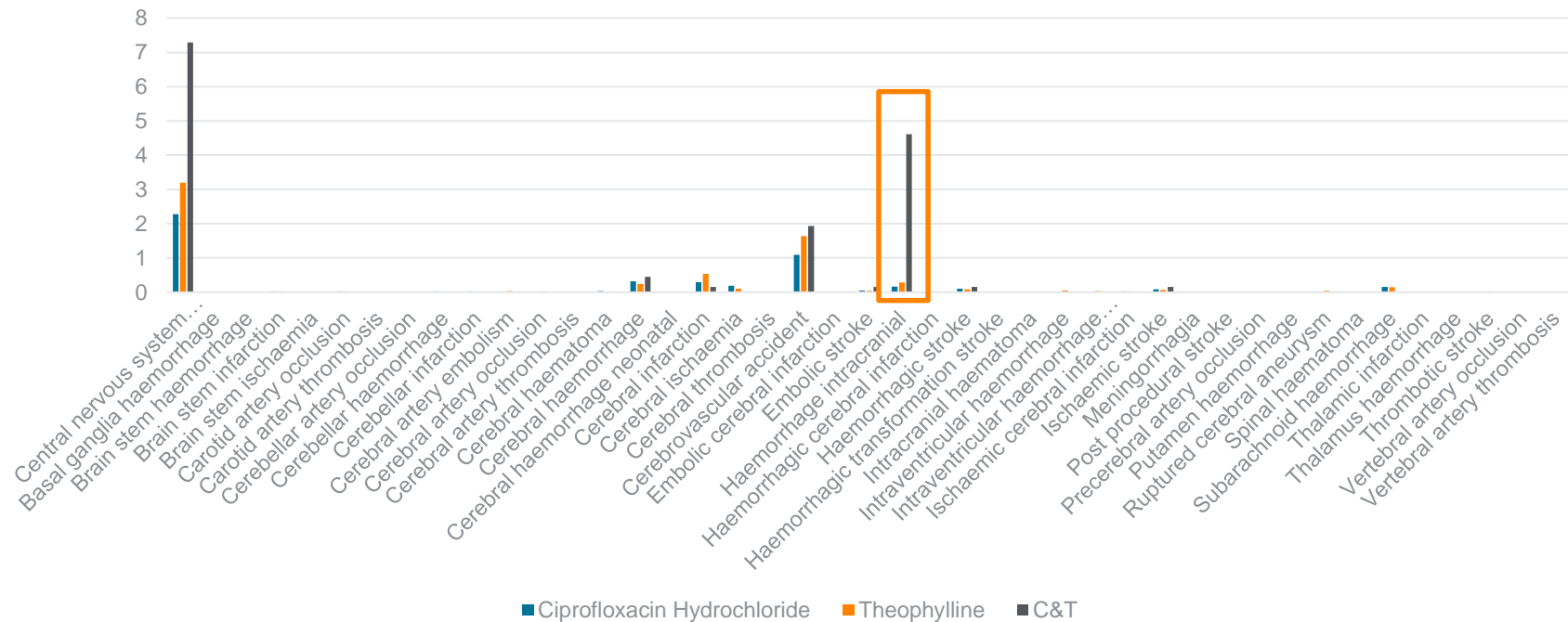
1	2	3	4	A	B	C	D
5					Ciprofloxacin Hydrochloride	Theophylline	C&T
6				Total	77575	26948	672
7				Blood and lymphatic system disorders	11031	2303	125
196				Cardiac disorders	9591	4824	160
447				Congenital, familial and genetic disorders	934	231	5
784				Ear and labyrinth disorders	2666	393	33
857				Endocrine disorders			
960				Eye disorders			
1315				Gastrointestinal disorders			
1958				General disorders and administration site conditions			
2350				Hepatobiliary disorders			
2495				Immune system disorders			
2592				Infections and infestations			
3524				Injury, poisoning and procedural complications			
3603				Investigations			
4957				Metabolism and nutrition disorders			
5179				Musculoskeletal and connective tissue disorders			
5563				Neoplasms benign, malignant and unspecified			
6288				Nervous system disorders			
6905				Pregnancy, puerperium and perinatal conditions			
7037				Psychiatric disorders			
7421				Renal and urinary disorders			
7677				Reproductive system and breast disorders			
7972				Respiratory, thoracic and mediastinal disorders			
8337				Skin and subcutaneous tissue disorders			
8663				Social circumstances			
8790				Surgical and medical procedures			
8794				Vascular disorders			
9054							

