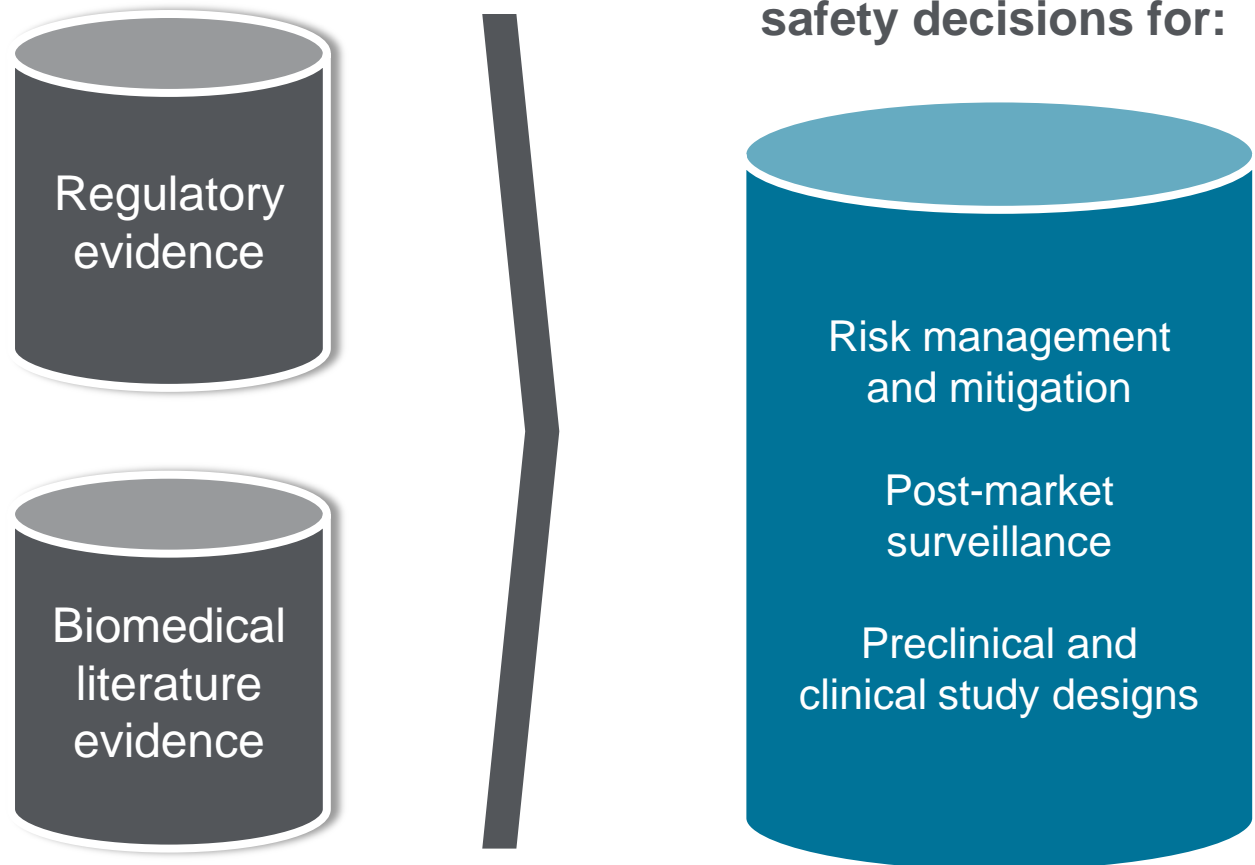




PharmaPendium® and Embase™:

