



iPLEDGE™
Committed to Pregnancy Prevention

Isotretinoin Pregnancy Risk Management Program

Agenda

iPLEDGE Overview

Bonnie Southorn, PhD
Genpharm Inc.

Review of iPLEDGE

James Shamp
Covance Inc.

Phase II Enhancements

Review of Year 1 Data

Daniel Reshef, MD, PhD
Hoffmann-La Roche Inc.

Summary

Sponsors' Meeting Objectives

- Update Advisory Committee on the progress of the iPLEDGE program including enhancements to meet stakeholders needs
- Inform the Advisory Committee of next steps and timing for iPLEDGE Phase II implementation
- Present the iPLEDGE Year 1 data

Isotretinoin Manufacturers

Isotretinoin	Manufacturer	Approval Date
Accutane	Hoffmann-La Roche Inc.	May 1982
Amnesteem	Mylan/Genpharm	November 2002
Sotret	Ranbaxy	December 2002
Claravis	Barr Laboratories, Inc.	April 2003

Public Health Goals

- No woman who is pregnant should receive isotretinoin therapy
- No woman should become pregnant during or for one month after receiving isotretinoin therapy

Basis for iPLEDGE RiskMAP

- Isotretinoin is a known teratogen
- Approved under Subpart H with a restricted distribution program
- An enhanced risk minimization action plan (RiskMAP) designed to minimize drug exposure during pregnancy

Comparison of Previous RiskMAPs to iPLEDGE (1)

Previous RiskMAPs	iPLEDGE
Voluntary program	Mandatory program
Limited data through voluntary survey	100% data capture through iPLEDGE
No patient denominator	Patient denominator
Prescriber enrolled	Comprehensive program (all stakeholders enrolled)
Sponsors spontaneous reporting	Single centralized pregnancy registry <ul style="list-style-type: none">• Root cause analysis• Mandatory reporting of pregnancies• Lost to follow up process

Comparison of Previous RiskMAPs to iPLEDGE (2)

Previous RiskMAPs	iPLEDGE
The yellow sticker affixed to the prescription served to identify a negative pregnancy test was completed	Performance Linked Access system requiring pregnancy test results and contraception choices
Non-laboratory pregnancy test acceptable	Monthly pregnancy tests must be performed by a CLIA-certified lab

History of iPLEDGE

Pregnancy Risk Management (1)

2004

- Sponsors propose a single enhanced pregnancy risk management program (Voluntary to a Mandatory Program)
 - For all isotretinoin products
 - Registry for prescribers, pharmacies, and patients
 - Single centralized pregnancy registry
- Advisory Committees agreed with Sponsors' proposal with the following additional feedback
 - Registration of all health care professionals prescribing or dispensing isotretinoin
 - Comprehension testing of the educational materials
 - Mandatory patient follow-up survey
 - Launch of program should not be delayed by a pilot program or cost analysis

History of iPLEDGE

Pregnancy Risk Management (2)

2005

- FDA Approval for iPLEDGE

2006

- January 1: Voluntary participation
- February 10: Advisory Committee meeting
 - Sponsors provided an operational review of the iPLEDGE program and received stakeholder feedback
- March 1: Mandatory participation

Where We Are Today?

2007

- February 16: Supplement 58 submitted, responses exchanged with FDA
- Currently in process
 - Additional system design, program, test and release activities for next release
 - Updates to educational materials to reflect changes
 - Target launch date pending Advisory Committee meeting recommendations and FDA approval
- June 1: FDA notified the Sponsors of the August 1 – Advisory Committee Meeting
 - Request for Sponsors to :
 - Provide overview of the iPLEDGE Program
 - Review the Phase II changes
 - Status on year 1 iPLEDGE data

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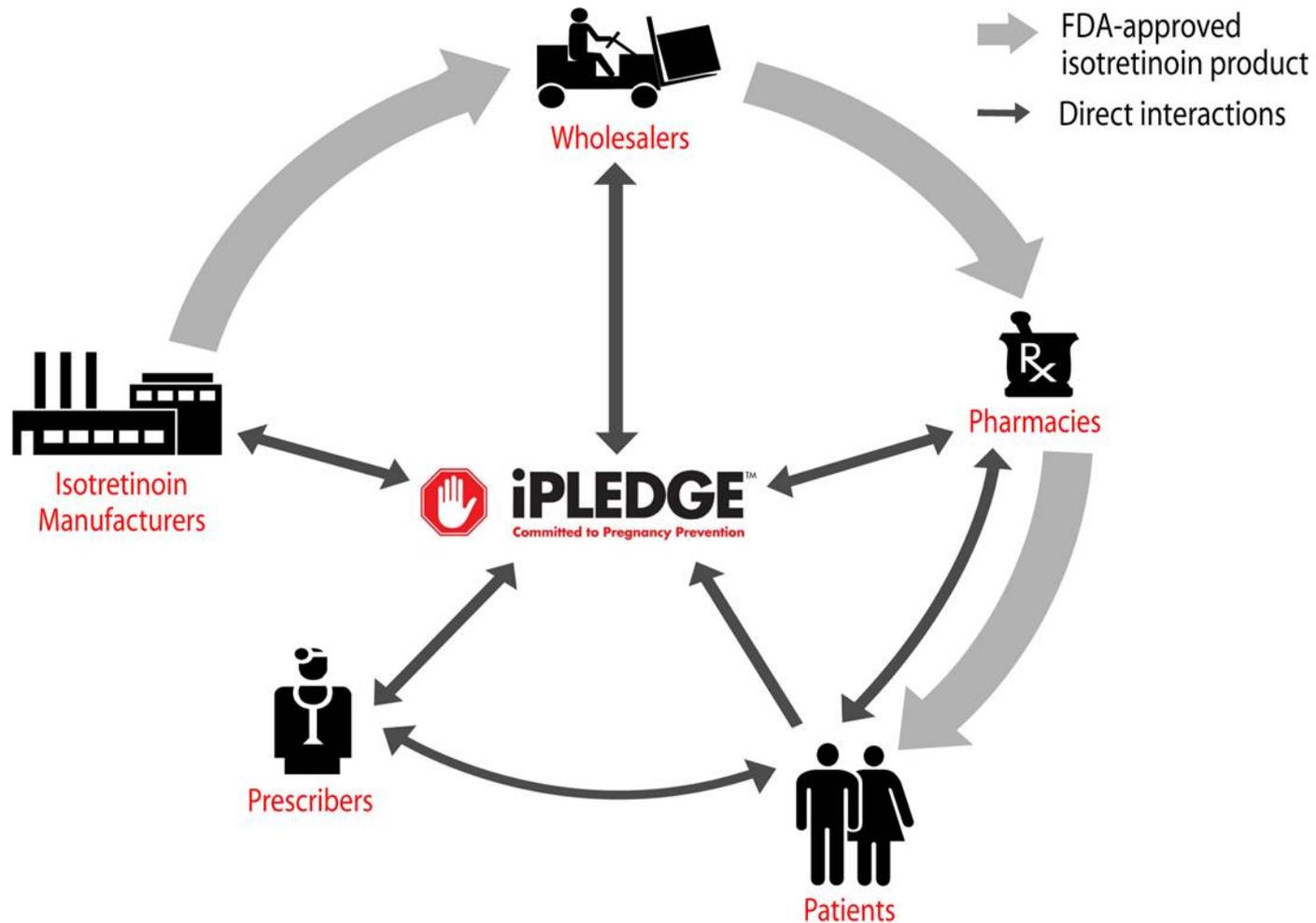
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Summary