6325	Cerebral haematoma	24	2	0
6326	Cerebral haemorrhage	244	64	3
6327	Cerebral haemorrhage neonatal	1	2	0
6328	Cerebral infarction	223	144	1
6329	Cerebral ischaemia	145	28	0
6330	Cerebral thrombosis	10	3	0
6331	Cerebrovascular accident	844	440	13
6332	Embolic cerebral infarction	2	4	0
6333	Embolic stroke	35	10	1
6334	Haemorrhage intracranial	125	77	31
6335	Haemorrhagic cerebral infarction	8	5	0
6336	Haemorrhagic stroke	78	22	1
6337	Haemorrhagic transformation stroke	8	0	0
6338	Intracranial haematoma	3	0	0
6339	Intraventricular haemorrhage	11	12	0
6340	Intraventricular haemorrhage neonatal	0	9	0
6341	Ischaemic cerebral infarction	18	5	0
6342	Ischaemic stroke	67	18	1
6343	Meningorrhagia	2	0	0
6344	Post procedural stroke	0	2	0
6345	Precerebral artery occlusion	0	2	0
6346	Putamen haemorrhage	0	3	0
6347	Ruptured cerebral aneurysm	2	11	0
6348	Spinal haematoma	1	0	0
6349	Subarachnoid haemorrhage	118	38	0
6350	Thalamic infarction	9	1	0
6351	Thalamus haemorrhage	1	3	0
6352	Thrombotic stroke	1	6	0
6353	Vertebral artery occlusion	0	1	0
6354	Vertebral artery thrombosis	1	0	0

Convert to % (of total AEs), then create a chart

	Total AEs reported				77575				25942				872		
	Coprilactam hydrochloride	Theophylline	C&T		Coprilactam hydrochloride	Theophylline	C&T		Coprilactam hydrochloride	Theophylline	C&T		Coprilactam hydrochloride	Theophylline	C&T
Central nervous system haemorrhages and cerebrovascular accidents	175	55	49	Central nervous system haemorrhages and cerebrovascular accidents	2,250,735	3,195,751	7,291,667	Cerebrovascular accident	544	440	13	Cerebrovascular accident	1,057,927	1,622,742	1,934,534
Basal ganglia haemorrhage	1	0	0	Basal ganglia haemorrhage	0,001,259,075	0	0	Embolic cerebral infarction	2	4	0	Embolic cerebral infarction	0,002,970	0,014,434	0
Brain stem haemorrhage	6	1	0	Brain stem haemorrhage	0,007,244,51	0,003,710,551	0	Embolic stroke	25	10	1	Embolic stroke	0,045,117,623	0,037,055,03	0,145,81
Brain stem infarction	16	6	0	Brain stem infarction	0,002,625,201	0,002,285,103	0	Haemorrhage intracranial	125	77	31	Haemorrhage intracranial	0,161,134,356	0,057,254,91	4,613,095
Brain stem ischaemia	3	1	0	Brain stem ischaemia	0,003,587,225	0,003,710,551	0	Haemorrhagic cerebral infarction	5	5	0	Haemorrhagic cerebral infarction	0,010,312,601	0,018,554,253	0
Cerebral artery occlusion	19	7	0	Cerebral artery occlusion	0,004,924,217	0,002,575,254	0	Haemorrhagic stroke	76	22	1	Haemorrhagic stroke	0,100,547,557	0,081,627,12	0,145,81
Cerebral artery thrombosis	3	1	0	Cerebral artery thrombosis	0,005,445,375	0,003,710,551	0	Haemorrhagic transformation stroke	6	0	0	Haemorrhagic transformation stroke	0,010,312,601	0	0
Cerebellar artery occlusion	0	1	0	Cerebellar artery occlusion	0	0,003,710,551	0	Intracranial haematoma	2	0	0	Intracranial haematoma	0,003,587,225	0	0
Cerebellar haemorrhage	15	3	0	Cerebellar haemorrhage	0,019,336,126	0,011,132,552	0	Intraventricular haemorrhage	11	12	0	Intraventricular haemorrhage	0,014,175,238	0,044,303,006	0
Cerebellar infarction	20	3	0	Cerebellar infarction	0,025,751,502	0,011,132,552	0	Intraventricular haemorrhage neonatal	0	5	0	Intraventricular haemorrhage neonatal	0	0,002,575,254	0
Cerebral artery embolism	12	5	0	Cerebral artery embolism	0,016,757,976	0,002,555,504	0	Ischaemic cerebral infarction	16	5	0	Ischaemic cerebral infarction	0,002,303,352	0,018,554,253	0
Cerebral artery occlusion	5	6	0	Cerebral artery occlusion	0,005,445,375	0,002,285,103	0	Ischaemic stroke	67	16	1	Ischaemic stroke	0,086,350,031	0,067,953,03	0,145,81
Cerebral artery thrombosis	6	3	0	Cerebral artery thrombosis	0,007,244,51	0,011,132,552	0	Meningorrhage	2	0	0	Meningorrhage	0,002,970	0	0
Cerebral haematoma	24	2	0	Cerebral haematoma	0,002,625,201	0,007,421,701	0	Post procedural stroke	0	2	0	Post procedural stroke	0	0,007,421,701	0
Cerebral haemorrhage	244	64	2	Cerebral haemorrhage	0,145,242,22	0,027,494,434	0,445,423	Precentral artery occlusion	0	2	0	Precentral artery occlusion	0	0,007,421,701	0
Cerebral haemorrhage neonatal	1	2	0	Cerebral haemorrhage neonatal	0,001,259,075	0,007,421,701	0	Pulaman haemorrhage	0	3	0	Pulaman haemorrhage	0	0,011,132,552	0
Cerebral infarction	222	144	1	Cerebral infarction	0,257,483,745	0,034,362,476	0,145,81	Ruptured cerebral aneurysm	2	11	0	Ruptured cerebral aneurysm	0,002,970	0,045,117,623	0
Cerebral ischaemia	145	25	0	Cerebral ischaemia	0,155,755,555	0,102,925,15	0	Spinal haematoma	1	0	0	Spinal haematoma	0,001,259,075	0	0
Cerebral thrombosis	10	3	0	Cerebral thrombosis	0,012,590,181	0,011,132,552	0	Subarachnoid haemorrhage	115	25	0	Subarachnoid haemorrhage	0,152,105,55	0,141,012,22	0
								Thalamic infarction	9	1	0	Thalamic infarction	0,016,016,76	0,003,710,551	0
								Thalamic haemorrhage	1	2	0	Thalamic haemorrhage	0,001,259,075	0,011,132,552	0
								Thrombotic stroke	1	6	0	Thrombotic stroke	0,001,259,075	0,002,285,103	0
								Vertebral artery occlusion	0	1	0	Vertebral artery occlusion	0	0,003,710,551	0
								Vertebral artery thrombosis	1	0	0	Vertebral artery thrombosis	0,001,259,075	0	0