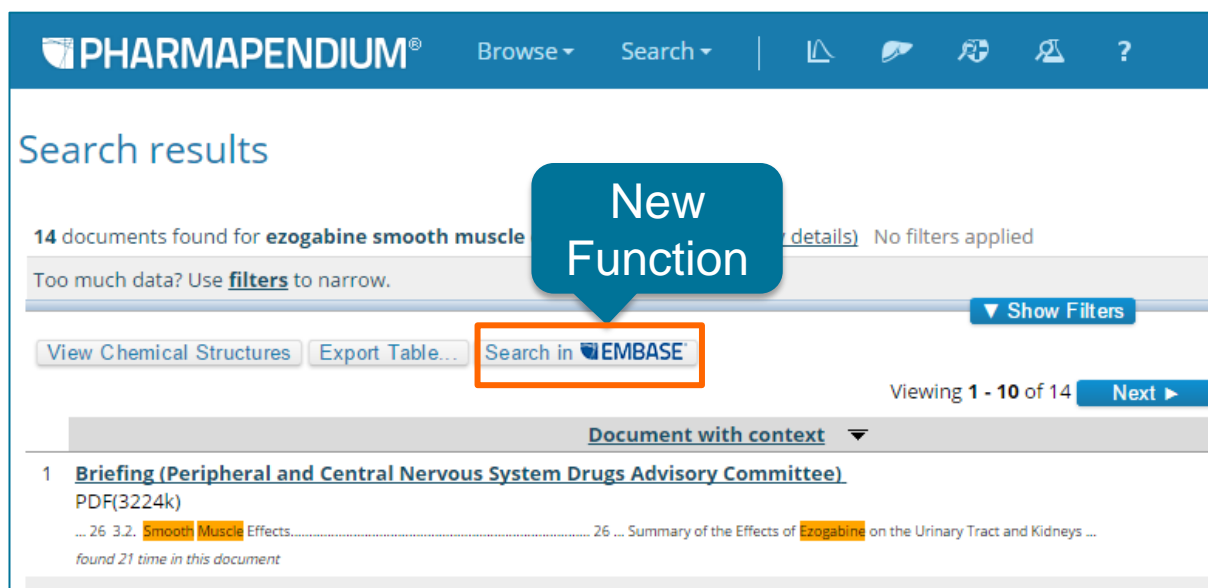
Improving drug safety
decisions with more
comprehensive searches

PP-EM can impact critical drug safety decisions with needed evidence



New Functionality in PharmaPendium links to Embase

- A new “Search in Embase” button appears on the PharmaPendium “Quick Search” results page



Look for this
PharmaPendium
by March 3,
2015, or sooner

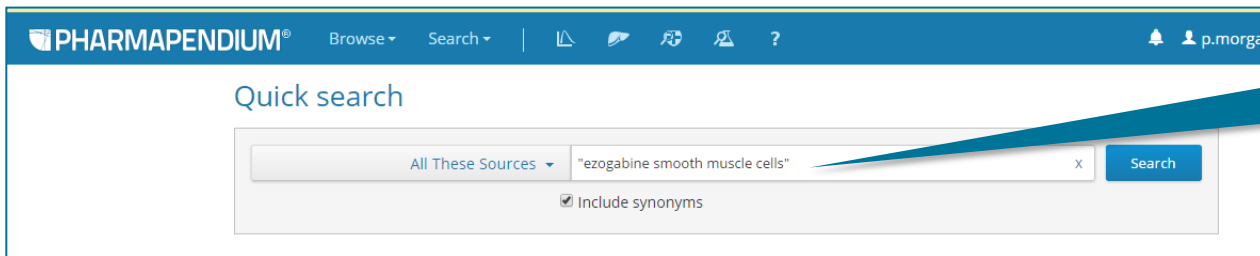
- Duplicates PharmaPendium search query directly into Embase
- Saves time and provides more consistent search results between the two products

Example: Use PP-EM to support experimental findings on cardiac safety

Find evidence to support an indication for a new drug candidate that acts on smooth muscle cells and has few cardiovascular adverse effect .The drug is very similar to one on market. The company wants to have more supportive evidence.

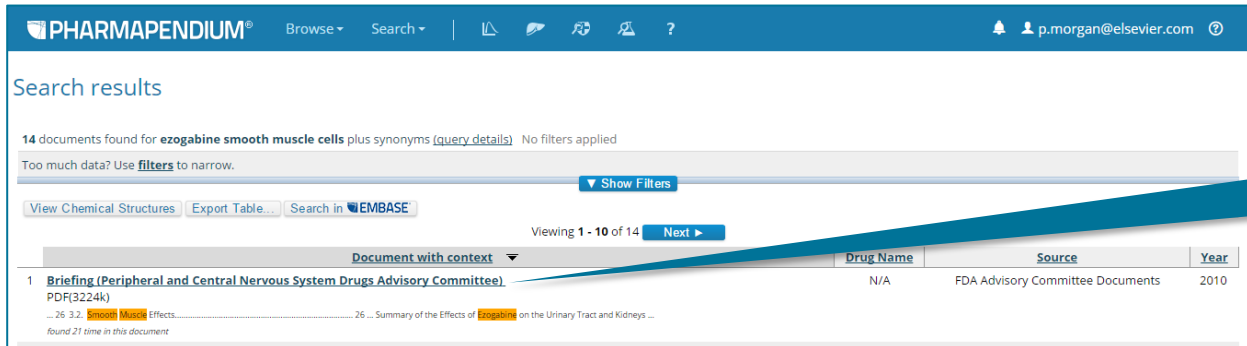
- Ezogabine, an antiepileptic drug as adjunctive therapy for partial-onset seizures in patients 18 years and older. Approved in 2011.What data was submitted about Ezogabine effects on smooth muscle cells and the effect on cardiac tissue?

