Drug approval, the FDA and the era of COVID: What prescribers should know

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OHSU CME, 2020

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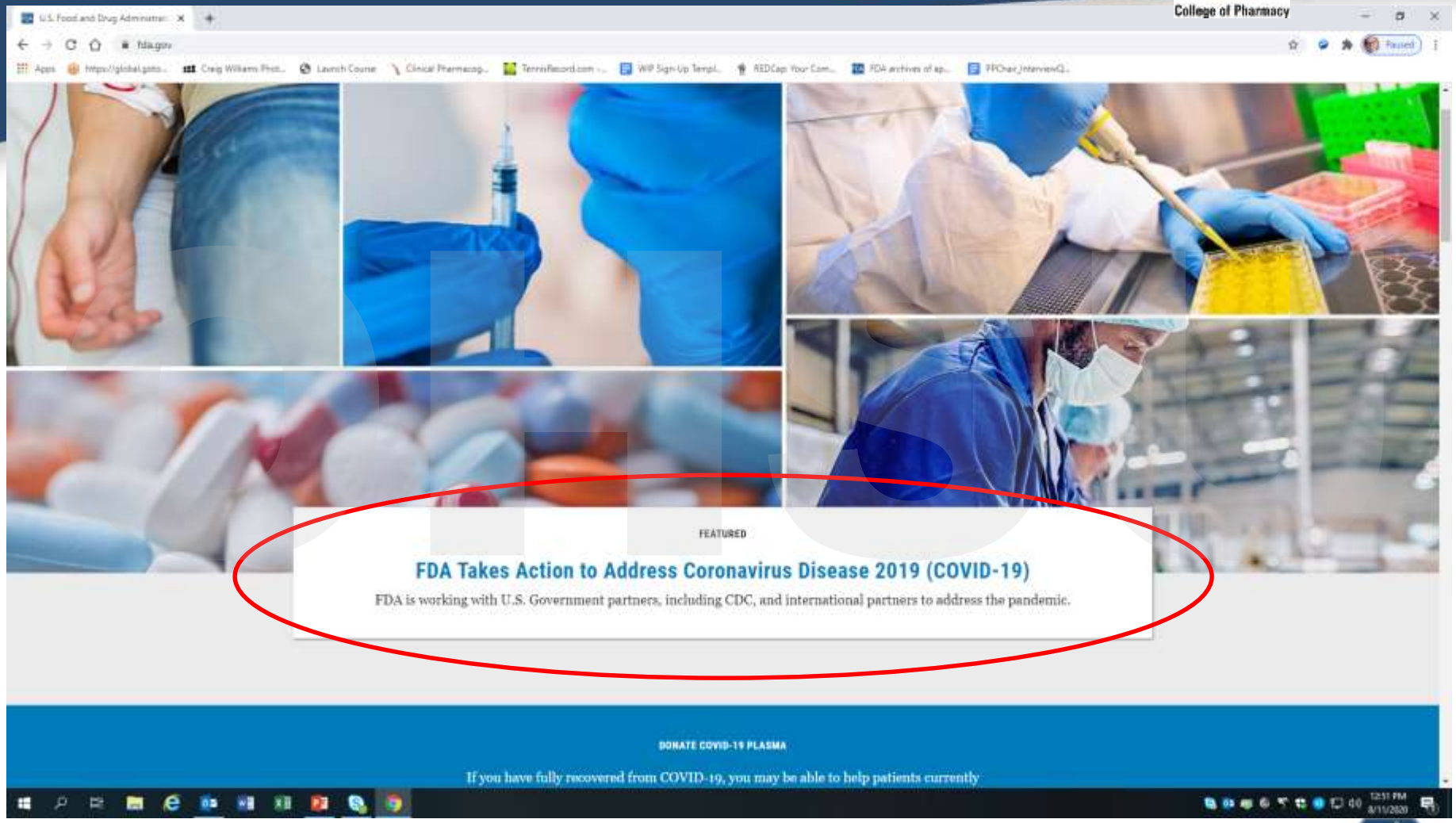
No conflicts of interest

FDA Home page: www.fda.gov accessed Aug 12, 2020



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Coronavirus Disease 2019 (COVID-19)

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Safety warning: FDA Updates on Hand Sanitizers Consumers Should Not Use

On this page:

Donate COVID-19 Plasma

If you have fully recovered from COVID-19, you may be able to help patients currently fighting the infection by donating your plasma.

Medical Devices (PDF) | Therapeutics (PDF)

How FDA facilitates development and availability of medical devices and therapeutics to combat COVID-19.

Resources for Health Professionals

Key resources for health professionals during the COVID-19 pandemic.

Content current as of:
08/10/2020

Topic(s)
Emergencies

Health Topic(s)
Infectious Disease
Coronavirus

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Coronavirus Disease 2019 (COVID-19) Resources for Health Professionals

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This page contains key resources for health professionals during the COVID-19 pandemic. Check back regularly for updates. You can sign up to receive the FDA's COVID-19 email updates and follow us on twitter @US_FDA.