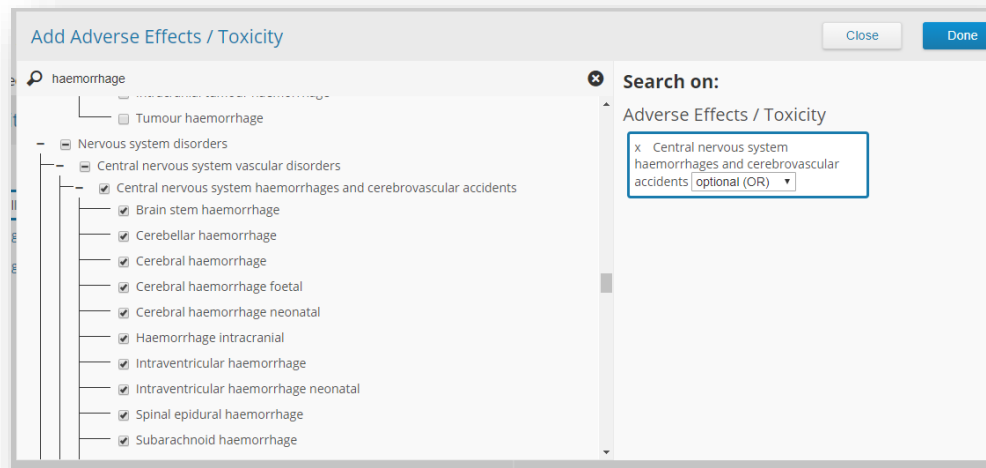
Central nervous system AE reports



What other information in PP can be examined to answer this question?

1) Drug safety module:

- 1) Search theophylline + Central nervous system haemorrhages and cerebrovascular accidents = 0 results
- 2) Search Ciprofloxacin Hydrochloride + Central nervous system haemorrhages and cerebrovascular accidents = 26 results



Click on the first result, search text for theophylline

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Browse Search My tools new

Safety data search results

26 records from Safety data: [Ciprofloxacin Hydrochloride 26]] AND [Central nervous system haemorrhages and cerebrovascular accidents (26)]

Preclinical Data Clinical Data Post-Marketing Reports (AERS) All Data Preclinical and clinical data

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
1	Ciprofloxacin Hydrochloride	Cerebral thrombosis	Human	0.4-1.2 g/day	Repeated	Intravenous	FDA approval package document: Approval Package (Page:47) PDF 11732k	2004
2	Ciprofloxacin Hydrochloride	Cerebral thrombosis	Human	Therapeutic				
3	Ciprofloxacin Hydrochloride	Cerebral thrombosis	Human	100-750 mg/1-2 times				
4	Ciprofloxacin Hydrochloride	Cerebral thrombosis	Human	0.4-1.2 g/day				
5	Ciprofloxacin Hydrochloride	Cerebral thrombosis	Human	250-750 mg/twice a day				
6	Ciprofloxacin	Cerebral thrombosis	Human	0.4-1.2 g/day				

