New Drug Update 2014-15
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Faculty Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

• I do not speak for or consult with any pharmaceutical manufacturer.

Zoster Vaccine

March 24, 2011 FDA approved – Zostavax for patients age 50-59 years

• Compared with placebo, ZOSTAVAX significantly reduced the risk of developing zoster by 69.8% (95% CI [54.1 - 80.6%]) in 22,439 subjects 50 to 59 years of age. Data from the Shingles Prevention Study demonstrated 64% (95% CI 56-71%) efficacy in patients age 60-69 years and 41% (95% CI 28 -52%) efficacy for patients age 70-79 years and. only 18% (95% CI -29 – 48%) efficacy in patients age 80 and above.
Zostavax in Patients with a History of Shingles?

- Administration of the varicella vaccine in older people with a recent history of shingles does not confer additional immunity, a population-based study from Kaiser Permanente in Southern California suggests. The findings, published online June 4, 2012 in the Journal of Infectious Diseases, indicate that immediate vaccination may be unwarranted.
- Dr. Oxman, national chairman of VA Cooperative Study #403—The Shingles Prevention Study, but was not involved in the current study made the following comments:
  - "A case of shingles boosts your cell-mediated immunity to the varicella virus. It's clear that [infection] gives you a maximum response to the varicella virus, so giving the vaccine is like bringing coal to Newcastle,"
  - "If I knew for certain that a patient had a real case of shingles with plenty of blisters indicating plenty of virus and virus antigen, I would tell them to wait 2 or 3 years [before receiving the vaccine]."

Immunization Update – New Zoster Vaccine?

- GSK has just reported the initial results of ZOE-50 a randomized, observer-blind, placebo-controlled, multi-center, multinational phase III efficacy study designed to assess HZ/su (herpes zoster/sub-unit vaccine) in 16,160 patients age 50 and older.
  - viral protein (gE) combined with the adjuvant system - AS01B (a liposome-based adjuvant system containing immunoenhancers) (Not a live attenuated vaccine)
  - 2-dose schedule at 0 and 2 months.
  - The vaccine efficacy (defined as the reduction in disease incidence in the vaccinated group compared to the unvaccinated group) in adults 50 years and older was 97.2%, compared to placebo.
    - Study 110390. 2014. Available at: http://www.gsk-clinicalstudyregister.com/*

CDC Recommends Immunocompromised Adults Get Prevnar 13 Vaccine

- June 21, 2012 the Centers for Disease Control and Prevention's Advisory Committee on Vaccine Practices voted 14 to 0 that adults "with AIDS, cancer, organ transplants, advanced kidney disease and other immune-weakening conditions" should be given pneumococcal vaccine Prevnar 13, including those "who've already had Pneumovax 23" The panel has not yet decided if "all adults 50 years old and older should get Prevnar 13."
ACIP Recommendations for PCV13 and PPSV23 Use

- Adults with specified immunocompromising conditions who are eligible for pneumococcal vaccine should be vaccinated with PCV13 during their next pneumococcal vaccination opportunity.
- Pneumococcal vaccine-naive persons. ACIP recommends that adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, and who have not previously received PCV13 or PPSV23, should receive a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later. Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk. Specifically, a second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia and for persons with immunocompromising conditions. Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose.

— MMWR October 12, 2012 / 61(40);816-819

ACIP Recommendations for PCV13 and PPSV23 Use

- Previous vaccination with PPSV23. Adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, who previously have received ≥1 doses of PPSV23 should be given a PCV13 dose ≥1 year after the last PPSV23 dose was received. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.

— MMWR October 12, 2012 / 61(40);816-819

CAPiTA Trial Preliminary Results

- The 85,000-patient study in the Netherlands, called CAPiTA, showed that Prevnar 13 prevented invasive pneumococcal disease, meaning infections of Streptococcus pneumoniae bacteria in patients age 65 and older.
  - 45.56% fewer first episodes of vaccine-type CAP among Prevnar 13-vaccinated subjects than in subjects who received placebo (P=0.0006).
  - Secondary objectives, the Prevnar 13 group experienced 45.00 % fewer first episodes of non-bacteremic/non-invasive vaccine-type CAP (P=0.0067) and 75.00 % fewer first episodes of vaccine-type IPD (P=0.0005) compared with the placebo group.
  - To be reviewed by ACIP and FDA

— 10/20/2015
CAPiTA Trial

- Confirmed community-acquired pneumonia
  - Per-protocol analysis 49 cases with vaccine vs. 90 cases with placebo - Vaccine Efficacy 45.6%, 95% CI (21.8 to 62.5) p<0.001 (over 42,000 patients per group!) Rates are 0.213% vs. 0.116%, ARR = 0.097, NNT = 1031

- Invasive pneumococcal disease
  - Per-protocol analysis 7 cases with vaccine vs. 28 cases with placebo – Vaccine Efficacy 75.0%, 95% CI (41.4 to 90.8) p<0.001. Rates are 0.066% vs. 0.0166%, ARR = 0.05, NNT = 2000

MMWR New Recommendations
September 19, 2014 / 63(37):822-825

- Both PCV13 and PPSV23 should be administered routinely in series to all adults aged ≥65 years:
  - Pneumococcal vaccine-naive persons. Adults aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23. The dose of PPSV23 should be given 6–12 months after a dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit. The two vaccines should not be co-administered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks.