Emergency Use Authorizations | Personal Protective Equipment | Medical Products

Emergency Use Authorizations (EUAs)

This page lists products that the FDA has authorized for emergency use in response to the COVID-19 public health emergency, including:

- Diagnostic and antibody tests
- Personal protective equipment
- Ventilators and other medical devices
- Drug products

This video provides a brief overview of EUAs.

Medical Products

Medical Products

Testing

Coronavirus Testing Basics provides general information about the types of available tests for SARS-CoV-2, the virus that causes COVID-19 and may be helpful for your patients to understand what they are being tested for, how they will be tested, and what their result means. For more detailed information about testing, including links to additional information, see our page for health professionals and industry.

- Find Community-Based Testing Sites for COVID-19

Drug Products

At this time, there are no FDA-approved drug products to treat COVID-19, but the FDA has issued EUAs for drugs that may be used to treat COVID-19 given that there are currently no approved alternatives. Each EUA has factsheets for health care providers and patients/caregivers and information on how to obtain the drug and currently available data.

- Remdesivir EUA FAQs

Objective(s)

- Be able to explain the FDA approval process under ordinary circumstances.
- Understand the pitfalls of the current drug approval process and why it leads to prescribers usually knowing less about a an approved drug than the drug's manufacturer or the FDA
- Describe the FDA's Emergency Use Authorization (EUA) process and how it differs from the ordinary drug approval process

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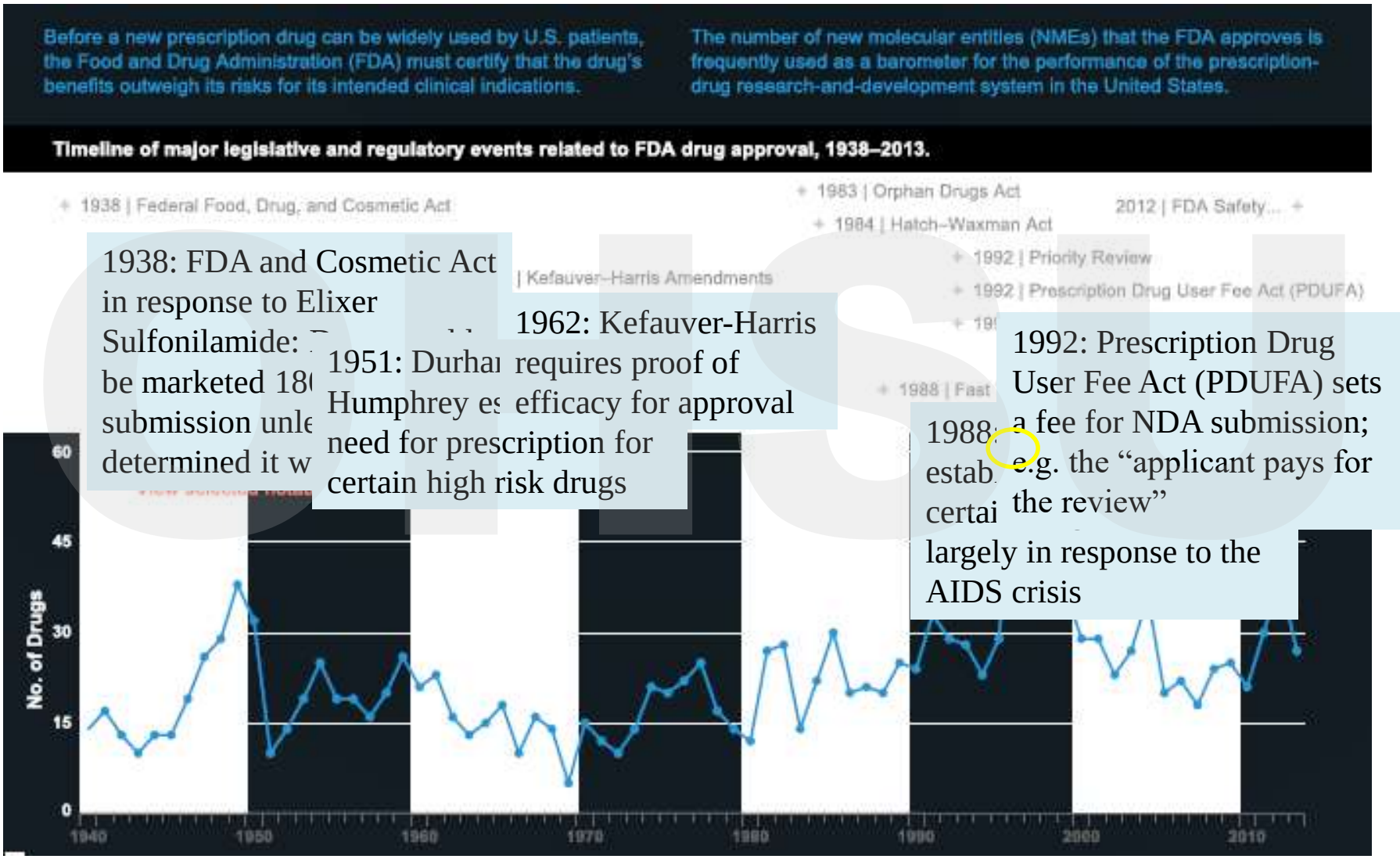
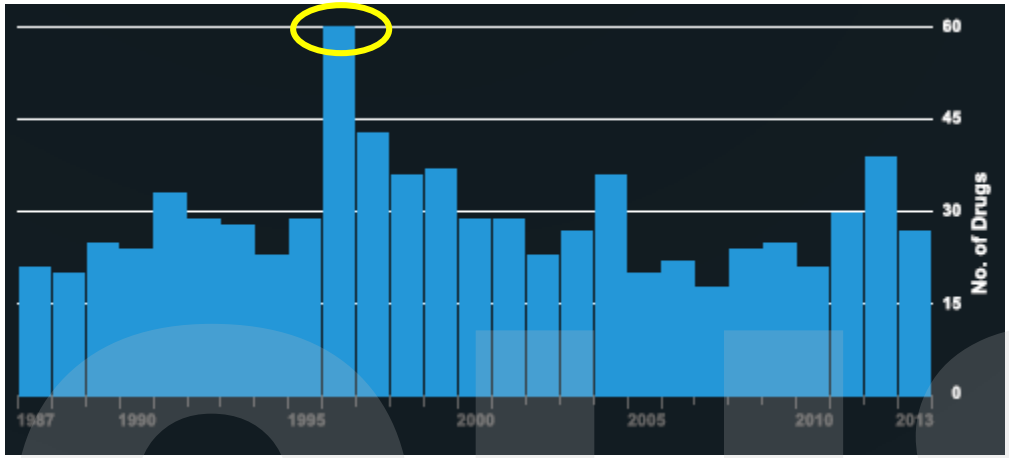
The number of drugs approved in U.S. every year is fairly stable