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FDA Approval Package

Search this FDA Package

- 2004-03-25 PDF(11732k) Approval Package 019857/S-031; 019537/S-049; 020780/S-013; 019847/S-027
- 2004-03-15 PDF(3422k) Approval Package 021...
- 2003-08-28 PDF(647k) Approval Package 021...
- 2003-08-28 PDF(695k) Approval Package 021...
- 2003-08-28 PDF(914k) Approval Package 021...
- 2003-08-28 PDF(578k) Approval Package 021...
- 2003-08-28 PDF(839k) Approval Package 021...
- 2003-08-28 PDF(426k) Approval Package 021...

FDA Approval Package - Ciprofloxacin Hydrochloride > Approval Package

Approval Package 019857/S-031; 019537/S-049; 020780/S-013; 019847/S-027

theophylline

rather than 1 hour, whereas there is no delay observed when CIPRO suspension is given with food. The overall absorption of CIPRO Tablet or CIPRO Suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See PRECAUTIONS.)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See PRECAUTIONS.)

Special Populations: Pharmacokinetic studies of the oral (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS: Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See DOSAGE AND ADMINISTRATION.)

11 of 184

What other information in PP can be examined to answer this question?

2) Pharmacokinetic module:

1) Search theophylline and limit parameter to AUC

Pharmacokinetic data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

x Theophylline

- + Add drugs by drug class or drug name
- + Add drugs by primary target or primary target class

Add parameter ranges

Type parameter ranges to search

- + ☐ Absorption
- + ☐ Binding
- + ☐ Biotransformation
- ☒ Distribution
 - + ☐ Accumulation
 - ☒ Area under the curve
 - ☒ AUC
 - ☐ AUMC
 - ☐ LAUC
 - + ☐ Permeation
 - + ☐ Steady state
 - + ☐ Time value
 - + ☐ Tissue distribution
 - + ☐ Volume of distribution
- + ☐ Elimination

Close

Done

Search on:

Parameter ranges

x AUC

Above

below

ug*h/mL

Export data. Filter results to those with ciprofloxacin as a concomitant & theophylline (same dose, no concomitant)

Export data Deselect all columns Select all columns

Select columns for export

- ☐ Chemical Structure
- ☐ Radiolabelled
- ☒ Species
- ☐ Study Number
- ☒ Study Group
- ☐ Study Name
- ☐ #N
- ☐ Sex
- ☐ Age
- ☒ Dose
- ☐ Assay
- ☒ Parameter
- ☒ Parameter Value
- ☒ Parameter Normalized Value (only standard units are normalized)
- ☒ t
- ☒ Concomitant
- ☐ Comments
- ☒ Source

Export date: 29-04-2018

Pharmacokinetic Data Search Results For: Drugs: [Theophylline]ANDParameter

Total results: 933

Sort order: Drug (Ascending);

Export as Excel d...
Export as Excel d...
Export as tab deli...
Export as comma...

Drug	Species	Dose	Route	Parameter	Value	Units	Normalized Value (only standard units)	Init (only stan	SD	t	Concomitant
Theophylline	Human	300 mg	Oral	AUC(0-inf)	222	mg*h/L	222 (122 to 322)	ug*h/mL	100.0		Ciprofloxacin 500 mg
Theophylline	Human	300 mg	Oral	AUC(0-inf)	68.3	ug*h/mL	68.3 (46.199999999999996 to 90.4)	ug*h/mL	22.1		Ciprofloxacin 500 mg
Theophylline	Human	400 mg	Oral	AUC(0-inf)	222	mg*h/mL	222000 (182000 to 262000)	ug*h/mL	40.0		Ciprofloxacin 500 mg
Theophylline	Human	400 mg	Oral	AUC(0-inf)	144	mg*h/mL	144000 (115000 to 173000)	ug*h/mL	29.0		Ciprofloxacin 500 mg
Theophylline	Human	400 mg	Oral	AUC(0-inf)	207	mg*h/mL	207000 (170000 to 244000)	ug*h/mL	37.0		Ciprofloxacin 500 mg
Theophylline	Human	5 mg/kg	Intravenous	AUC(0-24h)	109	mg*h/L	109 (-171 to 389)	ug*h/mL	280.0		Ciprofloxacin 500 mg
Theophylline	Human	5 mg/kg	Intravenous	AUC(0-24h)	156	mg*h/L	156 (124 to 188)	ug*h/mL	32.0		Ciprofloxacin 500 mg
Theophylline	Human	5 mg/kg	Intravenous	AUC(0-24h)	196	mg*h/L	196 (151 to 241)	ug*h/mL	45.0		Ciprofloxacin 500 mg
Theophylline	Human	5 mg/kg	Intravenous	AUC(0-24h)	83.2	ug*h/mL	83.2 (54.3 to 115)	ug*h/mL			

Clear increase in AUC when ciprofloxacin is co-administered

What other information in PP can be examined to answer this question?