MMWR New Recommendations
September 19, 2014 / 63(37):822-825

- Previous vaccination with PPSV23. Adults aged ≥65 years who have previously received ≥1 doses of PPSV23 also should receive a dose of PCV13 if they have not yet received it. A dose of PCV13 should be given ≥1 year after receipt of the most recent PPSV23 dose. For those for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given 6–12 months after PCV13 and ≥5 years after the most recent dose of PPSV23
  - The recommendations for routine PCV13 use among adults aged ≥65 years will be reevaluated in 2018 and revised as needed.
What will Medicare Do?

• Currently, Medicare only pays for one dose of pneumococcal vaccine for patients older than 65.
  - CMS is updating the Medicare coverage requirements to align with the updated ACIP recommendations. An initial pneumococcal vaccine may be administered to all Medicare beneficiaries who have never received a pneumococcal vaccine under Medicare Part B. A different, second pneumococcal vaccine may be administered 1 year after the first vaccine was administered (i.e., 11 full months have passed following the month in which the last pneumococcal vaccine was administered).
  - CMS 12-3-2014 implementation 2-15-2015

ACIP Meeting 6-24-25, 2015

• The recommended interval for adults receiving the 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar13, Wyeth) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax 23, Merck) from 6 months to at least 1 year apart, regardless of sequence. This increase would enable the elderly to have both vaccinations covered by Medicare or Medicaid, and may also increase immune response.
  - “We don’t [want to] commit our seniors to that financial burden.” Jonathan Temte, MD, PhD, of the School of Medicine and Public Health at the University of Wisconsin, said during the meeting.
  - A decision regarding the recommended interval for those aged 2 to 18 years with underlying health conditions was considered as well, but a vote was postponed until October.

ACIP and AAP Expanded use of PCV 13

• The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend the expanded use of PCV13 in children 6 through 18 years of age with certain conditions that place them at elevated risk of IPD.
  - A single dose of PCV 13 should be given to children 6 through 18 years of age who have immunocompromising conditions, including HIV infection and functional or anatomic asplenia, including sickle cell disease; CSF leaks; or cochlear implants and who have not previously received PCV13.
  - Recommendations for the use of PCV13 in healthy children and for pneumococcal polysaccharide vaccine (PPSV23) remain unchanged.
  - Pediatrics Vol. 134 No. 6 December 1, 2014 pp. 1230-1233
ACIP Meeting June 25, 2014

• The advisory panel voted to advise doctors that LAIV4 or FluMist nasal spray is a bit better at preventing flu in healthy young kids. The recommendation is specific to ages 2 through 8 only.
  – Some studies have found that kids within that age group are about half as likely to get the flu if they had the live attenuated vaccine instead of the killed vaccine.
  – It appears to prompt a better immune response in children who may have never been infected with flu before, but there isn’t a clear difference in adults.
  – If doctors don’t have FluMist in stock, flu shots are perfectly fine - both work. FluMist costs about $23; injectables range from about $8 to $22.
  – MedImmune/Astra Zeneca is increasing production to supply about 18 million doses for this year.

New MMWR Recommendations

• LAIV should be used for healthy children aged 2 years through 8 years who have no contraindications or precautions. However, inactivated influenza vaccine (IIV) should be used if LAIV is not immediately available. Vaccination should not be delayed to get LAIV.
  – MMWR August 15, 2014 / 63(32):691-697

Live attenuated influenza vaccine, quadrivalent (LAIV4)- FluMist

• In addition, ACIP recommends LAIV4 not be used for pregnant women, immunosuppressed persons, persons with egg allergy, and children aged 2–4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months.
  • LAIV should not be administered to persons who have taken influenza antiviral medications within the previous 48 hours. Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt.
  – MMWR August 15, 2014 / 63(32):691-697
ACIP Meeting Feb 26, 2015

- Faced with new data that conflict with older findings, the US Advisory Committee on Immunization Practices (ACIP) today voted to drop its advice that the nasal-spray influenza vaccine should be preferred over injectable vaccines for children from 2 through 8 years old.
- The committee's action was prompted by findings that the intranasal vaccine was not effective against influenza A/H1N1 in children in 2013-14 and that it—like other flu vaccines—has not worked well against A/H3N2 in children this season, the Centers for Disease Control and Prevention (CDC) said in a press release.
- The ACIP, which shapes the CDC's vaccine guidance, "recommends that children 6 months and older get annual influenza vaccine with no preference stated for either the nasal spray vaccine or the flu shot," the CDC said. The committee vote was 14-0, with one abstention.

