

Integration of pre-clinical, clinical and post-marketing safety data

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October, 2006





Agenda

- Drug safety - background
- Safety and the drug development process
- Drug safety teams - needs and challenges
- Summary

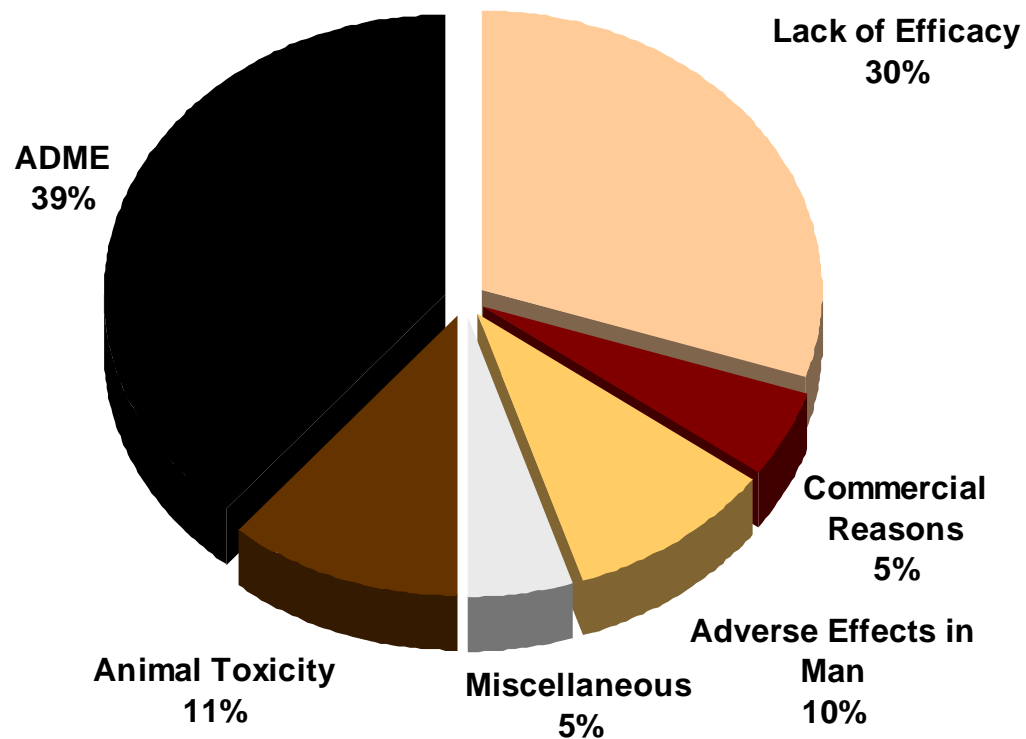


Drug Safety - Background

- Often referred to as pharmacovigilance
- Focuses on gathering, detecting, and analyzing adverse events information to prevent further or future related events in humans.
- Not necessarily limited to medications
 - **Herbal and other supplements/biologicals**
- Can be very complex
 - **Drug–Drug interactions**
 - **Rare effects**

ADME-Tox Liabilities Account for 60% of NCE Failures

Failure of New Chemical Entities (n=198)



ADME: Absorption/Distribution/Metabolism/Elimination
DDT Vol 2, No. 10, October 1997





**“Managing Toxicology for the Future” An excerpt
from D&MD's Market Analysis Report; By Mike
Silver, PhD and Brigitta Tadmor, PhD January 2003**

*“About one third of all drugs fail preclinical or clinical testing because of apparent or suspected drug toxicities. **According to industry estimates, companies spend about \$2 billion annually on toxicity-related drug failures.** The inaccuracy of safety screens in place today can also lead to enormous lost opportunity costs. Termination of a single potential blockbuster drug in development or on the market can lead to lost revenue far exceeding the total direct cost of industry failures. **Despite the staggering financial losses associated with toxicity-related drug failures, companies typically spend only about 5% of their total R&D budget on drug safety evaluations.**” **<emphasis added>***



<http://www.drugandmarket.com/default.asp?section=feature&article=011403>



Post-market failures

- Vioxx had \$2.5B in sales when it was pulled from the market in Fall 2004
 - Merck Inc. stock fell 33% in less than a month
- Not an isolated incident
 - Rezulin
 - Seldane
 - Baycol
 - Fen-Phen
- Millions spent in litigation, settlements and fines