Start in PharmaPendium



The screenshot shows the PharmaPendium Quick search interface. At the top, there is a navigation bar with 'PHARMAPENDIUM®', 'Browse', 'Search', and several icons. A user profile 'p.morgan' is visible in the top right. Below the navigation bar, the 'Quick search' section features a search bar with the text 'All These Sources' on the left and 'ezogabine smooth muscle cells' in the center. To the right of the search bar is a blue 'Search' button. Below the search bar, there is a checkbox labeled 'Include synonyms' which is checked.

Type in search term(s)



The screenshot shows the PharmaPendium Search results interface. At the top, there is a navigation bar with 'PHARMAPENDIUM®', 'Browse', 'Search', and several icons. A user profile 'p.morgan@elsevier.com' is visible in the top right. Below the navigation bar, the 'Search results' section displays '14 documents found for ezogabine smooth muscle cells plus synonyms (query details)'. Below this, there is a bar with 'Too much data? Use filters to narrow.' and a 'Show Filters' button. Below the bar, there are buttons for 'View Chemical Structures', 'Export Table', and 'Search in EMBASE'. Below these buttons, there is a table with columns 'Document with context', 'Drug Name', 'Source', and 'Year'. The table contains one row with the following data: '1 Briefing (Peripheral and Central Nervous System Drugs Advisory Committee) PDF(3224k)', 'N/A', 'FDA Advisory Committee Documents', and '2010'. Below the table, there is a snippet of text: '... 26 3.2. Smooth Muscle Effects ... 26 ... Summary of the Effects of Ezogabine on the Urinary Tract and Kidneys ... found 21 time in this document'.

Click on document link to view it

Example: Use PP-EM to support experimental findings on cardiac safety

Find evidence to support an indication for a new drug candidate that acts on smooth muscle cells and has few cardiovascular adverse effect The drug is very similar to one on market. The company wants to have more supportive evidence.

- Ezogabine, an antiepileptic drug as adjunctive therapy for partial-onset seizures in patients 18 years and older. Approved in 2011. What data was submitted about Ezogabine effects on smooth muscle cells and the effect on cardiac tissue?

The screenshot displays the PHARMAPENDIUM website interface. The top navigation bar includes the PHARMAPENDIUM logo, a 'Browse' dropdown, a 'Search' dropdown, and a user profile icon for 'p.morgan@elsevier.com'. The main content area is titled 'Ezogabine - FDA Approval Package' and 'Pharmacology Review 022345/S-000 Part 07'. A sidebar on the left lists various document sections: '2010-Nov-30 PDF(1367k) Pharmacology Review 022345/S-000 Part 06', '2010-Nov-30 PDF(690k) Pharmacology Review 022345/S-000 Part 07', 'Medical/Clinical Review', 'Clinical Pharmacology and Biopharmaceutics', 'Chemistry Review', 'Statistical Review', 'Summary Review', 'Review', 'Approval Letter', 'Label', 'Administrative documents', and 'Other Important Information from FDA Letter'. The main text area shows a paragraph discussing the effects of retigabine on KCNQ channels and smooth muscle contractility. A blue callout bubble points to a specific sentence in the text.