Who Is Part of iPLEDGE?



What Are the iPLEDGE Program Components?

- Website
- IVR (Phone System)
- Educational Materials
 - Publications
 - Checklists
 - Forms
 - DVD
- Spanish Translations
 - IVR Phone Scripts
 - Patient Educational Materials
- Pregnancy Registry



Qualitative and Quantitative Test of Education Materials

- Personal interviewing was conducted in 26 geographically dispersed markets
- Respondents were given a copy of the appropriate guide(s) to read, and were questioned about the contents based on their reading of the material (post-exposure)
- At the end of the interview, respondents were asked a series of “True/False” questions
- Sample
 - 500 FCBP
 - 101 Males and FNCBP
 - 50 Pharmacists
 - 152 Physicians

Consumer Feedback

- **The Program Guides** are very successful in communicating key information about the program
- The **Birth Control Workbook** also successfully communicates the following to FCBPs:
 - Three in four feel the most important information in the workbook is the necessity of using 2 forms of birth control every time you have sex if taking isotretinoin
 - Almost all (99.8%) understand that two forms of birth control are recommended, and more than nine in ten say they would personally use two or more forms
 - They also recall the importance of taking birth control pills every day
 - A majority said they would take immediate action if they had unprotected sex or became pregnant (96-98%) while on isotretinoin, primarily by calling their doctor

Major Activities – Wholesaler

- Register (initial and annually)
- Distribute only FDA approved product
- Provide drug only to activated pharmacies
 - Verified by the wholesaler using a daily list of active pharmacies

Major Activities – Prescriber

- Register (initial)
- Activate (initial and annually)
- Register patients
- Obtain consent form(s)
- Counsel patient (monthly)
 - Enter patient contraception choices
- Enter pregnancy test results

Major Activities – Pharmacy

- Register (initial)
- Activate (initial and annually)
- Designate Responsible Site Pharmacist (RSP)
 - Train all pharmacists in store
- Authorize all prescriptions in iPLEDGE
- Adhere to “Do not dispense after date” provided by system
- Dispense no more than 30-day supply

Major Activities – Patient

All Patients

- Sign patient consent form
- Schedule monthly office visits
- Do not donate blood or share drug
- Pick up prescription within “7-day prescription window”

Female Patients of Childbearing Potential (FCBP)

- Sign additional consent form
- Monthly pregnancy test
- Monthly contraception choices
- Monthly comprehension questions

Prescription Denials

- If a required responsibility of the prescriber, pharmacy, or patient is not fulfilled, the end result leads to a prescription denial, which is a measure that the guidelines of the iPLEDGE program are effective

Reasons for Prescription Denials

- Females of Childbearing Potential:
 - Patient was in the 7-day window and she attempted to fill a prescription without answering her monthly questions
 - Patient was in the 7-day window and she attempted to fill a prescription but prescriber did not enter pregnancy results
 - 7-day window expired
 - Prescriber did not confirm patient counseling
 - Only one prescription can be filled per month
- Males and non-Childbearing Females:
 - The prescriber did not confirm patient counseling
 - Patient missed the 7-day prescription window
 - Only one prescription can be filled per month

iPLEDGE Compliance Process

- For the purposes of the iPLEDGE Program, the definition of non-compliance is a stakeholder (patient, pharmacy, prescriber, or wholesaler) operating outside of the guidelines of the iPLEDGE program
- The Sponsors follow non-compliance reporting procedures

iPLEDGE Compliance Process

- A traceable letter is sent to the stakeholder for suspected non-compliance activity
- The stakeholder is contacted and provided education on the iPLEDGE guidelines
- Follow up is performed with the stakeholder to ensure corrective actions have been completed
- The stakeholder may be de-activated in iPLEDGE if the violation is severe or if corrective action is not taken
 - 2 prescribers de-activated
 - 1 pharmacy de-activated

15 Day Reportable to the FDA

- 15 Day Reportable violations are reported to the FDA
- Non-compliant incidents that are considered 15 Day Reportable to the FDA:
 - If a wholesaler sells isotretinoin to an unregistered and/or un-activated pharmacy or to an unregistered wholesaler
 - If a pharmacy that is not registered and activated in iPLEDGE dispenses isotretinoin
 - Any severe violation of the iPLEDGE guidelines as deemed necessary by the sponsors