3) Metabolising enzyme & transporter module:

- 1) Search ciprofloxacin with no limits (goal is to identify all studies where theophylline was a concomitant). Export data

Metabolizing Enz. & Transporters search results 914 records from ME&T data: Ciprofloxacin Hydrochloride (914)

Show/hide columns > Show drugs in... > Save Export

Preclinical Data Clinical Data All Data Preclinical and Clinical Data

ID	Drug	Dose	Route
1	Ciprofloxacin Hydrochloride	SD	Oral
2	Ciprofloxacin Hydrochloride	SD	Oral
...			
3	Ciprofloxacin Hydrochloride	SD	Oral
4	Ciprofloxacin Hydrochloride	SD	Oral
5	Ciprofloxacin Hydrochloride	SD	Oral

Export data Deselect all columns Select all columns

Select columns for export

<input type="checkbox"/> Chemical Structure	<input checked="" type="checkbox"/> Test system	<input checked="" type="checkbox"/> Parameter	<input type="checkbox"/> Experimental Details
<input type="checkbox"/> Study Number	<input checked="" type="checkbox"/> Species	<input checked="" type="checkbox"/> Value	<input type="checkbox"/> Experimental Conditions
<input checked="" type="checkbox"/> Parent/Metabolite	<input checked="" type="checkbox"/> Dose	<input checked="" type="checkbox"/> Result (qualitative)	<input type="checkbox"/> Time
<input checked="" type="checkbox"/> Substance Studied	<input checked="" type="checkbox"/> Route	<input type="checkbox"/> Effect	<input type="checkbox"/> Comment
<input checked="" type="checkbox"/> Data Type	<input checked="" type="checkbox"/> Substance measured	<input type="checkbox"/> Degree	<input checked="" type="checkbox"/> Source
<input checked="" type="checkbox"/> Enzyme/Transporter	<input checked="" type="checkbox"/> Concomitant	<input type="checkbox"/> Reaction	<input checked="" type="checkbox"/> Year

> Export as Excel document (.xls)

> Export as Excel document (.xlsx)

> Export as tab delimited (.tsv)

> Export as comma delimited (.csv)

Filter results for theophylline as concomitant

Export date: 29-04-2018

Metabolizing Enzymes And Transporters Data Search Results For: Drugs: [Ciprofloxacin Hydrochloride]

Total results: 914

Sort order: Concomitant (Descending); Drug (Ascending);

Drug	nt/Me	Substance Stud	Data Type	Enzyme/Transp	Test system	Speci	Dose	Route	Substance mea	Concomitant	Parameter	Result (qualitative)
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Inhibitor (in vivo)	Unreported	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	CL decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	T1/2 increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	T1/2 increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	CL decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	Enzyme activity decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	T1/2 increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	CL decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Inhibitor (in vivo)	Unreported	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydro	Enzyme Inhibitor (in vivo)	CYP 1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes

94 lines of data with qualitative changes to MET parameter being measured

Example result

fluoroquinolones, including ciprofloxacin. CIPRO IV should be avoided in patients with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes (for example, congenital long QT syndrome, uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (quinidine, procainamide), or Class III antiarrhythmic agents (amiodarone, sotalol), tricyclic antidepressants, macrolides, and antipsychotics). Elderly patients may also be more susceptible to drug-associated effects on the QT interval. (See **PRECAUTIONS, Drug Interactions** and **Geriatric Use**.)

Cytochrome P450 (CYP450)

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug. (See **PRECAUTIONS, Drug Interactions**.)

PRECAUTIONS

General

INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINISTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local IV site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used. (See **ADVERSE REACTIONS**.)

Central Nervous System

Example: what information is available on surrogate endpoints for diabetes

- 2 steps:
 - 1) Text search validated surrogate (within 5 words) and diabetes and unvalidated surrogate (within 5 words) and diabetes – do this to demonstrate information in FDA Advisory committee meeting reports
 - 2) Extracted information search: Look for information on specific surrogate endpoint (e.g., Hba1c) – search across endpoints

Search for validated surrogate endpoints for diabetes

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Advanced search

Search criteria

Find results

... with **all** the words: ... within at least words of one another... with **at least** one of the words: ... **without** the words: ☒ Include synonyms