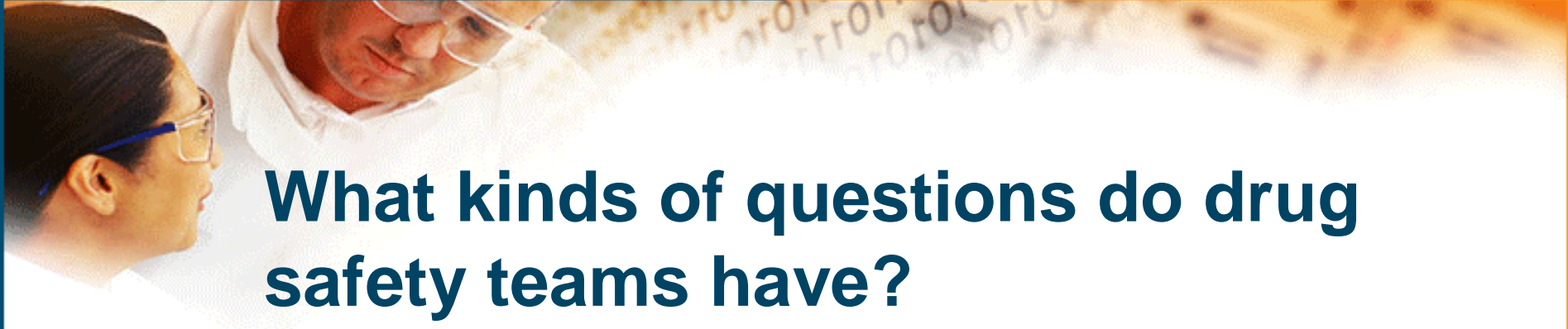
Changes in approach

- Drug safety teams becoming more interdisciplinary and horizontal
 - More interaction and communication with researchers at all stages
 - Greater attention paid to safety issues from the beginning of development
 - Information from all stages of drug development fed back into the early phases of the research process



What do drug safety teams do?

- Conduct toxicity studies and evaluate the results
- Handle regulatory reporting
- Monitor safety issues
 - **Existing drugs and new candidates**
- Compile safety assessments



What kinds of questions do drug safety teams have?

- What do we know about the toxicological mechanism of this compound or compounds like it? What can we predict?
- What side effects are we seeing in humans?
- How does this compare to the preclinical results?
- Do our competitors have any similar compounds in their pipeline or approved? Why was research on competitor drug X terminated?
- Do any of the above have implications on our developing pipeline?



Where is the needed data?

- In-house data
 - **ADME/tox screening data, etc.**
- Journal articles
- Conferences
- Regulatory submissions (multiple countries)
 - **From new drugs to post-marketing feedback**
 - **Clinical study results**
- Books
- Commercial and Public Databases
- Personal contacts

