Solumatrix Fine Particles Technology, New Era in Pain Management.

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“Our Industry is poised to translate our most promising scientific Breakthroughs into meaningful treatments capable of tackling the most urgent and vexing medical challenges of our times. We stand committed to driving progress for patients Today and Hope For Tomorrow.”

Kenneth C. Frazier Chairman and CEO Merck
Outline

1. Introduction
2. The Innovative Technology
3. Solumatrix in details
4. Solumatrix in pain management: Value to NSAIDS
5. Conclusion on Value to Patients and Healthcare professionals
Introduction

• For patients, new medicines offer improved quality of life, and importantly, extended lives.
• However, developing new medicines is a long, and a complex process.
• Although, the rapid pace of scientific advances is enabling a greater understanding of diseases at the molecular level, the scientific, technical, and regulatory challenges related to drug development are creating complexities.
• As a result, the process for researching and developing new medicines is growing in difficulty and length.
• The average cost to research and develop each successful drug is estimated to be $2.6 billion. This number incorporates the cost of failures – of the thousands and sometimes millions of compounds that may be screened and assessed early in the R&D process, only a few of which will ultimately receive approval.
Introduction

• The overall probability of clinical success (the likelihood that a drug entering clinical testing will eventually be approved) is estimated to be less than 12%.

• Success requires immense resources — the best scientific minds, highly sophisticated technologies, ever-evolving manufacturing processes, and complex project management.
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1. Introduction
2. The Innovative Technology: **Solumatrix Fine Particles Technology**,  
3. Solumatrix in details  
4. Solumatrix in pain management: Value to NSAIDS  
5. Conclusion on Value to Patients and Healthcare professional
Solumatrix Fine Particles Technology,

• This innovative technology consists of developing new forms, based on existing and proven drugs, and to generate a new efficacy/safety profile

• An approach that benefits from rapid development programs, enabling an accelerated time to market.

• The use of safety proven registered molecules ensures a low risk of late stage project failure.
Technology that fuels new product development by enabling meaningful clinical benefits and creating new intellectual property protection.
How SoluMatrix works

The SoluMatrix technology improves the performance of pharmaceuticals by dramatically changing how the drug dissolves and is absorbed. By making submicron-sized particles of a drug, it is possible to:

- improve the bioavailability and reduce the variability of a drug
- speed up the activity of the drug
- reduce the amount of drug required to achieve a desired plasma level
- remove or eliminate food effects
- change the mode of administration of a drug
Many orally-administered cancer drugs are not very soluble in water, which restricts the body’s ability to absorb the drug. To overcome this problem, larger doses often need to be delivered in order to achieve a therapeutic dose, and this can result in highly-variable blood levels of the drug and unwanted side effects. The SoluMatrix™ Fine Particle Technology can be used to create improved cancer drugs with potentially enhanced properties, such as significantly reduced dose required to achieve a therapeutic level of the drug, reduced side effects and potentially improved efficacy.
Respiratory Disease

One of the key challenges to the development and commercialization of respiratory products is formulating inhalable medicines to achieve consistent and efficacious dosing. iCeutica has created a range of inhaled product candidates addressing asthma, COPD and allergic disease that are characterized by their consistent content uniformity, aerodynamic properties and nano-structured increased surface area.

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**ICE 1202**  
Available for Partnering

**ICE 1203**  
Available for Partnering

**ICE 1204**  
Available for Partnering
Solumatrix / Pain & Inflammation

Pain & Inflammation

The SoluMatrix™ Fine Particle Technology can dramatically increase the speed-of-action of a pain drug, often at much lower doses than current dosages and with potentially fewer side effects than full-dose products.

- Three FDA approved NSAIDs (SoluMatrix® diclofenac, SoluMatrix® indomethacin, and SoluMatrix® meloxicam) to help advance the science of responsible pain management.
SoluMatrix Fine Particle Technology- FDA Approved Technology

• Technology works to create new branded medicines by combining the SoluMatrix™ Fine Particle Technology with the well established molecules having known product experience and commercial insights.