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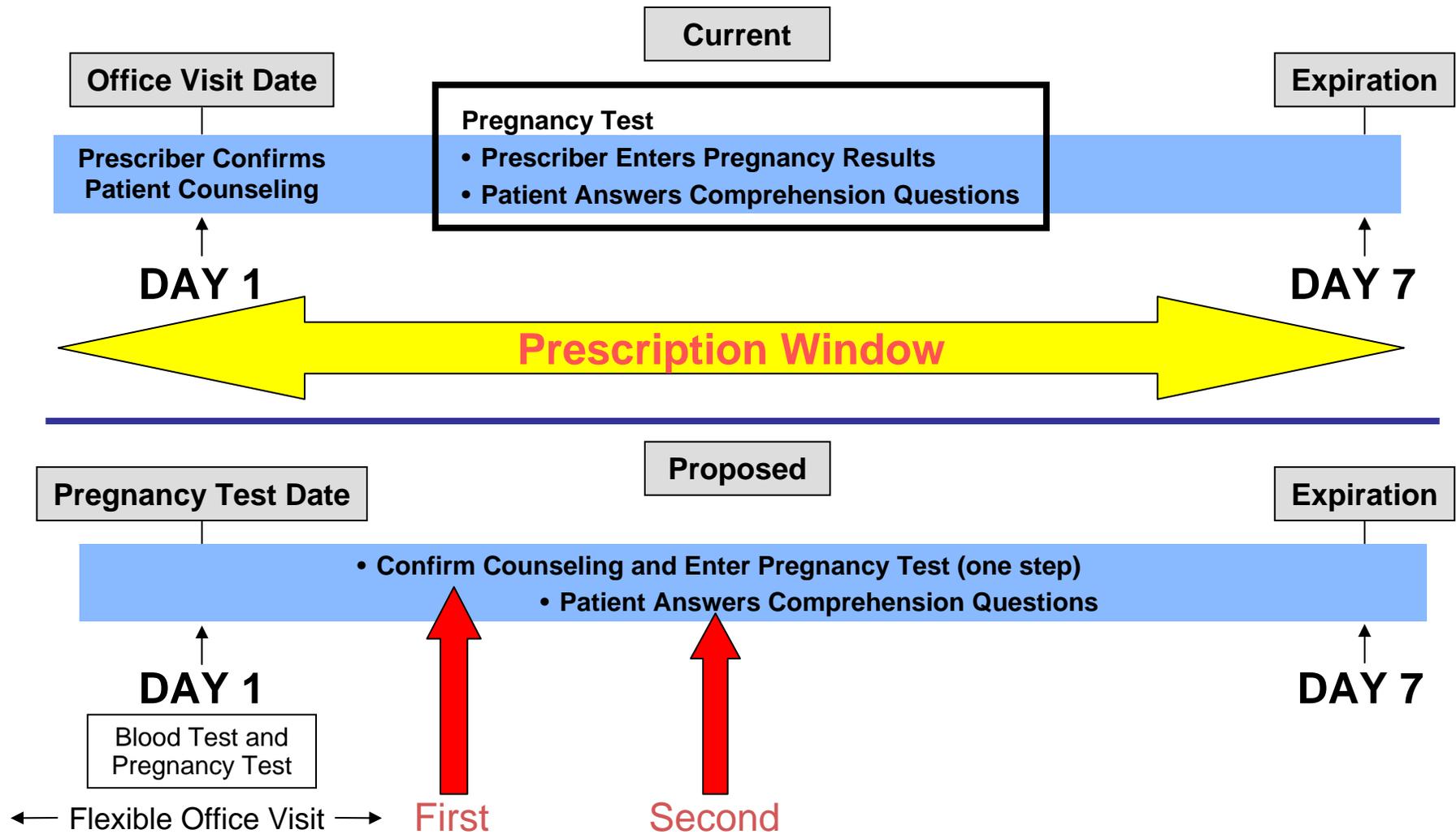
Triggers for the Phase II Changes

- Observations from initial months of operation
 - Call Center Issues
 - Prescription Denials
- Stakeholder Interaction
- Scientific Advisory Board (SAB)
- FDA
- Professional Organizations (AADA, HDMA, NACDS)
- Sponsors

Proposed Label Changes

- Capability to start new window on Day 8 after previous window (FCBP) except for the first 30 days
 - Removes 23-day lockout
 - Requirements must be repeated
- Start 7-day window at Pregnancy Test Date (FCBP Only)
 - Date of serum/urine collection is Day 1 of 7-day window
 - Blood work/pregnancy test results prior to writing prescription
 - Combines “Confirm Patient Counseling” and “Enter Pregnancy Test”
- Extension of Prescription window from 7 to 30 days for males patients and FNCP
- Allow male latex condom with or without spermicide

FCBP Prescription Window



Program Enhancements

- Enhanced display of patient status and data
- Enhanced system messages to users
- Enhanced user navigation in the system
 - Patient Registration Wizard
 - Manage Patient screen
 - Designee navigation items
 - Prescription Fill Wizard
 - Intelligent Activation buttons



iPLEDGE™

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Welcome 1001006844

[Logout](#)

Have Questions? Call our toll-free number **1-866-495-0654**

Monday to Saturday, 9 AM - 12 AM (Midnight) EST

THE ONLY WAY

HOME

**PRESCRIBER
ACTIVATION**

**REGISTER NEW
PATIENT**

**ABOUT
ISOTRETINOIN**

**ABOUT
iPLEDGE**

**MANAGE
PATIENTS**

**PRESCRIBER
INFORMATION**

Order Materials

Update Personal Details

Accept Patient

Manage Delegates/Designees

My Program Status

Find a Participating Pharmacy

FAQs

Patient Program Status as of 12/14/2006 2:00 PM Eastern Time

Patient Name: Jane Doe
Program Status: **Requires Confirmation**
Action: [Confirm Patient](#)

Prescriptions Filled

12/10/2006

Instructions: The patient must have a pregnancy test and be counseled by you. You must confirm this counseling and enter the results of the pregnancy test in the iPLEDGE system. [More...](#)

December

Sun	Mon	Tue	Wed	Thu	Fri	Sat
3	4	5	6 First day of window More...	7 More...	8 First day patient may demonstrate comprehension More...	9 Patient may demonstrate comprehension More...
10 Patient may pick up prescription More...	11 Patient may pick up prescription More...	12 Patient may pick up prescription More...	13 First day patient may have next pregnancy test More...	14	15	16

Key

- Today or future day for an active 7 day window
- A past day for a 7 day window
- A 7 day window that has expired without prescription fill
- Action may occur on this date or any date after

You may click on underlined text to perform the required action

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FCBP confirmed on the 8th with pregnancy test on 6th. Today is the 14th. <mm/dd/yyyy hh:mm> signifies current system date (not local) and time of the page opening.