N Engl J Med; June 2014

The 1996 Drug approval spike: 60 new molecular entities (NME)



Notable successes: atorvastatin (Lipitor); olanzapine (Zyprexa); meropenam (Merrem); mirtazapine (Remeron)

Notable failures: Dexfenfluramine (cousin of "fen" in Phen-fen cocktail for weight loss later withdrawn over debate about heart valve defects); A me-too quinolone later withdrawn for excessive QTc effects (sparfloxacin); A leukotriene synthesis inhibitor, zileuton (Zyflo) which caused enough liver problems to severely limit use

Also-rans: Another ACEI and another ARB (trandolopril, valsartan); Donepezil (Aricept); Another leukotriene antagonist (zafirlokast); fexofenadine (Allegra); an intravenous version of phenytoin (Fosphenytoin)

So even with full approval process, the FDA doesn't always get it right

Step 1: Animals investigated in "pre-clinical" phase of drug development

Step 2: Investigational New Drug (IND) application filed. The company often seeks advice from FDA and "must show the FDA what they plan for human testing."

n <100

Step 3: Phase 1 testing in healthy, volunteers to look for obvious toxicities (transaminitis, QTc prolongation, subjective symptoms, etc) and determine pharmacokinetics (peak concentrations, average half-life, etc) for purposes of establishing dose

n=100
-500

Step 4: Phase 2 testing to look for efficacy. Patients with condition are studied. Surrogate endpoints common (A1C, systolic BP, LDLc)

N=1000
-3000

Step 5: Phase 3 testing typically after consultation with FDA to look for clinical endpoints. Different dosages and often combinations of drugs are studied.

Once Phase I, II and III research completed, the "molecular entity" becomes a "drug" with hopes for $$billions in sales:

NDA: New Drug Application submitted with all pre-clinical and clinical data. The FDA has 60 days to decide whether to review. Goal is to complete 90% of reviews within 10 months of acceptance of submission.

Phase 4, post-marketing surveillance is "required" but is an area of much criticism for drug manufacturers. The FDA is more often requiring specific Phase 4 research to be conducted

HEALTH INC.

FDA Approves Drugs Faster Than Ever But Relies On Weaker Evidence, Researchers Find

January 14, 2020 · 11:03 AM ET
Heard on All Things Considered

SYDNEY LUPKIN

2-Minute Listen + PLAYLIST

Where can things go wrong and what should prescribers know?

1. Relatively few patients may be exposed to a new drug prior to it becoming available and surrogate endpoints may be used. An adverse event with a frequency < 1/500 will not be detected; <1/100 may not be detected.

2. The Prescription Drug User Fee Act (PDUFA) means that substantial resources flow to the FDA from the pharmaceutical industry. FDA maintains that it simply allows the maintenance of adequate infrastructure to keep up reviews. Watchdogs are critical:

Are the foxes in charge of the henhouse?