Advanced Search Tips

- Use the 1st field for proximity searching. Proximity term NEAR operator.
The proximity search does NOT search for synonyms
Wildcards (* or ?) can be used here.
The number at the end (distance) is how close in the document the phrases to be. The maximum distance for this search is 1000.
Proximity Searches can also be done on the Quick Search.
.... termN = Distance]

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IP-authorized

Search results 126 records from Documents: [surrogate.validated=5] AND (diabetes) with synonyms [\[QUERY DETAILS\]](#)

Refine search results:

Jump to: [Show/hide columns](#)[Show drugs in...](#)[Save](#)[Export](#)[Search in EMBASE](#)

Drugs ▾

Sources ▾

Years ▾

ID

Document with context

Drug name ▾

Source ▾

Year ▾

1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk: Diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of ...	Fenofibrate; Pravastatin Sodium	EMA approval documents	2011
2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... diabetes mellitus ; N Engl J Med. 1999;341:1127-33. 4. Frank RN. Diabetes retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical 1\7630dft.doc 02/13/08 Guidance for Industry Diabetes Mellitus ...	N/A	FDA Advisory Committee Documents	2012
4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any diabetes AE Diabetes Mellitus Blood glucose	N/A	FDA Advisory Committee Documents	2009

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Browse Search My tools ^{new}

Search results 126 records from Documents: [surrogate,validated=5] AND (diabetes) with synonyms [QUERY DETAILS]

Refine search results:

Apply Clear All

Jump to: page 1 Show/hide columns Show drugs in... Save Export Search in EMBASE

	ID	Document with context	Drug name	Source	Year
Drugs	1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk): Diabetes mellitus aggravated diabetes mellitus exacerbated, worsening of ...	Fenofibrate; Pravastatin Sodium	EMA approval documents	2011
Sources	2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... diabetes mellitus ; N Engl J Med. 1999;341:1127-33. 4. Frank RN. Diabetic retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
Years	3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical I:7630dft.doc 02/13/08 Guidance for Industry Diabetes Mellitus ...	N/A	FDA Advisory Committee Documents	2012
	4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any diabetic AE Diabetes mellitus Blood glucose	N/A	FDA Advisory Committee Documents	2009

Need to text search 'surrogate'

The screenshot displays the PharmaPendium website interface. On the left, a sidebar titled 'EMA Approval Package' contains a search bar and a list of links: '+ All Authorized Presentations', '+ ANNEX I', '- Assessment Report' (which is expanded to show a PDF link for '2011-01-01 PDF(756k) Assessment Report EM...'), '+ Marketing Authorization Steps', '+ Other Information from EMA', and '+ Public Assessment Report'. The main content area is titled 'EMA Approval Package - Fenofibrate; Pravastatin Sodium > Assessment Report' and 'Assessment Report EMEA/H/C/001243; EMEA/H/C/001243'. A toolbar at the top of the document viewer includes icons for zooming, navigating, and a search bar. The search bar contains the text 'surrogate' and is highlighted with an orange box. Below the toolbar, the document text is visible, showing a paragraph about cardiovascular events and a section titled 'Benefit-risk balance'. The word 'surrogate' is highlighted in yellow in the text. The bottom of the page shows a section titled '2.8.1. Discussion on the benefit-risk balance'.

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Browse Search My tools new

EMA Approval Package

Search this EMA Package

- + All Authorized Presentations
- + ANNEX I
- Assessment Report
 - 2011-01-01 PDF(756k) Assessment Report EM...
- + Marketing Authorization Steps
- + Other Information from EMA
- + Public Assessment Report

EMA Approval Package - Fenofibrate; Pravastatin Sodium > Assessment Report

Assessment Report EMEA/H/C/001243; EMEA/H/C/001243

115% surrogate 2/2 Go

fenofibrate/simvastatin combination therapy to reduce cardiovascular events in the majority of dyslipidaemic high CV risk patients with type 2 diabetic patients. Indeed, only beneficial effects on cardiovascular endpoints were observed in patients with high TG and low HDL-C values. This has also been extensively discussed during Article 31 referral on fenofibrate. Thus, finally, only an indication that will be limited to this specific population subgroup can be granted by the CHMP.

Benefit-risk balance

Based on the provided data, benefits on lipid parameters (surrogate endpoints) were effectively demonstrated in the subgroup of patients with mixed dyslipidaemia defined by TG >204mg/dl and HDL-C <34mg/dL levels. Results are however insufficient to recommend an extensive use in patients with high TG or low HDL-C levels as originally claimed. Nevertheless, the importance whether these biological effects could translate into benefits on cardiovascular endpoints was considered by the CHMP during the first step of the Pravafenix procedure in the context of the long term use of the statin/fenofibrate combination. After reviewing data from the ACCORD study, it would appear that there is a detrimental effect of the long term use of a statin/fenofibrate combination on women. This gender issue has been extensively discussed during referral on fibrates. Overall, the biological benefit expressed in the newly worded and approved indication can be recognised for the pravastatin/fenofibrate combination.