PHARMAPENDIUM® Browse Search | ? p.morgan@elsevier.com

Browse FDA Package Ezogabine - FDA Approval Package

Search this FDA Package: Go

2010-Nov-30 PDF(1367k) Pharmacology Review 022345/S-000 Part 06

2010-Nov-30 PDF(690k) Pharmacology Review 022345/S-000 Part 07

Medical/Clinical Review

Clinical Pharmacology and Biopharmaceutics

Chemistry Review

Statistical Review

Summary Review

Review

Approval Letter

Label

Administrative documents

Other Important Information from FDA Letter

Pharmacology Review 022345/S-000 Part 07

The finding that retigabine appears to act exclusively on KCNQ2-5 isoforms without affecting cardiac KCNQ1 channels is considered clinically important in minimizing adverse effects on cardiac function. However, "neuronal" KCNQ channels (KCNQ4 and 5) have recently been found to be expressed in vascular smooth muscle cells where they seem to play a role in controlling arterial tone (Yeung et al, Br J Pharmacol 151:758-770,2007). Flupirtine, a structural analogue of retigabine (approved as an analgesic in Europe), has been reported to lower systolic blood pressure in rats and humans, presumably via relaxation of vascular smooth muscle (Mackie and Byron, Mol Pharmacol 74:1171-79,2008). This effect was demonstrated by the sponsor in safety pharmacology studies of retigabine in dogs and pigs, which was noted that the decrease in blood pressure was not accompanied by the expected reflex tachycardia, which may indicate other nonvascular effects such as on the heart or its nervous system regulation (eg, baroreceptor neurons). A modest decrease in heart rate in response to flupirtine reported by Mackie et al (J Pharmacol Exp Ther 325:475-483,2008), was thought to possibly be a consequence of nonvascular KCNQ channel activation (eg, a reduction of sympathetic ganglionic nerve activity).

A role for KCNQ channels in controlling peripheral smooth muscle contractility appears to extend to the urinary bladder and gallbladder. In isolated rat urinary bladder tissue, retigabine reduced both the contractility and overall tone of bladder tissue independent of the mode of stimulation, and these effects could be reversed by the KCNQ channel inhibitor XE991 (Rode et al, Eur J Pharmacol 638:121-

2 of 19

Data from a dog and pig study suggest that a slight decrease in blood pressure was not accompanied by the expected reflex tachycardia.

Example: Use PP-EM to support experimental findings on cardiac safety

Launch Embase through the “Search in Embase” function to see if any Post-Market study updates have been published as further evidence.

The screenshot shows the Pharmapendium search results page. The search query is 'ezogabine smooth muscle cells'. The results show 14 documents found. A callout box points to the 'Search in EMBASE' button.

Search results

14 documents found for **ezogabine smooth muscle cells** plus synonyms ([query details](#)) No filters applied

Too much data? Use [filters](#) to narrow.

[View Chemical Structures](#) [Export Table...](#) [Search in EMBASE](#)

Viewing 1 - 10 of 14 [Next](#)

Document with context	Drug Name	Source	Year
1 Briefing (Peripheral and Central Nervous System Drugs Advisory Committee) PDF(3224k) ... 26 3.2. Smooth Muscle Effects... 26 ... Summary of the Effects of ezogabine on the Urinary Tract and Kidneys ... found 21 time in this document	N/A	FDA Advisory Committee Documents	2010

Click on
Search in Embase

The screenshot shows the Embase search results page. The search query is 'retigabine/de AND smooth AND muscle AND cells'. The results show 16 results for search #1. A callout box points to the first result.

EMBASE™ Search Browse Results Tools

Search

History Save Delete Print view Export Email Combine using And Or

16 results for search #1

Sort by: Relevance Publication Year Entry Date

Selected: 0 (click) or Select number of items

1 [Vasorelaxant effects of novel Kv7.4 channel enhancers ML213 and NS15370](#)
Jepps T.A., Bentzen B.H., Stott J.B., Povstyan O.V., Sivaloganathan K., Dalby-Brown W., Greenwood I.A.
[article in press] *British Journal of Pharmacology* 2014

Embase [Abstract](#) [Index Terms](#) [View Full Text](#)

Examine results

Example: Use PP-EM to support experimental findings on cardiac safety

Launch Embase through the “Search in Embase” function to see if any Post-Market study updates have been published as further evidence.