Phase II Summary

- iPLEDGE program is an integrated program that supports the iPLEDGE public health goals
- Label Change Program Enhancements included in submitted supplement
- Increase user capability to meet program requirements
- Planned Activities
 - Production of new Educational Materials
 - Communication of changes to stakeholders
 - Distribution of new Educational Materials
 - Training of Call Center staff to handle questions during transition
- Target launch date pending advisory committee meeting recommendations and FDA approval



iPLEDGETM
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Summary

Review of Year 1 Data

- FCBP Interactions with the System
- Pregnancy Data
- Observations of Patient Knowledge / Behavior

Patient Path: Females of Child-Bearing Potential

Potential
Patient
for
Isotretinoin

Patient Path: Females of Child-Bearing Potential

iPLEDGE



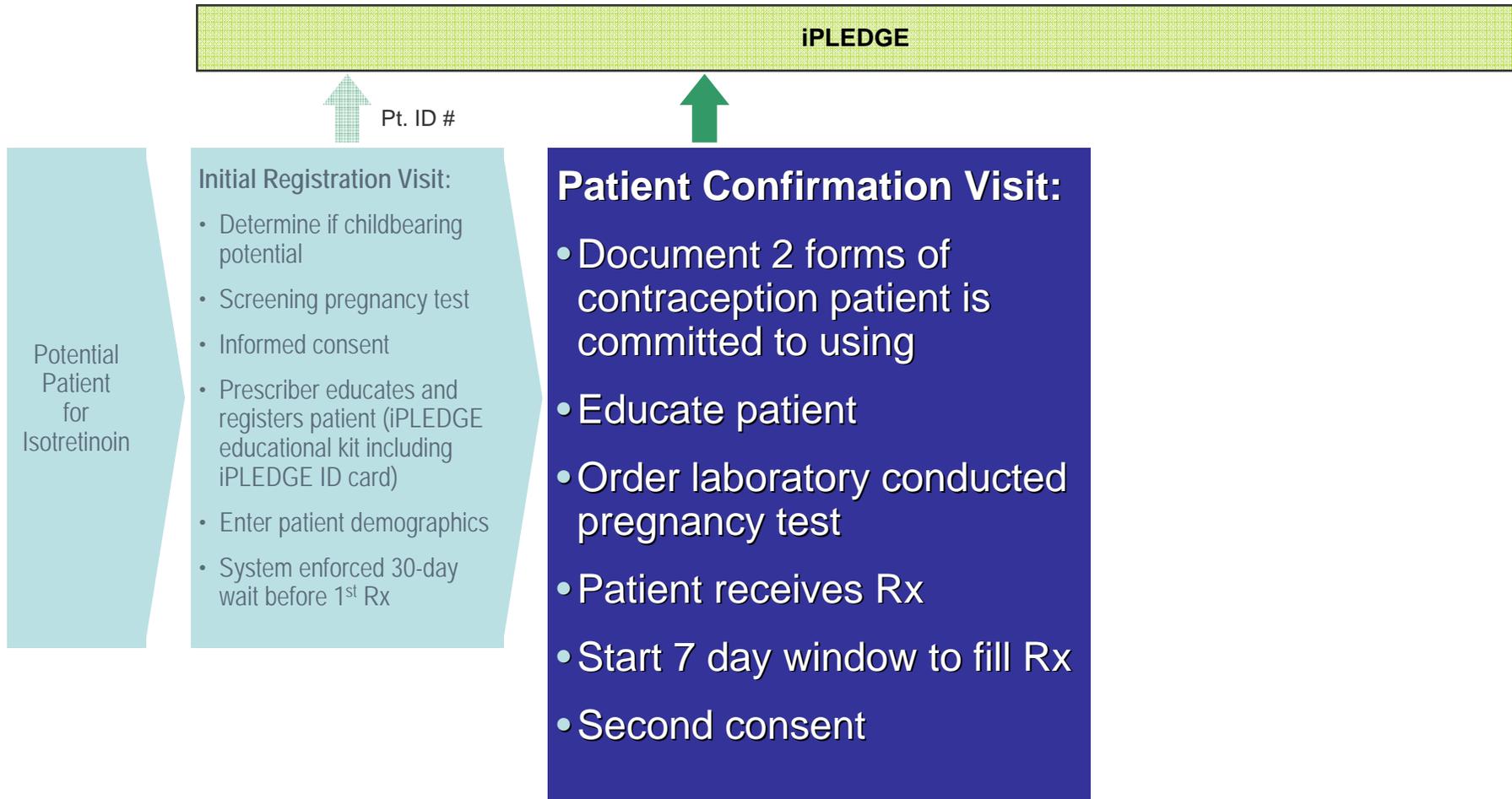
Pt. ID #

Potential
Patient
for
Isotretinoin

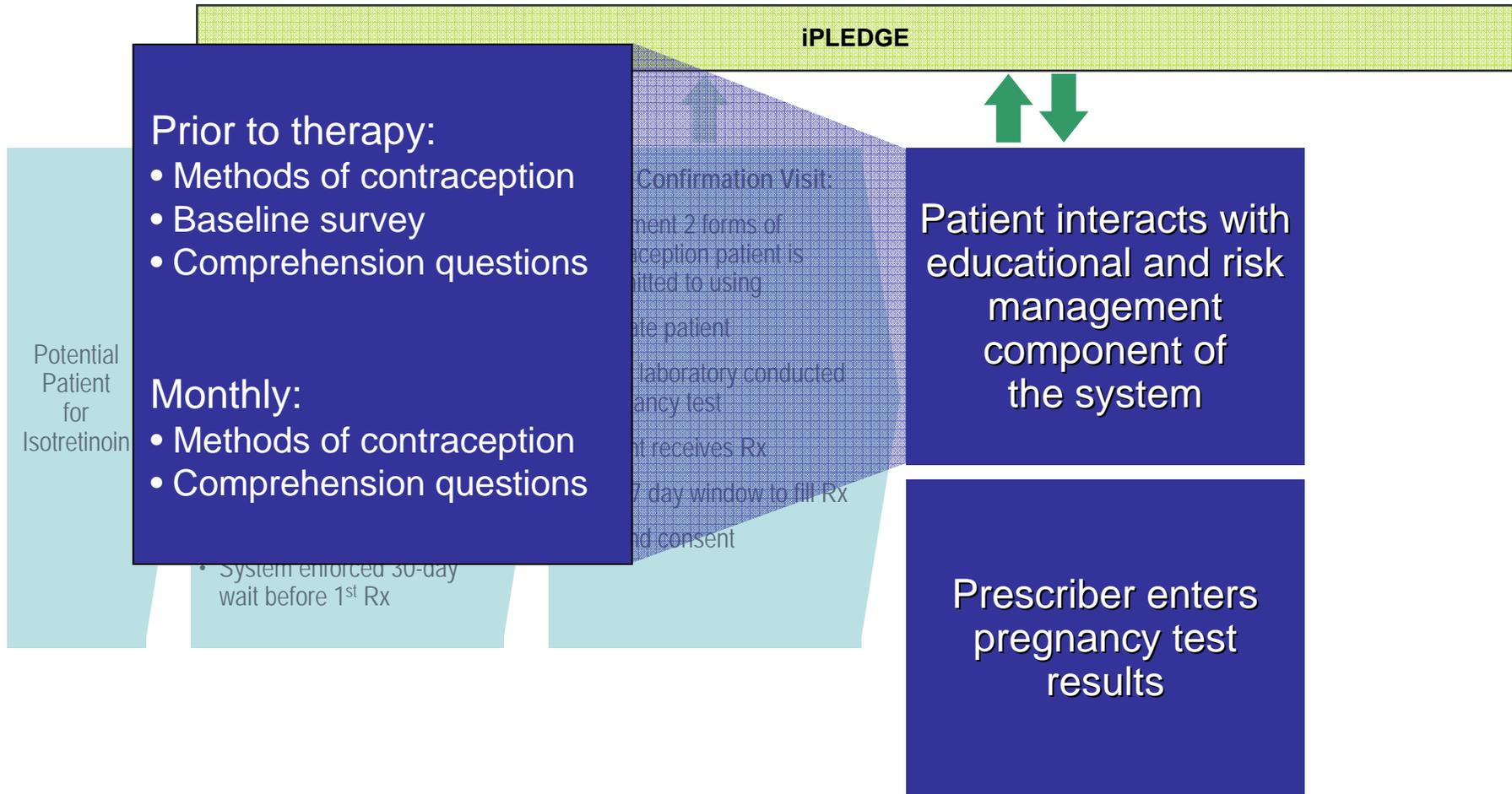
Initial Registration Visit:

- Determine if childbearing potential
- Screening pregnancy test
- Informed consent
- Prescriber educates and registers patient (iPLEDGE educational kit including iPLEDGE ID card)
- Enter patient demographics
- System enforced 30-day wait before 1st Rx

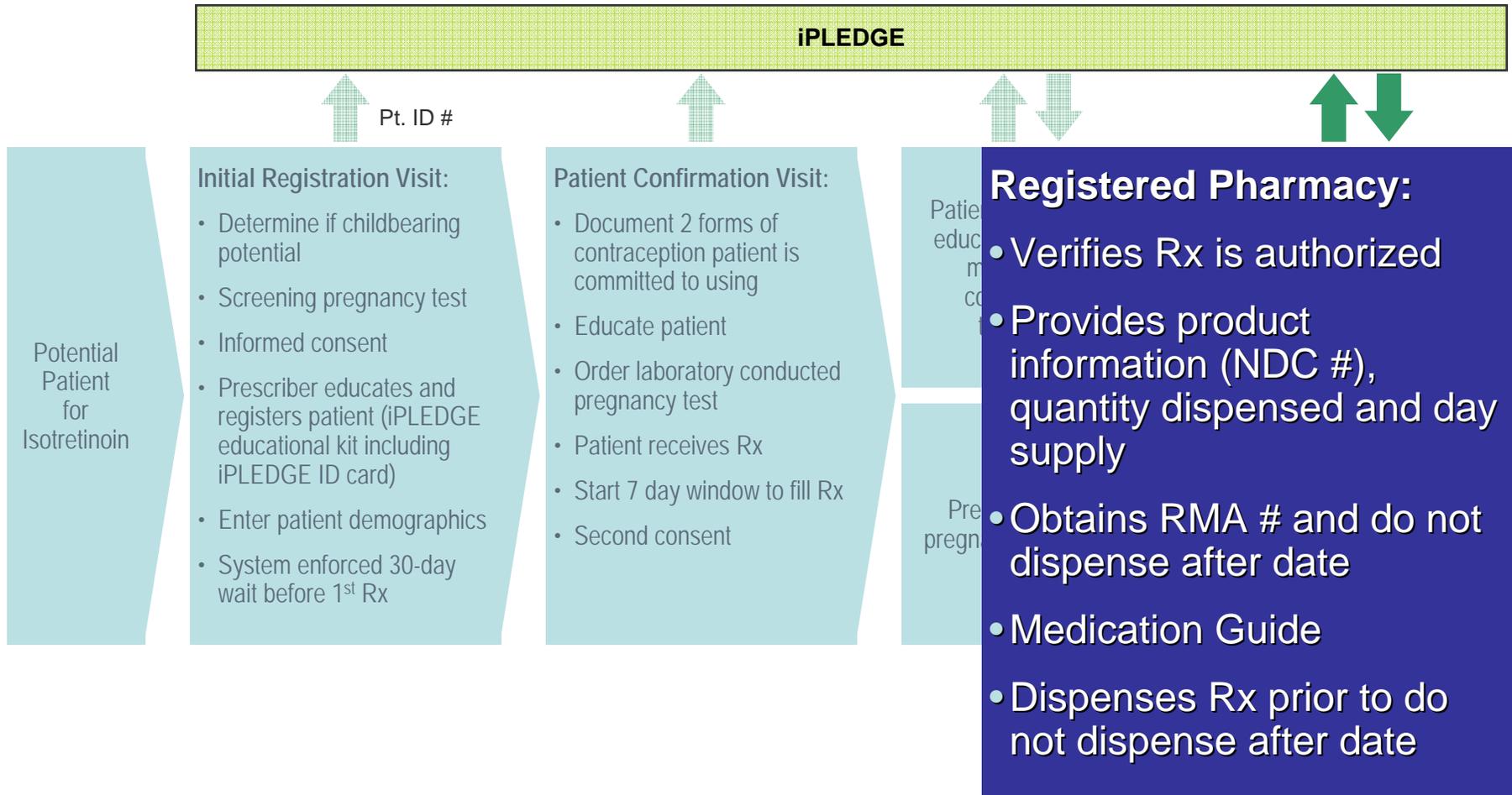
Patient Path: Females of Child-Bearing Potential