2.8.1. Discussion on the benefit-risk balance

Based on the provided data and the rationale above, Pravafenix is aimed to offer an alternative to a specifically targeted population; i.e. high CHD-risk adult patients with mixed dyslipidaemia characterised by high TG and low HDL-C whose LDL-C are adequately controlled while on a treatment with pravastatin 40mg monotherapy.

Change to unvalidated surrogate search

Advanced search

Search criteria

Find results

... with **all** the words:

... within at least words of one another

... with **at least** one of the words:

... **without** the words:

☒ Include synonyms

Advanced Search Tips

- Use the 1st field for proximity searching. Proximity terms (NEAR operator). The proximity search does NOT search for synonyms. Wildcards (* or ?) can be used here. The number at the end (distance) is how close in the document phrases to be. The maximum distance for this search is 20. Proximity Searches can also be done on the Quick Search

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Browse ▾ Search ▾ My tools new



Search results

12 records from Documents: [surrogate,unvalidated=5] AND (diabetes) with synonyms [\[QUERY DETAILS\]](#)

Jump to:

Show/hide columns >

Show drugs in... >

Save

ID	Document with context	Drug name ▾	Source ▾	Year ▾
1	Briefing 4355 Part 01 (Blood Products Advisory Committee) PDF 432k ... unvalidated surrogate endpoint at this time. For the secondary endpoints attack severity and attack duration ...	N/A	FDA Advisory Committee Documents	2008
2	Briefing 4355 Part 02 (Blood Products Advisory Committee) PDF 466k ... addition, the secondary endpoint of C1INH levels must be considered an unvalidated surrogate endpoint at ...	N/A	FDA Advisory Committee Documents	2008
3	Approval Package 020604/S-040 PDF 2381k ... -related events including new onset diabetes mellitus and diabetic ketoacidosis led to a language upgrade ...	Somatropin, Biosynthetic	FDA approval packages	2011
4	Background Part 17 (Cardiovascular and Renal Drugs Advisory Committee) PDF 2057k ... of 224 Tolvaptan (OPC-41061) NDA 204441 that TKV is an unvalidated surrogate TKV was chosen as the ...	N/A	FDA Advisory Committee Documents	2013
5	Transcript Part 01 (Peripheral and Central Nervous System Drugs Advisory Committee) PDF 2384k ... , to understand 16 that concluding that an effect on an unvalidated surrogate will	N/A	FDA Advisory Committee Documents	2012

Again, need to search for 'surrogate' in the document

The screenshot displays the PharmaPendium website interface. The top navigation bar includes 'Browse', 'Search', and 'My tools'. The main content area is titled 'FDA Advisory Committee - Cardiovascular and Renal Drugs Advisory Committee > 2013-Aug-05' and 'Background Part 17'. A search bar on the left is labeled 'Search this FDA Advisory Committee'. The search results list several documents, with '2013-08-05 PDF(2057k) Background Part 17' selected. The document viewer shows a search for 'surrogate' on page 77 of 224. The search results highlight the word 'surrogate' in the text: 'that TKV is an unvalidated surrogate, TKV was chosen as the primary endpoint for this trial because if no effect were seen in TKV, it was believed no other clinical benefits would be conveyed to patients.' The document also mentions 'Tolvaptan (OPC-41061)' and 'NDA 204441'. The footer indicates '11 of 39' pages.

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Browse Search My tools

IP-authorized

FDA Advisory Committee

Search this FDA Advisory Committee

2013-08-05 PDF(2057k) Background Part 17

2013-08-05 PDF(2581k) Background Part 18

2013-08-05 PDF(1603k) Background Part 19

2013-08-05 PDF(471k) Background Part 20

2013-08-05 PDF(3399k) Background Part 21

2013-08-05 PDF(644k) Background Part 22

2013-08-05 PDF(315k) Minutes

2013-08-05 PDF(202k) Other documents

2013-08-05 PDF(249k) Questions Part 01

2013-08-05 PDF(235k)

FDA Advisory Committee - Cardiovascular and Renal Drugs Advisory Committee > 2013-Aug-05

Background Part 17

progression. Its ability to detect changes over a relatively short (3-year) period of the disease's slow course of progression permitted estimation of power for what would be a clinically relevant degree of change (20% reduction). While the sponsor acknowledges

Page 77 of 224

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Tolvaptan (OPC-41061) NDA 204441

that TKV is an unvalidated surrogate, TKV was chosen as the primary endpoint for this trial because if no effect were seen in TKV, it was believed no other clinical benefits would be conveyed to patients.