ACIP Meeting 6-24-25, 2015

- ACIP affirmed the addition of A/Switzerland/9715293/2013 (H3N2)-like virus in place of A/Texas/30/2012 and B/Phuket/3073/2013-like (Yamagata lineage) virus in place of B/Massachusetts/2/2012 for the 2015-2016 seasonal influenza vaccine.
- The ACIP also recommended the inclusion of influenza A(H1N1)pdm09 to the algorithm determining the number of seasonal influenza vaccine doses for children aged 6 months to 8 years. Under this recommendation, children who had received two or more doses in previous seasons would only need a single dose during the current influenza season, while children with fewer previous doses would receive two.

CDC Recommended Dosage and Duration

- Treatment: (5 day duration BID)
  - Oseltamivir (Tamiflu)
    - Children <1 y/o 3mg/Kg BID
    - 1 y/o and older (wt. based)
      - <15 Kg: 30 mg BID
      - >15-23 Kg: 45mg BID
      - >23-40 Kg: 60mg BID
      - >40 Kg to adults: 75mg BID
- Prophylaxis (7 day duration QD) dosage is the same but only once a day.
  - Generally not recommended for children less than 3 mo old unless life threatening
  - Oral suspension 6 mg/ml (2011 reduction from 12 mg/ml)
  - Capsules 30, 45, and 75 mg
**CDC Recommended Dosage and Duration**

- **Treatment:** (5 day duration BID)
  - Zanamivir – Relenza (for inhalation only)
    - FDA approved and recommended only for children 7 y/o and older
      - Two 5 mg inhalations (10 mg) BID age 7 to adult
- **Prophylaxis:** (7 day duration QD)
  - Recommended or children age 5 and older
    - 2 inhalations of 5 mg (10 mg) once a day
      - FDA label suggest 10 Day duration in households and 28 days in the community
      - 5 mg blisters in a rotadisk for use in a diskhaler

**CDC Recommended Dosage and Duration**

- On December 19, 2014 the FDA approved Rapivab (peramivir) by BioCryst Pharmaceuticals to treat influenza infection in adults.
  - Peramivir is the first neuraminidase inhibitor approved for intravenous (IV) administration and is administered as a single IV dose. It is intended for patients 18 years and older who have acute uncomplicated influenza and have shown symptoms of flu for no more than two days.
  - Patients receiving a single dose of peramivir 600 mg IV had their combined influenza symptoms alleviated 21 hours sooner and became a febrile 12 hours sooner, on average, than those receiving placebo.
    - Common side effects include diarrhea. Rare but serious side effects include serious skin or hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme.
    - Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness and should be monitored for abnormal behavior. These events have been reported with neuraminidase inhibitor drugs and may or may not be drug related?

**MMWR 2014 Recommendations for Patients with Egg Allergy**

- Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine. Because relatively few data are available for use of live attenuated influenza vaccine in this setting, inactivated influenza vaccines (IIV), or trivalent recombinant influenza vaccine (RIV3) Flublok should be used. RIV3 may be used for persons aged 18 through 49 years who have no other contraindications. However, IIV (egg- or cell-culture based) may also be used, with certain additional safety measures.
  - MMWR August 15, 2014 / 63(32):691-697
Flublok by Protein Sciences Corporation

- Flublok (Influenza Vaccine) Sterile Solution for Intramuscular Injection contains purified HA proteins produced in a continuous insect cell line (expresSF+) that is derived from Sf9 cells of the fall armyworm, Spodoptera frugiperda, and grown in serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts.
- Flublok is now approved for use in persons 18 and older
- Flublok has a shorter shelf life, with an expiration period of 26 weeks from the production date, as compared to currently available inactivated influenza vaccines which carry an expiration date of June 30
  - For the 2012-2013 influenza season it is formulated to contain 135 mcg HA per 0.5 mL dose, with 45 mcg HA of each of the following 3 influenza virus strains: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), and B/Wisconsin/1/2010.