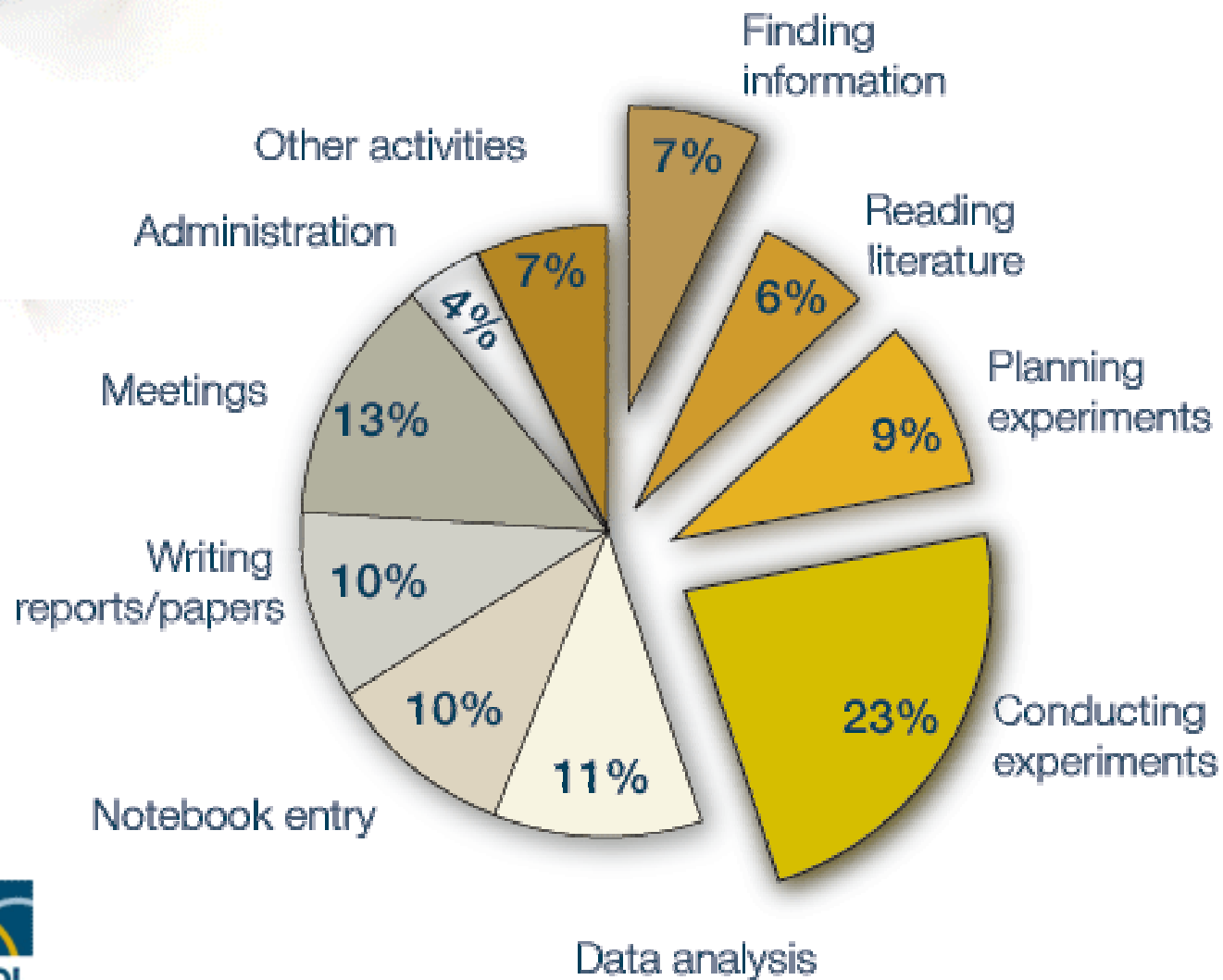


Drug safety - The information challenge

- Much of published safety data and precedent is held in disparate sources
 - **inconsistent or non-existent indexing**
 - **information difficult to find quickly**
 - **Sources are in different formats**
 - **No longitudinal view of the data**
 - **Must integrate different data types**
 - Preclinical/clinical/post-market
- Never sure of comprehensiveness



How scientists spend their time?





The Need - Drug Safety

- “..... people in our toxicology department spend 40% of their time searching for safety information...and usually have no confidence that they have found all of what is available...”

– *A Global VP, Preclinical Dev*



What do drug safety teams need?

- Better safety data
- Integrated preclinical, clinical and post-marketing data
- Better data organization and context

..... and make it easy to use



Better Safety Data

- FDA Approval Packages
 - **Extremely rich source of information available via the Freedom of Information Act**
 - **Generally Untapped**
 - Not well indexed or searchable
 - Formats: paper, microfiche, bitmap
 - Tedious to find specific facts (side effects or adverse events)
 - Finding class/target/effect/dose relationships can be impossible



FDA Approval Packages - Examples of Original Documents

Reviewer: Kimberly A. Benson, Ph.D.

NDA No. 21-335

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 19-839/S-035
20-990/S-003*

SPONSOR: Pfizer Pharmaceuticals Group

DRUG: Zoloft (Sertraline HCl) Tablets and Oral Concentrate

DATE OF DOCUMENT: 5/25/2001

DATE RECEIVED: 5/29/2001

I. REVIEW:

These supplemental new drug applications listed above provide for the use of Zoloft (sertraline HCl) to Zoloft (sertraline HCl) oral concentrate for the long-term treatment of post-traumatic stress disorder (PTSD).