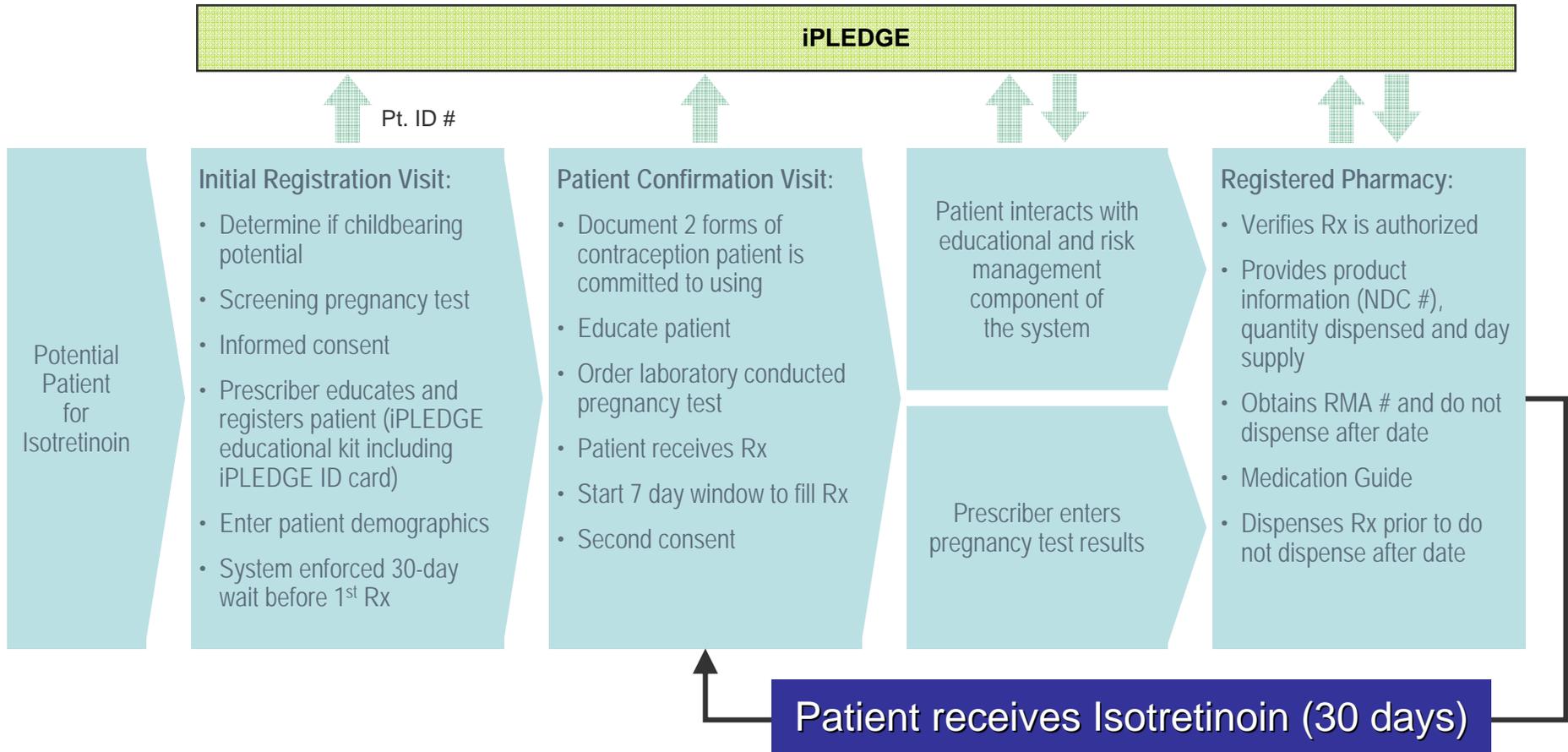
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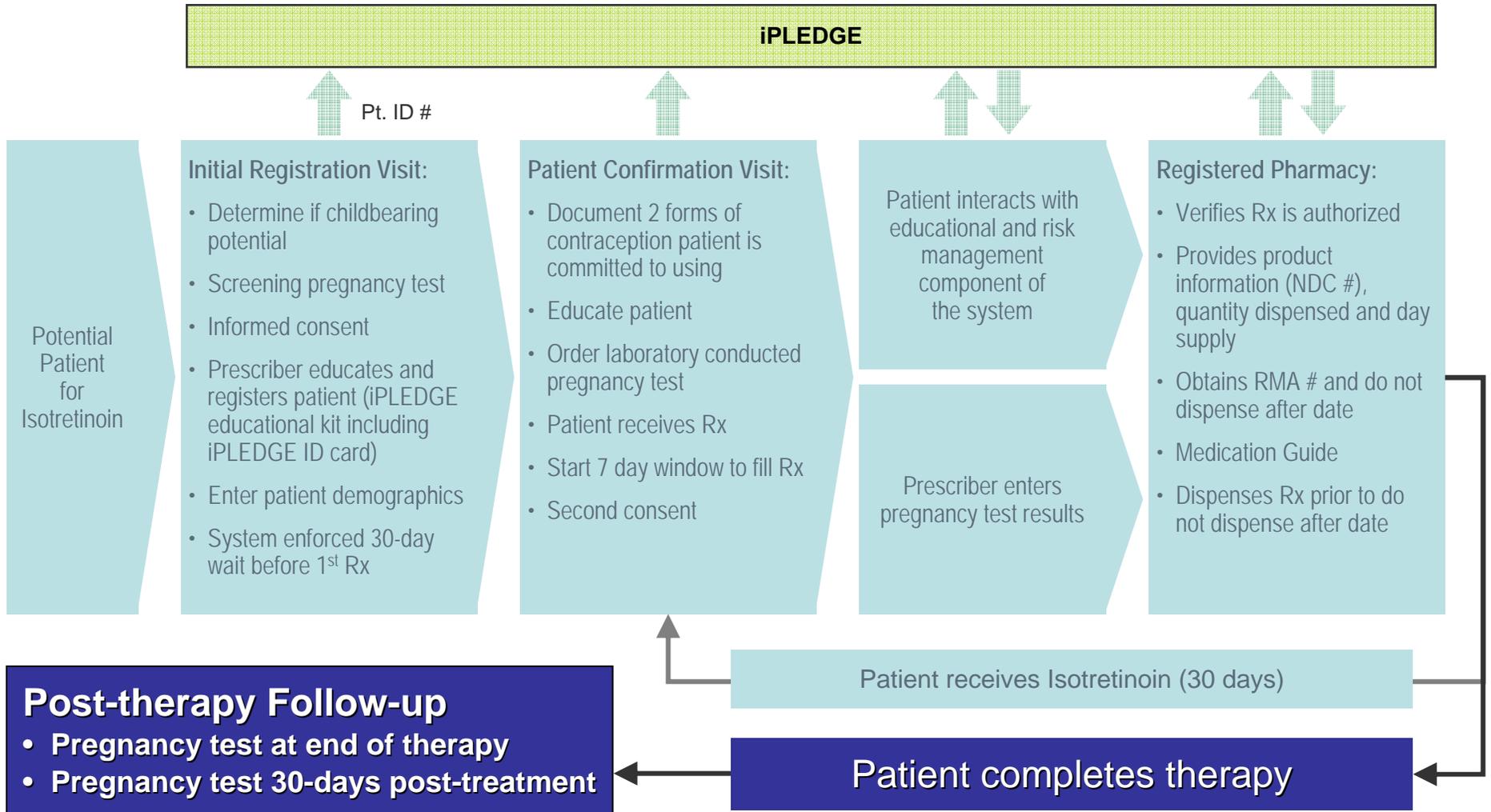
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Patient Path: Females of Child-Bearing Potential