3. The manufacturer knows the most about a drug, the FDA knows almost as much and prescriber knows some fraction of that (the problem of the “package insert”)

4. The FDA is little concerned with magnitude of effect (the drug just needs to beat placebo [or current standard of care]) or the costs of that benefit

U.S. FOOD & DRUG ADMINISTRATION

FY 2021 PDUFA Program Fee Invoices and FY 2021 PDUFA Fee Rates

Dear Colleague,

The fiscal year (FY) 2021 PDUFA program fee invoices were emailed on **Friday, August 14, 2020**. Please note that the invoices are only sent out to firms which have PDUFA user fee eligible products. If you do not receive your invoice by August 14, and believe you should receive a program fee invoice, please contact PDUFA User Fee staff at CDERCollections@fda.hhs.gov.

The FY 2021 PDUFA fee rates were published in the Federal Register (FR) on August 3, 2020. The fee rates for FY 2021 are shown below:

User Fee Type	FY 2020	FY 2021
Application Fee - Clinical Data Required	$2,942,965	$2,875,842
Application Fee - No Clinical Data Required	$1,471,483	$1,437,921
Program Fee	$325,424	$336,432

</div<>

For more information regarding the FY 2021 fee rates, please see the FR notice available at: https://www.federalregister.gov/documents/2020/08/03/2020-16833/prescription-drug-user-fee-rates-for-fiscal-year-2021

2021 PDUFA fee for an IND with clinical data: $2,875,842

Where can things go wrong and what is particularly notable in process?

1. Relatively few patients may be exposed to a new drug prior to it becoming available and surrogate endpoints may be used. An adverse event with a frequency < 1/500 will not be detected; <1/100 may not be detected.

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Few patients and surrogate endpoints:

A phase 2 study in NEJM: 2004

ORIGINAL ARTICLE

Effects of an Inhibitor of Cholesteryl Ester Transfer Protein on HDL Cholesterol

METHODS

We conducted a single-blind, placebo-controlled study to examine the effects of torcetrapib, a potent inhibitor of CETP, on plasma lipoprotein levels in 19 subjects with low levels of HDL cholesterol (<40 mg per deciliter [1.0 mmol per liter]), 9 of whom were

RESULTS

Treatment with 120 mg of torcetrapib daily increased plasma concentrations of HDL cholesterol by 61 percent (P<0.001) and 46 percent (P=0.001) in the atorvastatin and

The Phase 3 study, NEJM: 2007

Effects of Torcetrapib in Patients at High Risk for Coronary Events

METHODS

We conducted a randomized, double-blind study involving 15,067 patients at high cardiovascular risk. The patients received either torcetrapib plus atorvastatin or

RESULTS

for all comparisons). There was also an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; P=0.001) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; P=0.006). Post hoc analyses

What should clinicians be aware of in the drug approval process

1. Relatively few patients may be exposed to a new drug prior to it becoming available and surrogate endpoints may be used. It is generally accepted that an adverse event with a frequency < 1/500 will not be detected

2. The Prescription Drug User Fee Act (PDUFA) means that substantial resources flow to the FDA from the pharmaceutical industry. FDA maintains that it simply allows the maintenance of adequate infrastructure to keep up reviews. Watchdogs are critical:

Are the foxes in charge of the henhouse?

3. The manufacturer knows the most about a drug, the FDA knows almost as much and prescriber knows some fraction of that (the problem of the “package insert”)

4. The FDA is little concerned with magnitude of effect – the NDA just needs to be superior to placebo

October 29th, 2009

Perspective

OCTOBER 29, 2009

Lost in Transmission — FDA Drug Information That Never Reaches Clinicians

Lisa M. Schwartz, M.D., and Steven Woloshin, M.D.

"Drug labels (package inserts) are written by drug companies, then negotiated and approved by the FDA."

and therefore……

"Much critical information that the FDA has at the time of approval may fail to make its way into the drug label and relevant journal articles."

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Original Investigation

Reporting Bias in Clinical Trials Investigating the Efficacy of Second-Generation Antidepressants in the Treatment of Anxiety Disorders

A Report of 2 Meta-analyses

Annelieke M. Roest, PhD; Peter de Jonge, PhD; Craig D. Williams, PharmD; Ymkje Anna de Vries, MSc; Robert A. Schoevers, MD, PhD; Erick H. Turner, MD