In response to our approvable letter, the sponsor has submitted the updated version of the proposed package insert taking into account the comments received from us. All of the suggestions received from the Agency were incorporated into the labeling with the exception of the following few items:

- Under INDICATIONS AND USAGE, PTSD, in the fourth and final paragraph of this subject term was deleted in the first sentence of this paragraph because the patients that enter open label 24-week treatment had already completed a 12-week placebo-controlled trial prior to entering the open label treatment.
- Under DOSAGE AND ADMINISTRATION, Maintenance Treatment, the three paragraphs submitted by the Agency were incorporated with a few minor revisions.

In the third sentence of the first paragraph of this section under the sub-heading of Depression term was deleted. It is Pfizer's position that this term is unnecessary because the data to which it refers is well described in the previous sentence. The phrase " " was deleted from the fourth sentence of the first paragraph of this section because the statement is repetitive and repeats what was previously been said about the dosing in the same paragraph.

Toxicokinetics:

Table 4.5-1. Summary of toxicokinetic data for CGP 671488

| | 3 mg/kg/day | | 15 mg/kg/day | | 75 mg/kg/day | |
|-----------------|--------------------------------|--------------------------|--------------------------------|--------------------------|--------------------------------|--------------------------|
| | AUC _{0-24h} (ng·h/mL) | C _{max} (ng/mL) | AUC _{0-24h} (ng·h/mL) | C _{max} (ng/mL) | AUC _{0-24h} (ng·h/mL) | C _{max} (ng/mL) |
| MALES: | | | | | | |
| Days 1/2 | 214 ± 156 | 37.2 ± 34.5 | 1650 ± 1240 | 216 ± 170 | 16000 ± 6390 | 1210 ± 325 |
| Days 91/92 | 230 ± 107 | 32.4 ± 18 | 1450 ± 1710 | 178 ± 236 | 16800 ± 6730 | 1080 ± 384 |
| FEMALES: | | | | | | |
| Days 1/2 | 218 ± 83.0 | 40.9 ± 20.8 | 2340 ± 1340 | 310 ± 182 | 18000 ± 4500 | 1230 ± 287 |
| Days 91/92 | 286 ± 61.1 | 44.6 ± 13.2 | 1960 ± 291 | 208 ± 99.0 | 16800 ± 4810 | 1280 ± 143 |

Table 7.1-11 Dose Normalized AUC_{0-24h} and C_{max}

| Dose (mg/kg/day) | AUC _{0-24h} (ng·h/mL) | | | | C _{max} (ng/mL) | | | |
|------------------|--------------------------------|--------|--------|--------|--------------------------|--------|--------|--------|
| | Male | | Female | | Male | | Female | |
| | Day 1 | Day 91 | Day 1 | Day 91 | Day 1 | Day 91 | Day 1 | Day 91 |
| 3 | 71.3 | 72.7 | 76.7 | 66.3 | 12.4 | 13.8 | 10.8 | 14.9 |
| 15 | 110 | 188 | 97 | 131 | 14.4 | 20.7 | 11.7 | 13.7 |
| 75 | 213 | 200 | 211 | 208 | 16.1 | 16.4 | 14.4 | 17.1 |

Summary of individual study findings:

Daily dosing daily for 13 weeks with imatinib at doses of 3, 15 and 75 mg/kg/day was not lethal in this monkey study. The highest dose administered did cause gastrointestinal effects, as evidenced by emesis in 9/10 animals. The toxicokinetic data indicates that the emesis seen in the HD monkeys did not interfere with the absorption of the administered dose of drug, as the expected increase in AUC with higher doses was evident. Four animals, two of each sex, at this dose did show a decrease in body weight during the first 3 weeks, all except one female began gaining weight after week 3. That HD female weighed 7% less at the end of the 13-week dosing than at the beginning of the testing. Hematological changes were seen, primarily in the HD