Patient Path: Females of Child-Bearing Potential

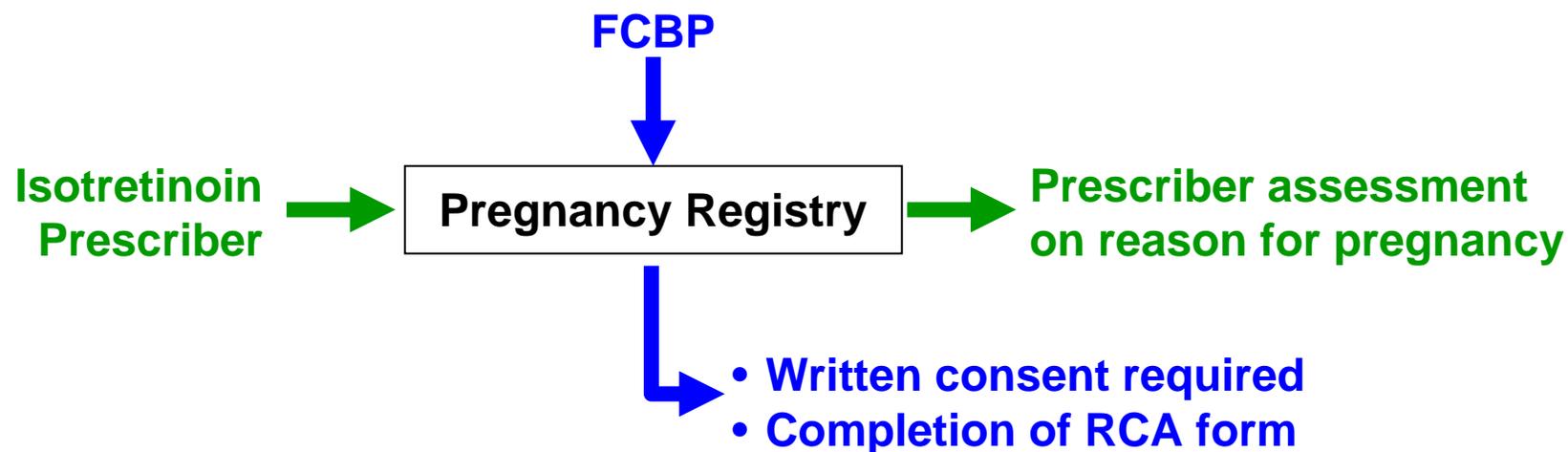


Isotretinoin Pregnancy Registry for Collecting Pregnancy Data

Objectives:

- Determine exposure status for each reported pregnancy
- Document the outcome for each exposed pregnancy
- Determine root cause analysis for each exposed pregnancy
 - Determine patient knowledge, attitudes, and behavior regarding iPLEDGE requirements
 - Determine the most likely reported cause of pregnancy
- Provide pregnancy data in periodic reports to FDA
- Develop centralized database of all isotretinoin pregnancy reports

Sources of Pregnancy Data (Process for Year 1)



- Sources of input for Root Cause Analysis
 - Prescriber
 - Patient
 - Root Cause Analysis form

Review of Year 1 Data

- FCBP Interactions with the System
- Pregnancy Data
- Observations of Patient Knowledge / Behavior

Year 1 iPLEDGE Patients Registered and RMA

	Registered	Patients with at least 1 RMA
Males	135,507	132,404
Females	132,708	102,680
<i>FCBPs</i>	120,737	91,894
<i>FNCBPs</i>	11,971	10,786

Note: In any 1 month, ~ 20% of FCBPs are in the 30 day wait period after registration and will have no other activity in iPLEDGE

iPLEDGE Year 1 Data

- Pregnancy Classification
 - Registered in iPLEDGE
 - Initial report received by March 31, 2007
 - Conception date before February 28, 2007
- FCBPs who received at least 1 RMA
 - 91,894 FCBPs for Year 1
- iPLEDGE Pregnancies
 - 122 reported pregnancies

iPLEDGE Year 1 Pregnancies Relative Timing to Isotretinoin Exposure

- 91,894 FCBPs with at least 1 RMA Number

Description of Conception Date	N (N=122)	%
Prior to starting isotretinoin treatment	10	8.2
During isotretinoin treatment	78	63.9
Within 30 days after isotretinoin treatment completion	8	6.6
Unknown (includes 15 indeterminate cases)	26	21.3

iPLEDGE Year 1 Pregnancies

Age at Time of Conception

Age Category	Non-Pregnant FCBPs		Pregnant FCBPs	
	N=97,886	%	N=122	%
<12	116	0.1	—	
12-15	11,579	11.8	2	1.6
16-19	30,653	31.3	24	19.7
20-29	34,550	35.3	68	55.7
30-39	14,846	15.2	23	18.9
40-44	4,296	4.4	5	4.1
45+	1,848	1.9	—	