JAMA Psychiatry, 2015

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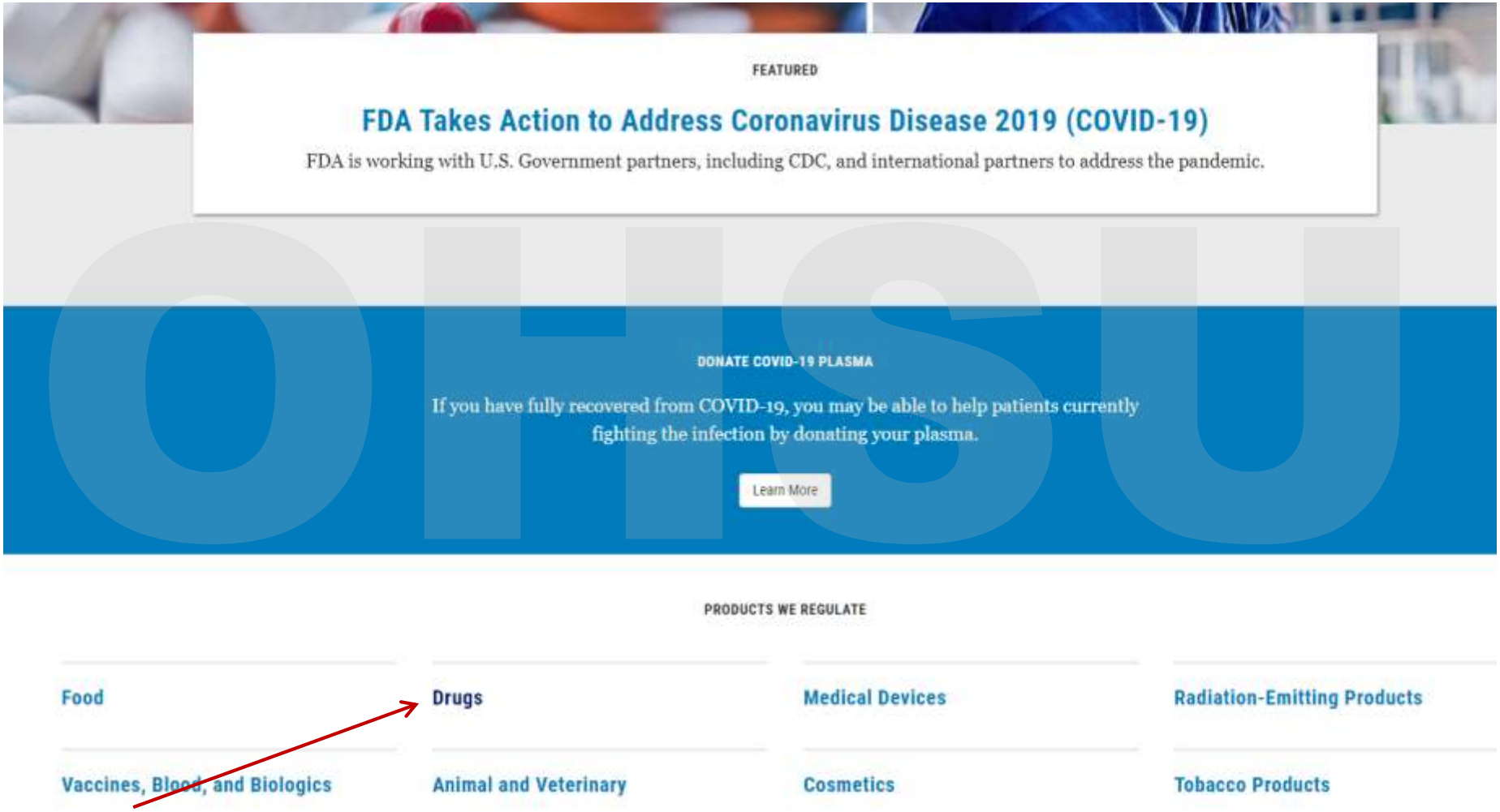
Back to home page: www.fda.gov.....