OCR Results

Page

Table 4.4-1: Summary of Pharmacokinetic Data for OIP 11188

| Sex | Day | Dose (mg/kg) | AUC _{0-24h} (ng·h/mL) | C _{max} (ng/mL) | t _{1/2} (h) |
|--------|-------|--------------|--------------------------------|--------------------------|----------------------|
| Male | 1/2 | 3 | 214 ± 156 | 37.2 ± 34.5 | 1660 ± 1240 |
| | | 15 | 230 ± 107 | 32.4 ± 18 | 1460 ± 1710 |
| | 91/92 | 3 | 216 ± 83.0 | 40.9 ± 20.6 | 2340 ± 1340 |
| | | 15 | 266 ± 61.1 | 44.6 ± 13.3 | 1960 ± 291 |
| Female | 1/2 | 3 | 214 ± 156 | 37.2 ± 34.5 | 1660 ± 1240 |
| | | 15 | 230 ± 107 | 32.4 ± 18 | 1460 ± 1710 |
| | 91/92 | 3 | 216 ± 83.0 | 40.9 ± 20.6 | 2340 ± 1340 |
| | | 15 | 266 ± 61.1 | 44.6 ± 13.3 | 1960 ± 291 |

Summary of individual study findings:

1 Daily dosing daily for 13 weeks with imatinib at doses of 3, 15 and 75 mg/kg/day was well tolerated in this monkey study. The highest dose administered did not cause gastrointestinal effects, as evidenced by mean to 5/10 animals. The toxicokinetic data indicates that the mean area under the curve (AUC) did not increase with the absorption of the administered dose of drug, as the expected increase in AUC with higher doses was evident. Four animals, two of each sex, at this dose did show a decrease in body weight during the first 3 weeks. All except one female began gaining weight after week 3. The HD female weighed 7% less at the end of the 13-week dosing than at the beginning of the testing. Hematological changes were seen, primarily in the HD animals, and had resolved by the end of the recovery period. Predominantly, these changes included red cell changes. Red blood cell count, hemocrit and hemoglobin were all significantly decreased by 20-30% from normal in the HD males during the 13-week administration. More modest decreases were seen in the HD females in hemocrit and hemoglobin, 14-19% less than control. These red cell changes could explain the pale gums seen in the HD monkeys, but even at the end of the recovery period, when the red cell parameters were not significantly lower than control, the pale gums were seen in 1/4 animals.

While blood cell parameters, mainly absolute neutrophils and lymphocyte counts, were significantly decreased in the HD male monkeys. These values returned to normal by the end of the recovery period.

Toxicokinetic data show no sex differences in the exposure levels of STS11 and no accumulation of the drug over the 13-week dosing schedule. The AUC_{0-24h} was proportional to the dose of STS11 administered. The C_{max} increased proportionally with higher doses.

STS11, administered daily to monkeys in doses of 3 and 15 mg/kg/day, was tolerated well by the animals with minimal toxicity. The high dose, 75 mg/kg/day, had hematological

Text

Reviewer Kimberly A. Benson, Ph.D.

Toxicokinetics:

Tab * 44H. Summary of toxicokinetic data for CC

| | 5mg/kg/day (ng·h/mL) | 15mg/kg/day (ng/mL) | (ng/mL) | (n) |
|------------------|-------------------------|------------------------|-------------|-----|
| MALE S: | | | | |
| Day 1/2 | 214 ± 156 | 37.2 ± 34.5 | 1660 ± 1240 | 21 |
| Days 91/92 | 230 ± 107 | 32.4 ± 18 | 1460 ± 1710 | 17 |
| FEMALE S: | | | | |
| Days 1/2 | 216 ± 83.0 | 40.9 ± 20.6 | 2340 ± 1340 | 31 |
| Days 91/92 | 266 ± 61.1 | 44.6 ± 13.3 | 1960 ± 291 | 20 |

Table 7.1-11: Doxorubicin AUC, M₁ am

| Dose (mg/kg) | AUC _{0-24h} (ng·h/mL) | C _{max} (ng/mL) | |
|--------------|--------------------------------|--------------------------|--------|
| | | Day 91 | Day 91 |
| 3 | 71.3 | 72.7 | 76.7 |
| 16 | 110 | 166 | 97 |
| 76 | 213 | 200 | 211 |

Summary of individual study findings:

Daily dosing daily for 13 weeks with imatinib at doses of 3, 15 and 75 mg/kg/day was well tolerated in this monkey study. The highest dose administered did not cause gastrointestinal effects, as evidenced by mean to 5/10 animals. The toxicokinetic data indicates that the mean area under the curve (AUC) did not increase with the absorption of the administered dose of drug, as the expected increase in AUC with higher doses was evident. Four animals, two of each sex, at this dose did show a decrease in body weight during the first 3 weeks. All except one female began gaining weight after week 3. The HD female weighed 7% less at the end of the 13-week dosing than at the beginning of the testing. Hematological changes were seen, primarily in the HD animals, and had resolved by the end of the recovery period. Predominantly, these changes included red cell changes. Red blood cell count, hemocrit and hemoglobin were all significantly decreased by 20-30% from normal in the HD males during the 13-week administration. More modest decreases were seen in the HD females in hemocrit and hemoglobin, 14-19% less than control. These red cell changes could explain the pale gums seen in the HD monkeys, but even at the end of the recovery period, when the red cell parameters were not significantly lower than control, the pale gums were seen in 1/4 animals.



FDA Approval Packages - Busulfan

Search All These Sources for

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Search this FDA Package: Go

7 documents found for tmax plus synonyms

- 1998-Aug-3 PDF(2436k)
[Clinical Pharmacology and Biopharmaceutics Review >](#)
[Clinical Pharmacology and Biopharmaceutics Review 020954](#)
...18.55 Cmax (ng/mL) 39 1284 1303
290 23 Tmax (hr) 39.00 2.10 2.00 0.25
11.71 T1/2...
found 33 times in this document
- 1999-Jun-14 PDF(568k)
[Clinical Pharmacology and Biopharmaceutics Review >](#)
[Clinical Pharmacology and Biopharmaceutics Review 020954/S-000 Part 02](#)
...18.55 Cmax (ng/mL) 39 1284 1303
290 23 Tmax (hr) 39.00 2.10 2.00 0.25
11.71 T1/2...
found 13 times in this document
- 1999-Jun-14 PDF(725k)
[Clinical Pharmacology and Biopharmaceutics Review >](#)
[Clinical Pharmacology and Biopharmaceutics Review 020954/S-000 Part 04](#)

Busulfan - FDA Approval Package

Clinical Pharmacology and Biopharmaceutics Review 020954/S-000 Part 02 (1999-Jun-14)

Find: Previous Next

OMC-BUS-3

Table 9
Summary of Intravenous Busulfan Pharmacokinetic Parameters from Dose 9 (BMT Day -5)

| Dose (mg) | Cmax (ng/mL) | Tmax (hr) | T1/2 (hr) | AUC _{0-∞} (uMol·min) | CL (mL/min) | Vz (L) | CL/ABW (mL/min/kg) |
|-----------|--------------|-----------|-----------|-------------------------------|-------------|--------|--------------------|
| 39.00 | 39 | 39.00 | 39.00 | 39 | 39.00 | 39.00 | 39.00 |
| 53.23 | 1284 | 2.10 | 3.47 | 1225 | 180.26 | 54.97 | 2.25 |
| 53.00 | 1303 | 2.00 | 3.09 | 1199 | 170.33 | 47.50 | 2.23 |
| 9.87 | 290 | 0.25 | 1.36 | 216 | 42.33 | 28.14 | 0.46 |
| 18.55 | 23 | 11.71 | 39.10 | 18 | 23.48 | 51.20 | 20.40 |

11.01 x 8.50 in 9 of 21



FDA Approval Packages database

- ~ 33,000 documents included
 - ~ 700,000 pages of information
 - ~ 300,000 extracted safety records

- Indexed and electronically searchable for the first time

Integration - preclin/clin/post-mktg

pharmaPendium™
the essential drug safety resource

Home Drugs Adverse Effects / Toxicity Targets

Log Out Search Tips Help

Search All These Sources for Include synonyms Advanced Search - Chemistry Search - Extracted Data Search

Post-Market Reports (AERS) for ECG investigations

Preclinical Data (452) Clinical Data (2063) **Post-Market Reports (AERS) (11632)**

PharmaPendium post market reports are taken from the [FDA AERS database](#).
This database is used as provided by the FDA CDER in PharmaPendium and may contain duplicate records, coding and classification errors.