• The resulting products provide meaningful clinical benefits for patients and have clearly defined pathways to regulatory and commercial success. There are numerous FDA approved and late-stage products in development that utilize SoluMatrix technology.
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SOLUMATRIX FINE PARTICLE TECHNOLOGY
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Innovative Technology founded in 2004

Reduced particle size increases surface area

Increased surface area leads to faster dissolution

Produces Drug Particles that are 200-800 nanometers in size
Allows Customization of Pharmacokinetics to Need
SoluMatrix Fine Particle Technology

- An innovative and proprietary manufacturing process

- Reduces particle size of the active pharmaceutical ingredient

- Particles range from 200 – 800 nm in size
  - Submicron Particles

- Increased surface area-to-mass ratio
  - Leading to faster dissolution

- Facilitating absorption in the GI track following oral administration
SoluMatrix Fine Particle Technology

A. API Drug Substance (1-50 micron meters)*

B. SoluMatrix™ Drug Substance (200-800 nm)*

* Images provided by iCeutica Inc.

Reference: Data on file, Iroko Pharmaceuticals, LLC.
SoluMatrix Fine Particle Technology

- Lowering the dose without delaying the rate of absorption
- Maintaining the therapeutic efficacy of the drug product
- Lower risk of Adverse Events
  - Because of lower dose
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THE NEED FOR LOW-DOSE NSAIDS
NSAIDs are among the most widely used medications in the world because of their demonstrated efficacy in reducing pain and inflammation.\(^1\)

NSAIDs are widely used in the management of arthritis, acute and chronic pain of many etiologies.\(^2\)
Risks of Serious GI, CV and Renal Complications with NSAID Use

- **Gastrointestinal**
  - Perforations
  - Ulcers
  - Bleeds

- **Cardiovascular**
  - Acute MI
  - Stroke

- **Renal**
  - Acute Renal Failure

CV, cardiovascular; GI, gastrointestinal.

Potential Consequences of NSAID Usage

Data from an observational study of patients with rheumatic diseases suggest that

• Each year, more than 100,000 patients are estimated to require hospitalization for NSAID-related gastrointestinal complications alone

• It is estimated that 16,500 patients die from NSAID-related gastrointestinal complications each year

NSAID Dose Has Been Shown to be an Important Risk Factor for Serious Adverse Events

Gastrointestinal

Adjusted Relative Risk of Upper GI Bleed and Perforation

CV, cardiovascular; GI, gastrointestinal.

Even Short-term NSAID Use Carries Risk of Serious Adverse Events

Perf, perforation; MI, myocardial infarction; OR, odds ratio; RR, relative risk.
Use the lowest effective NSAID dose for the shortest duration

* NICE recommendation with respect to use of NSAIDs in osteoarthritis.

References:
Recent FDA NSAID Drug Safety Communication Strengthens NSAID Cardiovascular Warnings

- July 2015, an FDA Drug Safety Communication announced that it is strengthening the existing prescription and over-the-counter labeling for all non-aspirin NSAIDs specifically regarding the increased risk of cardiovascular thrombotic events such as myocardial infarction and stroke.

- This communication continues to recommend that NSAIDs be prescribed at the lowest effective dose for the shortest duration as described in the 2005 FDA Public Health Advisory.

References:
SoluMatrix Fine Particle Technology

- Dry milling process reduces Diclofenac drug particles into a superfine powder
  - Consisting of submicron drug particles that are 200 to 800 nm in diameter
  - 20 times smaller than the starting active pharmaceutical ingredient
- Diclofenac free acid

Reference: Data on file, Iroko Pharmaceuticals, LLC.
Improved Formulation

• Absorption of Diclofenac is dose-dependent

• SoluMatrix Fine Particle Technology optimizes Pharmacokinetic Profile
  – Allows use of Diclofenac free acid form instead of salt forms (sodium, potassium..)
  – Allows faster dissolution through particle size reduction

Reference: Data on file, Iroko Pharmaceuticals, LLC.
A LOWER DOSE DICLOFENAC THAT IS EFFECTIVE AND SAFE
Estimated Risk Reduction

- Diclofenac 18mg
  - 45% risk reduction in Gastrointestinal (GI) events
    - Bleeding, perforation
  - 17% risk reduction in Cardiovascular (CV) events
    - Myocardial infarction

- Diclofenac 35mg
  - 18% risk reduction in GI events
  - 7% risk reduction in CV events

Diclofenac Pharmacokinetics Profile

* Based on a Phase I study in healthy subjects.

Reference: Data on file; Iroko Pharmaceuticals, LLC
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Solumatrix Fine Particle Technology
Value-addition

- SoluMatrix Fine Particle Technology has been used to lower the dose without delaying the rate of absorption and provide similar time to peak plasma concentrations

- Provides a lower systemic exposure and at the same time the similar time to peak plasma levels which allows for distribution into injured tissues in a timely manner
Thank you