Drugs@FDA: FDA-Approved Drugs

Search by Drug Name, Active Ingredient, or Application Number*

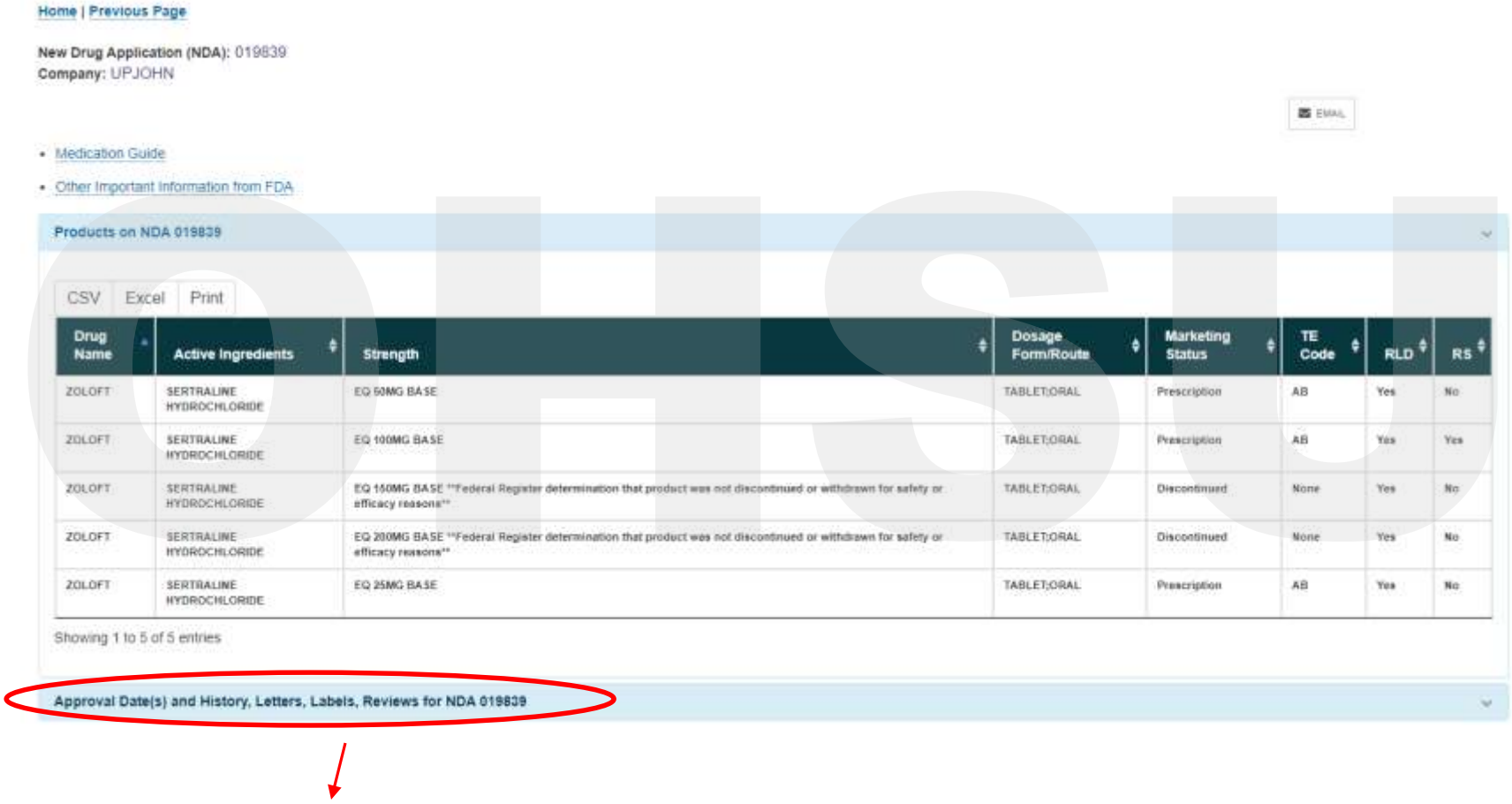
Enter at least 3 characters

Search Clear

Browse by Drug Name

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z 0-9

Results for sertraline (Zoloft):



Home | Previous Page

New Drug Application (NDA): 019839
Company: UPJOHN

EMAIL

- Medication Guide
- Other Important Information from FDA

Products on NDA 019839

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
ZOLOFT	SERTRALINE HYDROCHLORIDE	EQ 50MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
ZOLOFT	SERTRALINE HYDROCHLORIDE	EQ 100MG BASE	TABLET;ORAL	Prescription	AB	Yes	Yes
ZOLOFT	SERTRALINE HYDROCHLORIDE	EQ 150MG BASE **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	TABLET;ORAL	Discontinued	None	Yes	No
ZOLOFT	SERTRALINE HYDROCHLORIDE	EQ 200MG BASE **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	TABLET;ORAL	Discontinued	None	Yes	No
ZOLOFT	SERTRALINE HYDROCHLORIDE	EQ 25MG BASE	TABLET;ORAL	Prescription	AB	Yes	No

Showing 1 to 5 of 5 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 019839

Approval Date(s) and History, Letters, Labels, Reviews for NDA 019839

03/17/2000	032	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
01/03/2000	031	Package Change		Label is not available on this site.
12/07/1999	026	New or Modified Indication	Label (PDF) Letter (PDF) Review	
10/07/1999	030	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
10/07/1999	029	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
04/10/1998	024	Control Supplement		This supplement type does not usually require new labeling.
12/04/1997	023	Control Supplement		This supplement type does not usually require new labeling.
10/10/1997	018	Labeling Revision	Review (PDF)	Label is not available on this site.
10/10/1997	017	Patient Population Altered	Review (PDF)	Label is not available on this site.
07/08/1997	011	New or Modified Indication	Review (PDF)	Label is not available on this site.
04/07/1997	020	Control Supplement		This supplement type does not usually require new labeling.
10/25/1996	002	New or Modified Indication		Label is not available on this site.
03/06/1996	010	Control Supplement		This supplement type does not usually require new labeling.
03/05/1996	012	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
10/05/1995	009	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
09/14/1995	003	Labeling Revision		Label is not available on this site.
06/16/1995	008	Labeling Revision		Label is not available on this site.
06/16/1995	006	Labeling Revision		Label is not available on this site.
03/22/1995	007	Control Supplement		This supplement type does not usually require new labeling.
09/07/1994	005	Formulation Revision		Label is not available on this site.
06/22/1992	001	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
12/30/1991	000	Approval		Label is not available on this site.