Reasons for Pregnancy Reported by Prescriber and by Patient

Year 1 Data

iPLEDGE Year 1 Pregnancies Reason Reported by Prescriber

(87 of N=122)

Contraceptive Failure	23
Did Not Use 2 Forms of Birth Control	16
Failure to Use Contraceptive on Date of Conception	14
Unsuccessful at Abstinence	14
Used Ineffective Contraception	1
Unknown	42

Note: Prescriber may have selected more than one reason.

iPLEDGE Year 1 Pregnancies Reason Reported by Pregnant FCBP

(22 of N=122)

Did Not Use 2 Forms of Birth Control	9
Contraceptive Failure	7
Missing	6
Unsuccessful at Abstinence	2
Other	2
Unknown	1

Note: FCBP may have selected more than one reason.

Observations from the FCBP RCA Forms

- Most patients reported they were:
 - Counseled about the risks of birth defects
 - Instructed not to become pregnant
 - College graduates or had some college education
- Nearly half of the patients reported using one form or no form of birth control when having sexual intercourse during the month of conception

Improvements to Increase Collection of RCA Forms

Ongoing Year 2 Process

- Prescriber reported pregnancy
 - Direct patient contact after notification of her pregnancy by prescriber
 - Obtain verbal consent at initial contact to complete RCA Forms
- FBCP reported the pregnancy
 - Obtain verbal consent at initial contact to complete RCA Forms
 - Follow-up with primary prescriber for additional information

Proposed change under IRB review

- Obtain initial verbal consent to contact other healthcare provider (i.e., OB/GYN)

Review of Year 1 Data

- FCBP Interactions with the System
- Pregnancy Data
- Observations of Patient Knowledge / Behavior
 - Baseline Survey
 - Comprehension
 - Contraception Choices

Baseline Survey Prior to Therapy

- Comprised of 8 questions
- Patient logs-in to “Answer Questions”– Web or IVR System
- Content of survey:
 - Was told to avoid pregnancy
 - Has received the educational materials
 - Has reviewed the educational materials
 - From whom was birth control counseling received
- Survey presented before the comprehension questions

NOTE: No apparent difference between the non-pregnant and the pregnant patients

FCBPs Positive Responses to Baseline Survey (1)

	March 1, 2006-February 28, 2007			
	Non-Pregnant FCBPs		Pregnant FCBPs	
	N=97,151	(%)	N=113*	(%)
Told to avoid pregnancy	96,870	(99.7)	112	(99.1)
Received educational kit for female patients who may get pregnant	95,611	(98.4)	110	(97.3)
Read guide to isotretinoin for female patients who may get pregnant	95,250	(98.0)	109	(96.5)
Read birth control workbook	93,691	(96.4)	108	(95.6)
Watched "Be Aware" Video on effects of isotretinoin	53,922	(55.5)	77	(68.1)
Watched "Be Prepared Be Aware" Video on birth control	53,860	(55.4)	75	(66.4)

* 9 pregnant patients did not complete questions

FCBPs Positive Responses to Baseline Survey (2)

	March 1, 2006-February 28, 2007			
	Non-Pregnant FCBPs		Pregnant FCBPs	
	N=97,151	(%)	N=113*	(%)
Doctor offered to refer for birth control counseling	47,695	(49.1)	62	(54.9)
Question: From whom did you receive birth control counseling?				
Received from another healthcare provider	19,991	(20.6)	34	(30.1)
Received from doctor	63,870	(65.7)	64	(56.6)
Did not receive birth control counseling	13,289	(13.7)	15	(13.3)

* 9 pregnant patients did not complete questions

Monthly Comprehension Questions

- Patient must complete the comprehension questions correctly before the RMA number is issued
- Randomly selected from repository of questions
- Tailored to patients contraception choices
- Questions broken down into the following 6 categories:
 - General iPLEDGE program steps
 - General contraception requirements
 - Birth defects and pregnancy
 - Safety information (not sharing and not donating blood)
 - Filling a prescription
 - Contraception questions

Monthly Comprehension Questions Results per Patient for Year 1 of iPLEDGE

(N=98,008)

	Non-Pregnant FCBPs		Pregnant FCBPs	
	N	%	N	%
Passed first time	81,661	83.4	89	79.4
1 Failure	12,179	12.4	21	18.8
2 Failure	2,681	2.7	2	1.8
> than 2 Failures	1,375	1.4	–	–
Total	97,896	100.0	112*	100.0

- Majority of all FCBPs passed the comprehension questions first time
- No apparent difference between the non-pregnant and the pregnant patients in comprehension

* 10 pregnant patients did not take a comprehension test

Selection of Contraception Choices

- During the office visit, the prescriber and patient determine the appropriate methods of contraception for the FCBP
- The prescriber enters the selected contraception choices for the patient into the iPLEDGE system
- The patient enters her 2 chosen methods of contraception into the iPLEDGE system
- The primary method must match in order for the FCBP to continue the process

Methods of Contraception (Percent of Time Combinations Selected)

Primary	Secondary	All FCBPs N=98,008	Pregnant FCBPs N=112*
Birth control pills	Male condom	42.0	72.2
Abstinence		43.1	18.3
Hormonal Injection	Male condom	1.3	3.2
Vasectomy	Male condom	3.3	0.3
Other combinations		10.3	6.0
<i>Total</i>		<i>100%</i>	<i>100%</i>

* 10 pregnant patients did not take the comprehension test

iPLEDGE Program – Summary

- iPLEDGE program is an integrated program supporting the defined public health goals
- Proposed program changes are intended to:
 - Enhance flexibility
 - Reduce interruption of treatment
 - Reduce stakeholder burden
- Year 1 iPLEDGE data provide baseline information
- No identifiable difference between pregnant and non-pregnant FCBPs, based on these data
- Education messages are reaching the patients
- Individual patient behavior plays a key role in program outcome despite intense educational efforts