The screenshot displays the Embase search interface. The search bar contains the query: 'retigabine/de AND smooth AND muscle AND cells'. The search results are listed below the search bar, showing 16 results for search #1. The results are sorted by Relevance. The first result is titled 'Vasorelaxant effects of novel Kv7.4 channel enhancers ML213 and NS15370' by Jepps T.A., Bentzen B.H., Stott J.B., Povstyan O.V., Sivaganesan K., Dalby-Brown W., Greenwood I.A. (Article in Press) *British Journal of Pharmacology* 2014. The second result is titled 'Improving bronchodilator therapy by combining Kv7 channel activators with B2-adrenergic agonists' by Haick J., Brueggemann L., Schwarz J., Solway J., Byron K. *Basic and Clinical Pharmacology and Toxicology* 2014 115 SUPPL. 1(91-). The third result is titled 'Pharmacological dissection reveals functional roles for KCNQ channel subtypes in human urinary bladder smooth muscle contractility' by Provence A., Rovner E., Petkov G. *FASEB Journal* 2014 28:1 SUPPL. 1. The fourth result is titled 'A novel approach to bronchodilation: Combining the Kv7 channel activator retigabine with the B2-adrenergic agonist formoterol' by Haick J., Brueggemann L., Byron K. *FASEB Journal* 2014 28:1 SUPPL. 1. The fifth result is titled 'Differential activation of vascular smooth muscle Kv7.4, Kv7.5, and Kv7.4/7.5 channels by ML213 and ICA-069673' by Brueggemann L.L., Haick J.M., Cribbs L.L., Byron K.L. *Molecular Pharmacology* 2014 86:330-341. The sixth result is titled 'Molecular Expression and Pharmacological Evidence for a Functional Role of Kv7 Channel Subtypes in Guinea Pig Urinary Bladder Smooth Muscle' by Afeli S.A.Y., Malysz J., Petkov G.V. *PLoS ONE* 2013 8:9 Article Number e75875. The seventh result is titled 'Role of KCNQ channels in skeletal muscle arteries and periaortic vascular dysfunction' by Zavaritskaya O., Zhuravieva N., Schlieffenbaum J., Goe T., Devermann L., Kluge R., Mladenov M., Frey M., Gagov H., Fesus G., Gollasch M., Schubert R. *Hypertension* 2013 61:1(151-159) [Cited by 8](#). The search results are displayed in a table format with columns for Title, Author, Journal, and Year. The search bar also includes filters for Mapping, Date, Sources, Fields, Quick limits, EBM, Pub. types, Languages, Gender, Age, and Animal. The search results are displayed in a table format with columns for Title, Author, Journal, and Year. The search bar also includes filters for Mapping, Date, Sources, Fields, Quick limits, EBM, Pub. types, Languages, Gender, Age, and Animal.

This article suggests that Ezogabine could be a useful combination treatment for asthma.

Evidence suggest that Ezogabine may play a role in improving impaired periaortic vasoregulation and associated hypertension.

Example: Use PP-EM to support experimental findings on cardiac safety

Summary of findings

- From PharmaPendium:
 - Ezogabine data indicates “...little effect on heart and its nervous system..”
- From Embase, published information of post-market studies using Ezogabine:
 - Found 2 additional indications beyond that of partial-onset seizure control
 - Both act on smooth muscle cells
- Together, this information can help inform preclinical study designs to further characterize new drug candidates
 - Findings can be leveraged to further strengthen scientific data
 - Regulatory and literature evidence can support preclinical data package
 - Help uncover unanticipated clinical risks

Example: PP-EM can inform Clinical Study Designs

A company is interested in finding post-market published information on Tafluprost, a drug in the same class as one of the company's drug candidates that is entering clinical trials. This information could offer additional insights into potential testing that may be required during clinical development.

- First, explore post-market requirements for Tafluprost in PharmaPendium to determine if post-market studies were required and, if so, what were the designs?

PHARMAPENDIUM® Browse Search | [Icons] ?

Quick search

All These Sources [X] Search

☒ Include synonyms

Type in search term(s)

PHARMAPENDIUM® Browse Search | [Icons] ?

Browse FDA Package

Search this FDA Package: [Go]

Tafluprost - FDA Approval Package

Medical/Clinical Review 202514/S-000 Part 01

Document	Summary
2012-Jan-31 PDF(12568k) Medical/Clinical Review 202514/S-000 Part 01	Post-approval regulatory commitment, open label study in Japan.
2012-Jan-31 PDF(527k) Medical/Clinical Review 202514/S-000 Part 02	TAPROS ophthalmic solution 0.0015% Special Drug Use results Survey (Investigation on Long-term Use)
2012-Jan-31 PDF(984k) Medical/Clinical Review 202514/S-000 Part 03	Followed for 2, 12 and 24 months, follow-up of 6 months if discontinued TAPROS due to AE
	administration: 52 wk treatment period of patients (03/09)
	All patients enrolled to tafluprost PC by centralized registration system (TAPROS is the marketed tafluprost in Japan).
	4502 tafluprost PC
	Treatment Phase ongoing

Post-Market studies for Tafluprost approval

Example: PP-EM can inform Clinical Study Designs

Next, click on the “Search in Embase” link to see the Embase search results. An article that aligns to the requirements for additional post-market studies as stated in the table from PharmaPendium is found.

EMBASE™ Search ▾ Browse ▾ Results Tools ▾ (1) Register Login ?