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players

July, 1997 was the submission for review for Panic disorder…

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 019839/S011

TRADE NAME: Zoloft 25 mg, 50 mg, and 100 mg Tablets

GENERIC NAME: Sertaline HCl

SPONSOR: Pfizer Pharmaceuticals

APPROVAL DATE: 07/08/97

Four trials were conducted for Sertraline for Panic Disorder:

III. **Reviewer's Overall Comments**

Statistically, Study 629 showed reasonable statistical evidence, Study 630 showed moderate statistical evidence, Study 529 showed minimal statistical evidence (based on ratios to baseline) for 100 mg, and Study 514 showed almost no statistical evidence for the efficacy of sertraline. The overall statistical and numerical superiority of sertraline over placebo is marginally acceptable as providing some evidence, though not strong, in favor of the efficacy of sertraline in the treatment of panic disorder. The sponsor stated, "With a single exception in the 0514 study, all of these variables in all of the studies reveal numerically greater improvement at endpoint in the sertraline group relative to the placebo group, ..."

Side-by-side graphical comparison of all four studies based on 95% confidence intervals (multiple comparison adjustment not considered) for Average Number of Panic Attacks (considering the total time the patient is in the study) is presented in Figures 0.4.2 (Ratio to Baseline), 0.4.3 (Difference From Baseline), 0.4.4 (Ratio to Baseline, weighted by the time on study), 0.4.5 (Difference From Baseline, weighted by the time on study).

We have a good example, here, how non-significant results can be turned into significant results even by acceptable analyses. The

From Sertraline review package for Panic Disorder

IV. **Overall Conclusion**

The overall statistical and numerical superiority of sertraline to placebo is statistically marginally acceptable as providing some evidence, though not strong in view of the lack of robustness, in favor of the efficacy of sertraline in the treatment of panic disorder. The 100 mg dose showed overall better results than those shown by 50 mg and 200 mg.

Sertraline for panic attacks: Magnitude of benefit?

Table 514 - 4
Mean Change from Baseline in Total Number of Panic Attacks
Last Observation Carried Forward Analysis

Week	Treatment Groups								2-sided p-values for comparisons		
	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	38	7.03	38	17.28	36	7.71	38	9.59			
1	37	-1.26	38	-4.88	36	- .49	38	- .93	.496	.274	.969
2	38	-1.58	38	-11.01	36	- .57	38	-2.64	.952	.179	.995
3	38	-2.24	38	-12.30	36	-2.24	38	-3.43	.979	.383	.451
4	38	-2.66	38	-13.93	36	-3.07	38	-3.28	.499	.034	.146
5	38	-1.61	38	-14.04	36	-3.29	38	-3.96	.822	.073	.205
6	38	-2.66	38	-13.33	36	-3.65	38	-4.28	.416	.146	.398
7	38	-3.00	38	-14.09	36	-3.93	38	-3.83	.241	.075	.205
8	38	-3.11	38	-14.01	36	-3.88	38	-4.78	.624	.186	.444
9	38	-2.97	38	-13.67	36	-4.82	38	-4.70	.773	.287	.205
10	38	-2.74	38	-13.62	36	-4.96	38	-4.59	.940	.465	.241
11	38	-2.92	38	-14.59	36	-4.49	38	-4.86	.935	.229	.319
12	38	-3.16	38	-14.62	36	-4.65	38	-4.64	.523	.081	.224

Percent reduction: **45%** **84%** **60%** **48%** placebo

Sertraline 50mg

From sertraline (Zoloft) Package Insert:

Panic Disorder–ZOLOFT is indicated for the treatment of panic disorder in adults, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

From section of PI describing "Clinical Trials":

Panic Disorder–The effectiveness of ZOLOFT in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1-3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.

…and the negative trials are then often buried

JAMA Psych, 2015

Original Investigation

Reporting Bias in Clinical Trials Investigating the Efficacy of Second-Generation Antidepressants in the Treatment of Anxiety Disorders

A Report of 2 Meta-analyses

Annelieke M. Roest, PhD; Peter de Jonge, PhD; Craig D. Williams, PharmD; Ymkje Anna de Vries, MSc; Robert A. Schoevers, MD, PhD; Erick H. Turner, MD

RESULTS The findings of 41 of the 57 trials (72%) were positive according to the FDA, but 43 of the 45 published article conclusions (96%) were positive ($P < .001$). Trials that the FDA determined as positive were 5 times more likely to be published in agreement with that determination compared with trials determined as not positive (risk ratio, 5.20; 95% CI, 1.87

72% of studies reviewed by FDA were positive but 96% of published studies were positive.