▶ Viewing serious & nonserious reports
• [View serious reports only](#)

Limit to a specific Drug or Adverse Event:

Viewing 776 of 776

| Drug Name ▲ | # Reports | Adverse Events | Reports by Gender | Reports by Age |
|---|-----------|---|-------------------|-----------------|
| 1 Abacavir Sulfate drug info | 20 | <ul style="list-style-type: none"> Electrocardiogram abnormal (4) Electrocardiogram QT prolonged (4) Electrocardiogram ST segment abnormal (3) Electrocardiogram ST segment depression (3) Electrocardiogram ST segment elevation (3) Electrocardiogram change (2) Electrocardiogram QRS complex abnormal (2) Electrocardiogram T wave inversion (2) Electrocardiogram Q waves (1) Electrocardiogram repolarisation abnormality (1) view all... | M = 17 F = 1 | <20 1 20+ 15 |
| 2 Abacavir Sulfate; Lamivudine; Zidovudine drug info | 7 | <ul style="list-style-type: none"> Electrocardiogram QT prolonged (2) Electrocardiogram ST segment depression (2) Electrocardiogram T wave inversion (2) Electrocardiogram change (1) | M = 7 F = 0 | <20 0 20+ 7 |



Better data organization and context

Browse Drugs A-Z

Lookup: **Go**

- Antibiotics, penicillins
- Antibiotics, tetracyclines
- Anticholinergics
- Anticoagulants
- Anticonvulsants
- antimentia
- Antidepressants, miscellaneous
- Antidepressants, monoamine oxid
- Antidepressants, serotonin specif
 - Citalopram Hydrobromide
 - Escitalopram Oxalate
 - Fluoxetine Hydrochloride
 - Fluvoxamine Maleate
 - Olanzapine; Fluoxetine Hydroc
 - Paroxetine Hydrochloride
 - Paroxetine Mesylate
 - Sertraline Hydrochloride
- Antidepressants, tetracyclic
- Antidepressants, tricyclic
- Antidiabetic agents
- Antidiarrheals
- Antidiuretics
- Antidotes

Antidepressants, serotonin specific reuptake inhibitors

Drugs: [Citalopram Hydrobromide](#)
[Escitalopram Oxalate](#)
[Fluoxetine Hydrochloride](#)
[Fluvoxamine Maleate](#)
[Olanzapine; Fluoxetine Hydrochloride](#)
[Paroxetine Hydrochloride](#)
[Paroxetine Mesylate](#)
[Sertraline Hydrochloride](#)

Targets: [SERT](#), [Serotonin Transporter](#)

Adverse Effects / Toxicity *:

| | Preclinical Data view all 579 | Clinical Data view all 5418 | Post-Market Reports (AERS) view all 166156 |
|--|--|--|---|
| 5-hydroxyindolacetic acid in urine increased | no data | no data | 1 |
| Abasia | no data | no data | 43 |
| Abdominal adhesions | no data | no data | 4 |
| Abdominal discomfort | no data | 1 | 147 |
| Abdominal distension | no data | 1 | 136 |
| Abdominal haematoma | no data | no data | 1 |
| Abdominal hernia | no data | no data | 5 |
| Abdominal mass | no data | no data | 5 |
| Abdominal obesity | no data | no data | 2 |

.....and make it easy to use

- Applied user-centered design approach
- Not just “usefulness” but “ease of use” is key
- Know your user and their tasks
- Take into account
 - Perception
 - Language
 - Thinking
 - Memory
 - Motor function
- Iterative process





Summary

- Drug Safety is a critical business issue
- Safety data is examined throughout the research and development process
- New safety teams are becoming more interdisciplinary and horizontal
- New information resources must address the needs of this new drug safety paradigm



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pendium™

the essential drug safety resource



Unique online resource developed
to meet the needs of drug safety teams

- Information delivered in a longitudinal view for better scientific insight
- Best-in-class sources, including FDA Drug Approval Packages
- Usability that simplifies research efforts





Acknowledgements

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Luming Niu





Thank you