RESULTS FILTERS
Expand | Collapse all APPLY

SOURCES
DRUGS
DISEASES
DEVICES
FLOATING SUBHEADINGS
AGE
GENDER
STUDY TYPES
PUBLICATION TYPES
JOURNAL TITLES
PUBLICATION YEARS
AUTHORS
CONFERENCE ABSTRACTS
DRUG TRADE NAMES
DRUG MANUFACTURERS
DEVICE TRADE NAMES
DEVICE MANUFACTURERS

Search 'tafluprost/de AND 'post marketing''
Search Mapping Date Sources Fields Quick limits EBM Pub. types Languages Gender Age Animal

History Save Delete Print view Export Email Combine using And Or

#2 'tafluprost/de AND 'post marketing''
#1 'retigabine/de AND smooth AND muscle AND cells

1 results for search #2

Results View Print Export Email Order Add to Clipboard
Sort by: Relevance Publication Year Entry Date

1 Prospective observational post-marketing study of tafluprost for glaucoma and ocular hypertension: Short-term safety
Kuwayama Y, Nomura A
Advances in Therapy 2014 31:4(461-471)
Embase Abstract Index Terms View Full Text

Introduction: This study investigated the intraocular pressure (IOP)-lowering effects and safety of tafluprost ophthalmic solution 0.0015% in actual clinical practice. **Methods:** We started a mandatory prospective 2-year observational study, which collected IOP, conjunctival hyperemia score, corneal staining score, and adverse event data from glaucoma and ocular hypertension (OH) patients not previously treated with tafluprost at 2, 12, and 24 months. This report analyzes the 2-month findings. **Results:** Of the 4,180 patients from 553 medical institutions in Japan, most patients had primary open-angle glaucoma (POAG, 38.1%) or normal-tension glaucoma (NTG, 44.2%). After 2 months of tafluprost administration, IOP was significantly reduced by 4.3 ± 5.2 mmHg in POAG, 2.4 ± 2.5 mmHg in NTG, 3.6 ± 5.3 mmHg in primary angle-closure glaucoma, 5.6 ± 7.1 mmHg in other types of glaucoma, and 5.3 ± 4.8 mmHg in OH. IOP was significantly reduced by 4.3 ± 4.0 mmHg in the naive monotherapy group, 1.9 ± 3.5 mmHg in switching from prior treatment, and 3.7 ± 4.1 mmHg in the add-on therapy group. Among patients switched, the prostaglandin analog (PGA) latanoprost was the previous predominant drug (57.4%), followed by travoprost (13.8%). Significant IOP reductions were observed by 1.5 ± 3.4 mmHg in switching from latanoprost and 1.3 ± 3.7 mmHg in switching from travoprost. The conjunctival hyperemia score peaked at 1 month in the naive monotherapy and add-on therapy groups, whereas it was significantly decreased in patients switched from another PGA. The corneal staining score showed no particular changes. Incidence of adverse drug reaction (ADR) was 7.70 % (322/4,180 patients), and all major ADRs involved the eyes or skin around the eyes. **Conclusion:** Tafluprost showed significant IOP-lowering effects without any safety concerns in patients with various types of glaucoma and OH in daily clinical practice and tafluprost is highly effective in any therapeutic patterns. © 2014 Springer Healthcare.

Results View Print Export Email Order Add to Clipboard

Records per page: 25 ▾ Go to page: 1 of 1 Go

At the 2 month time point of a 2 year study, Tafluprost provided greater efficacy than the two other drugs.

Example: PP-EM can inform Clinical Study Designs

Summary of findings

- Tafluprost received approval with a commitment by the sponsor to complete several post-market studies
 - Several studies focused on Japanese patient populations
 - This information may be useful during agency reviews (cite, supporting evidence, clinical study designs for patient subgroups) and informing potential clinical trials study designs for specific patient populations
- As the study is over a 2 year period, information on long term use will emerge that could impact:
 - Post-market testing requirements
 - REMS planning to better understand how to mitigate any potential safety risks/concerns
 - Clinical trial designs for specific patient populations
- Data from this required post-market study was only found in Embase
- Critical information from both PharmaPendium and Embase helps support decisions on clinical trial designs

More comprehensive information and resources can impact drug safety decisions

Post-Market

- Help define potential post-market testing requirements
- Improve REMS planning by providing a better understanding of how to mitigate any potential safety risks/concerns
- Improve clinical trial designs for specific patient populations

Risk Management / Mitigation

- Leverage findings to further strengthen scientific data
- Support regulatory reviews with regulatory and literature evidence
- Help uncover unanticipated clinical risks



Thank you