Summary of FDA review and approval in ordinary times:

1. A drug has relatively few patient-years of exposure when first approved and brought to market.

2. Approval may be based on surrogate endpoints

3. Labeling for approved drugs is written by manufacturers and then negotiated with the FDA and often lacks quantitative data

4. The final PI does not represent all of the data on the drug and the FDA does not and cannot decide which studies get published and which do not

Back to COVID and FDA:

Medical Products

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- Remdesivir EUA FAQs

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Coronavirus Disease 2019 (COVID-19) Resources for Health Professionals

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For Health Professionals

- Coronavirus Disease 2019 (COVID-19) Resources for Health Professionals
- Convalescent Plasma Fact Sheets and Toolkit for Health Professionals
- Resources and Tools for Health Professionals
- **FDA-Health Professional Activities**
- **Learning Activities**
- **Stay Informed**

This page contains key resources for health professionals during the COVID-19 pandemic. Check back regularly for updates. You can sign up to receive the FDA's COVID-19 email updates and follow us on twitter @US_FDA.

Emergency Use Authorizations | **Personal Protective Equipment** | **Medical Products**

Emergency Use Authorizations (EUAs)

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- Drug products

This video provides a brief overview of EUAs.

EUA: Emergency Use Authorization

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About Emergency Use Authorizations (EUAs)

The Emergency Use Authorization (EUA) authority allows FDA to help strengthen the nation's public health protections against CBRN threats by facilitating the availability and use of MCMs needed during public health emergencies.

Chemical, biological, radiological and nuclear

Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives.

Section 564 of the FD&C Act was amended by the Project Bioshield Act of 2004 and was further amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), the 21st Century Cures Act of 2016, and Public Law 115-92 of 2017.

Medical Counter Measures

Remdesivir EUA: "…for certain hospitalized patients"

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FDA U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Remdesivir for Certain Hospitalized COVID-19 Patients

Q. What is an Emergency Use Authorization?

A: In certain types of emergencies, the HHS Secretary may issue a determination and declaration under the Food Drug and Cosmetic Act that permits FDA to issue emergency use authorizations (EUAs) to facilitate access to medical countermeasures (drugs, biologics, vaccines, and devices) that can be used to diagnose, treat or prevent a serious disease or condition in a public health emergency.

Products authorized for use in this way may not be approved by FDA for any use, or they may be approved for other uses but not for the emergency use. FDA decides whether the use of the product is likely to be more helpful than harmful for the emergency use; i.e., the agency determines that the known and potential benefits of the medical products for their intended uses outweigh their known and potential risks. This authorization is reserved for emergency situations and is NOT the same as FDA approval or licensure.

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Remdesivir is not “approved” since it did not go through Phase 1, 2 and 3 testing

Q. Is remdesivir approved by the FDA to treat COVID-19?

A. No. Remdesivir is an investigational antiviral drug. It is not currently FDA-approved to treat or prevent any diseases, including COVID-19.

So, there is no “Package Insert” or drug label for remdesivir @ fda.gov

What is the data for remdesivir?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

May, 2020

Quicker recovery in hospitalized patients: 11 days compared to 15

liminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received pla-

No mortality benefit but a strong trend….

Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events

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Treatment Guidelines for Adult Patients

Documentation for COVID-19: Adult

OHSU

Title: Treatment Guidelines for Adult Patients with COVID-19	Creation Date and Time:	03/25/2020 1800

1. Preferred treatment regimens
   - **Dexamethasone:** A preliminary report from the RECOVERY trial, a large randomized

A. **Remdesivir:** *The supply of remdesivir is limited resulting in drug shortages.

C. **Convalescent plasma:** Convalescent plasma has previously been found to improve

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Q: What about dexamethasone? Is it FDA approved for COVID? Available via EUA?

A: Neither


ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

NEJM, July 2020

Finding:

Dexamethasone 6 mg IV for an average of 6 days reduced mortality in patients on mechanical ventilation (36% RRR) or supplemental oxygen (18% RRR) but……. showed a non-significant trend for increased mortality in hospitalized COVID patients NOT receiving oxygen or intubation

So, corticosteroids (6 mg dex = 30 mg IV methylprednisone) SHOULD be used for hospitalized COVID patients needing support)

So why isn't dexamethasone "approved" treating those sicker COVID patients or why no EUA?

A: Because it is already on the U.S. market and widely available there is no need for an EUA. We can all just decide to use dexamethasone "off-label" for our sick COVID patients

And because dexamethasone has been generically available for years, it is unlikely that any company will bother submitting a formal NDA for review for this indication. It therefore will remain a common, off-label use of dexamethasone while we manage our sicker COVID patients

Conclusion:

- The FDA approval process ordinarily involves pre-human work in animals followed by Phase I, Phase II and Phase III human trials designed to first show safety and then prove efficacy

- The package insert for drugs approved by the FDA only tell part of the story. Remember that:
  - Magnitude of benefit does matter for FDA approval
  - Cost-effectiveness is NOT part of the approval process

- COVID is considered a biologic emergency and the "Emergency Use Authorization" (EUA) act allows the FDA to make drugs available without going through the formal review process

- Currently, remdesivir is available via EUA to reduce morbidity in hospitalized COVID patients and dexamethasone has shown to reduce mortality in hospitalized COVID patients requiring respiratory support