The TKV endpoint methodology established in the NIH CRISP program was adapted for the pivotal study and validated.⁵ Total kidney volume also served as a mechanism for prognostic enrichment: data available during protocol design supported an association of

11 of 39

What values have been seen for a known endpoint?

Add endpoints

Close

Done

hba1c

☐

Estimated treatment difference in HbA1c

☐

Estimated treatment ratio in HbA1c

☐

Mean change from baseline in HbA1c

☐

Mean HbA1c

☐

Mean Ratio to baseline in HbA1c

☐

Diabetes

☐

Clinical chemistry

☐

Fasting plasma glucose (FPG) and Glycated hemoglobin (HbA1c)

☐

%patients achieved and maintained control of blood glucose and Hb...

☒

Glycated hemoglobin (HbA1c)

☒

% of patients who had a fall in glycated hemoglobin A1c (HbA1c) of 1.0

☒

% of subjects achieving an HbA1c level < 7.0%

☒

% of subjects who achieved target HbA1c levels of <7.0%

☒

% of subjects with HbA1c level 7.0% to 7.5%

☒

% of subjects with HbA1c level 7.5% to 8%

Search on:

Endpoints

x Diabetes, Clinical chemistry, Glycat...

One step – see all clinical data for an endpoint

PharmaPendium®

Browse ▾ Search ▾ My tools ^{new}

Efficacy data search results 39299 records from Efficacy data: Diabetes, Clinical chemistry, Glycated hemoglobin (HbA1c)

Show/hide columns > Show drugs in... > Save Export

Preclinical Data Clinical Data

ID	Drug ▾	Study Number ▾	Phase ▾	Mono/Combination ▾	Study Design ▾	Species ▾	Sex ▾	Age ▾	
1	Acarbose	626.0	Not specified	Monotherapy	four arm, double blind adjunct study	Human		Adult	Di
2	Acarbose	D91-006	Not specified	Monotherapy	randomized, double-blind, multi-center, placebo-controlled study	Human			Di
3	Acarbose	D96-004	Not specified	Combination	26 week, multi-center, randomized, double-blind, placebo controlled, two arm, parallel group comparison study	Human		Adult	Di
4	Acarbose	642.0	Not specified	Monotherapy	placebo controlled double blind study	Human		Adult	Di
5	Acarbose	619.0	Not specified	Monotherapy	double blind study	Human		Adult-aged	Di

Feedback

Apply filters to pinpoint to a relevant results set

Efficacy data search results 5057 records from Efficacy data: [\[Diabetes, Clinical chemistry, Glycated hemoglobin \(HbA1c\)\]](#)

Refine search results:

[Apply](#) [Clear All](#)

Phase

- ☒ III (4745)
- ☒ IIIa (7)
- ☒ IIIb (305)

Data provider

- ☒ Reviewer (1482)
- ☐ Sponsor (2573)
- ☐ Unreported (1002)

Sources

Study design

Primary/Secondary

- ☒ co-primary (83)
- ☒ primary (4974)

Preclinical Data **Clinical Data**

ID	Drug	Study Number	Phase	Mono/Combination
1	Albiglutide	GLP114130	III	Monotherapy
2	Albiglutide	GLP112757; GLP112753	III	Combination
3	Albiglutide	GLP112757; GLP112753	III	Combination

Search for 'endpoint'

The screenshot displays the PharmaPendium website interface. At the top, the PharmaPendium logo is on the left, and navigation links for 'Browse', 'Search', and 'My tools' are in the center. A 'new' badge is next to 'My tools'. On the right, there are icons for various functions and a user profile icon labeled 'IP-authorized'.

The main content area is titled 'FDA Approval Package - Canagliflozin > Summary Review' and 'Summary Review 204042/S-000'. A search bar at the top of the content area contains the text 'endpoint', with a 'Go' button and a page indicator '5/11'.

On the left side, there is a sidebar with a search icon and the text 'Search this FDA Package'. Below this, a list of categories is shown with plus signs: Administrative documents, Approval Letter, Chemistry Review, Clinical Pharmacology and Bi..., Environmental Review, Label, Letter, Medical/Clinical Review, Medication Guide, Other Important Informatio..., Pharmacology Review, Review, Statistical Review, and Summary Review. The 'Summary Review' category is expanded, showing a document icon and the text '2013-03-25 PDF(3600k) Summary Review 2040...'.

The main text area contains two paragraphs. The first paragraph discusses the effect of canagliflozin on secondary efficacy endpoints, mentioning pre-specified sequential testing procedures and treatment differences. The second paragraph discusses non-glycemic secondary endpoints, including weight loss, systolic blood pressure changes, and lipid changes. A footer note indicates that the document shows original U.S. government data provided by the U.S. Food & Drug Administration and is available in the public domain. The Reference ID is 3281940. The page is labeled 'Page 12 of 27' and 'Division Director Review'.