FIXED DOSE COMBINATION (FDC) PRODUCTS OVERVIEW

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OUTLINE

• Rational

• Marketed and Developmental stage FDCs
  – Global picture
  – Large pharma
  – Ther. categories
  – Delivery Routes/DD technologies

• Conclusions
FIXED DOSE COMBINATIONS (FDC)

RATIONAL

• **Improved patient compliance:** Simplified disease management for chronic diseases (e.g. HIV, asthma, diabetes, lipid regulation, hypertension, etc.)

• **Better efficacy:** Synergistic mechanisms, improved ADME & drug resistance

• **Simplified/cost effective handling & distribution** especially for HIV drugs

• **Effective LCM strategy:** New products from proven molecules; patent/market exclusivity, may also combine formulation patent exclusivity
MARKETED FDC PRODUCTS
n=1597

MANY OLD MARKETED PRODUCTS
-Cough and cold
-Topicals, etc.
MARKETED FDC PRODUCTS
Includes, new combinations, indications and formulations and territories
Exclude Generic/OTC and approvals, n=230

- Growing number of Rx FDCs approved since 90’s
- 90% with 2 molecules and only 7% with 3 molecules
ROUTES FOR MARKETED FDC PRODUCTS
Includes, new combinations, indications and formulations and territories
Exclude Generic/OTC and approvals  n=206

- 25% based DD technology
- 83% Tablet

80% Topicals
MARKETED ORAL COMBO PRODUCTS
Includes, new combinations, indications and formulations and territories
Exclude Generic/OTC and approvals, n=30

Majority Matrix MR Tablets

25% (n=30) of all oral (n = 120) based DD technology
APPROVALS VS. INDICATIONS (GLOBAL)
Includes, new combinations, indications and formulations and territories
Exclude Generic/OTC and approvals, n=234

- Infections
  - HIV/AIDS
  - Bacterial infections

- Cardiovascular
  - Hypertension
  - Lipid Lowering

- Pain Management and Local Anesthesia

- Respiratory
  - Asthma
  - COPD

- Endocrine
  - Diabetes
  - Lipid lowering

- Skin Diseases
  - Acne
  - Skin Infections
  - Anti-inflammatories

- Womens’s Diseases
  - Contraceptives
  - Osteoporosis
  - Menopause
CARDIOVASCULAR FDCs
n=37

78% for Hypertension
Majority Hydrochlorothiazide combinations
Renin Inhibitor, AT I R and AT II R antagonist,
Ace Inhibitors, Ca+2 Channel blocker, etc.

Hydroxymethylglutaryl-CoA Reductase Inhibitor combos:
Vytorin, Caduet, Simcor ER,
Tredaptive, Advicor, etc.

FDCs are likely to improve adherence in a range of settings, but uncertainty remains about the size of these benefits
FDCs for INFECTION
n=35

Viral Infections; HIV/AIDS, etc.

- Old gold standard for HIV: Combivir an FDC of zidovudine and lamivudine -2xday
- Newer FDCs with once daily dosing and improved tolerability and toxicity profiles
- Simplified dosing/handling-improved compliance, better disease control
FDCs for ENDOCRINE/METABOLISM
n=20

FDCs are likely to improve adherence in a range of settings, but uncertainty remains about the size of these benefits.
ASTHMA/COPD FDCs, n=30

FDA recommends the use of FDCs containing an inhaled corticosteroid and a LABA because of the difficulty of ensuring compliance with both medications when they are administered separately.

- Advair (GSK) and Symbicort (AstraZeneca) combined sales $9.5bil-50% of Inhalation market %18b-20 products
FDC PIPELINE (GLOBAL)

- Majority with 2 molecules
- Only 18 with have 3 mol. (HIV, Pain, Diabetes, etc.)
- 1 has 4 molecules (HIV)
ROUTES FOR FDC PIPELINE
n=332
ORAL FDC PIPELINE

n=87

Oral MR
FDCs MARKETED by LARGE PHARMA
Marketed since 1990 (no OTC), n=58
FDC PIPELINE - LARGE PHARMA

n=45

Novartis has been most active
## TOP SELLING FDC PRODUCTS

<table>
<thead>
<tr>
<th>Name /Form</th>
<th>Molecules</th>
<th>Indication</th>
<th>Approval Year/Company</th>
<th>Sales 2009 ($Mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair Discus/DPI/HFA</td>
<td>fluticasone/salmeterol</td>
<td>Asthma/COPD</td>
<td>2000/GSK</td>
<td>7800</td>
</tr>
<tr>
<td>Hyzaar/Cozaar</td>
<td>losartan/HCT</td>
<td>Hypertension</td>
<td>1995/Merck &amp; Co.</td>
<td>3561</td>
</tr>
<tr>
<td>Truvada</td>
<td>emtricitabine/tenofovir</td>
<td>HIV/AIDS</td>
<td>Gilead/2004</td>
<td>2490</td>
</tr>
<tr>
<td>Atripla Tablets</td>
<td>efavirenz/emtricitabine/tenofovir</td>
<td>HIV/AIDS</td>
<td>2007/Gilead/BMS</td>
<td>2382</td>
</tr>
<tr>
<td>Vytorin</td>
<td>ezetimibe/simvastatin</td>
<td>Lipid regulation</td>
<td>2004/Merck/SP</td>
<td>2352</td>
</tr>
<tr>
<td>Symbicort/DPI/MDI</td>
<td>budesonide/formoterol</td>
<td>Asthma/COPD</td>
<td>2006/Astra Zeneca</td>
<td>2004</td>
</tr>
<tr>
<td>Avandamet Tablets</td>
<td>rosiglitane/metformin</td>
<td>Diabetes</td>
<td>2002/GSK</td>
<td>1200</td>
</tr>
<tr>
<td>Kaletra soft gel</td>
<td>lopinavir/ritonavir</td>
<td>HIV/AIDS</td>
<td>2000/Abbott</td>
<td>1366</td>
</tr>
<tr>
<td>Epzicom</td>
<td>abacavir/lamivudine</td>
<td>HIV/AIDS</td>
<td>2005/Shire</td>
<td>854</td>
</tr>
<tr>
<td>Combivir Tablets</td>
<td>lamivudine/zidovudine</td>
<td>HIV/AIDS</td>
<td>1997/Shire</td>
<td>665</td>
</tr>
</tbody>
</table>
## RECENT FDC APPROVALS

<table>
<thead>
<tr>
<th>Product</th>
<th>Molecules</th>
<th>Indications</th>
<th>Approval/Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ristfor Tablet</td>
<td>sitagliptin/metformin</td>
<td>Diabetes</td>
<td>March 10/Merck (EU)</td>
</tr>
<tr>
<td>Duodart</td>
<td>dutasteride/tamsulosin</td>
<td>BPH</td>
<td>March 10/GSK (EU) Tent. Approved Jan. 10 (USA)</td>
</tr>
<tr>
<td>DuoCover/DuoPlavin tablet</td>
<td>clopidogre/aspirin</td>
<td>ACS/MI</td>
<td>March 2010 BMS/SA (EU)</td>
</tr>
<tr>
<td>Azor Tablet</td>
<td>amlodipine/olmesartan</td>
<td>Hypertension</td>
<td>08/09/Daiichi Sankyo (USA &amp; EU)</td>
</tr>
<tr>
<td>EMBEDA Abuse resistant capsule</td>
<td>morphine/naltrexone</td>
<td>Pain</td>
<td>09/Alpharma/King Pharma (USA)</td>
</tr>
<tr>
<td>Lipsovir cream</td>
<td>acyclovir/hydrocortisone</td>
<td>Herpes</td>
<td>09/Medivir/Meda (USA)</td>
</tr>
<tr>
<td>Copalia HCT</td>
<td>amlodipine/valsartan/hydrochlorothiazide</td>
<td>Hypertension</td>
<td>09/Novartis (EU)</td>
</tr>
<tr>
<td>ACTOplus met XR Tablets</td>
<td>metformin/pioglitazone</td>
<td>Diabetes</td>
<td>09/Takeda (USA)</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• FDCs may offer better treatment through improving patient compliance
• Greater the noncompliance chance with individual drugs higher the chance of FDC product success
• New products with patent/market exclusivity. Overcome formulation challenges for stronger patents
• Growing number of products/pipeline for cardiovascular, lipid regulation, diabetes, pain, respiratory diseases and infections
• Majority are based on two molecules, and several 3 mol. FDCs for HIV, Diabetes, Hypertension, etc. and even 4 mol FDCs for HIV
• Majority are delivered as IR/MR tablets. Also Inhalation, Topical and Transdermal products
QUESTIONS?

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