ACIP Meeting 10-25-2013

- Fluzone High-Dose was 24.2% more effective in preventing influenza in 32,000 adults aged 65 years or older than regular Fluzone in a large-scale 2-year clinical trial conducted in the US and Canada, vaccine maker Sanofi Pasteur told the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention today.
- The rate of laboratory-confirmed influenza among participants receiving Fluzone High-Dose was 1.43% compared with 1.89% among patients immunized with Fluzone. For the FDA to deem Fluzone High-Dose as superior, the vaccine needed to demonstrate a relative efficacy rate of at least 9.1%. It achieved a rate more than twice that — RRR=24.2%, ARR = 0.46%, NNT 218

Meningitis type B

- Meningitis type B is responsible for about a third of U.S. meningitis cases, but is the only strain not currently preventable by an FDA-approved vaccine.
- In the last year MenB has infected more than a dozen students at Princeton, UC-Santa Barbara, and Drexel. CDC made investigational vaccine available under CDC protocol
- MenB is a potentially deadly disease which is easily misdiagnosed and can kill within 24 hours of onset. About one in 10 of those who contract the disease will die despite appropriate treatment. Up to one in five survivors may suffer from devastating, life-long disabilities such as brain damage, hearing impairment or limb loss.
Meningitis type B Vaccine – Trumenba
by Wyeth/Pfizer

- October 29, 2014 the US Food and Drug Administration (FDA) has approved Trumenba (Wyeth Pharmaceuticals), the first vaccine against invasive meningococcal disease caused by Neisseria meningitides serogroup B to be licensed in the United States.
  - sterile suspension composed of two recombinant lipidated factor H binding protein (fHBP) variants from N. meningitidis serogroup B, one from fHBP subfamily A and one from subfamily B (A05 and B01, respectively). The proteins are individually produced in E. coli.
- The vaccine is approved for use in individuals aged 10 through 25 years. (3 dose regimen at 0,2 and 6 month schedule) 0.5 cc prefilled syringe
- The CDC/ACIP have yet to make any recommendations.

Meningitis type B Vaccine – Bexsero
by Novartis (GSK)

- Efficacy: three randomized trials conducted in the United States and Europe in about 2800 adolescents. Among participants who were given three doses of the vaccine, 82% developed antibodies against four different N meningitidis serogroup B strains representative of those that cause serogroup B meningococcal disease in the United States compared with less than 1% before vaccination.
  - The most common solicited adverse reactions were pain at the injection site (≥85%), fatigue (≥40%), headache (≥35%), muscle pain (≥30%), and chills (≥15%).
Meningitis type B Vaccine – Bexsero

- Efficacy in three studies that looked at 2,600 adolescents and young adults demonstrated 68 to 88% of individuals who received two doses of Bexsero had antibodies against three strains of meningitis B, compared with 0 to 23% of study participants before vaccination.
- The most common solicited adverse reactions observed in clinical trials of ~5,000 patients were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

Meningococcal Type B Vaccines

Potential candidates for the vaccine???

- Age 10-25 y/o
  - With complement deficiency (~100,000 patients)
  - With asplenia including patients with sickle cell disease (~90,000 patients)
  - With outbreaks as we have seen on College campuses (5,000 to 25,000 patients in the recent outbreaks)
  - Researchers who work with the pathogen
  - Stay tuned to ACIP Meeting in Feb 2015
    - Dr Paul Offit, the Vaccine Education Center at the Children’s Hospital of Philadelphia, PA from Medscape 11-19-2014

ACIP Meeting Feb 26, 2015

- The Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) voted to recommend either of the serogroup B meningococcal vaccinations to help protect individuals at increased risk. Specifically, the ACIP voted to recommend serogroup B meningococcal vaccination for persons aged 10 years and older at increased risk for meningococcal disease, including:
  - Persons with persistent complement component deficiencies
  - Persons with anatomic or functional asplenia
  - Microbiologists routinely exposed to isolates of Neisseria meningitidis
  - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak
ACIP Meeting 6-24-25, 2015

• Serogroup B meningococcal vaccines series were approved by the committee as “category B” vaccination, defined as a vaccine for use on the basis of individual clinical decision-making, not for routine use among the recommended age group.

• The recommendations stated that the serogroup B meningococcal vaccine series is for patients aged 16 to 23 years, although ACIP suggests patients aged 16 to 18 years as the preferred recipients of the vaccine.

• Committee members also recommended that serogroup B meningococcal vaccine series be added to the immunization schedule table, as opposed to being added as a footnote.

• ACIP’s recommendation must be approved by the CDC before it becomes official policy.

Existing Quadrivalent Meningitis Vaccines

• MenACWY-CRM (Menveo) – recommended for younger children at 2, 4, 6, and 12 months
  – 1st booster 3 years after primary series and additional boosters every 5 years

• MenACWY-D (Menactra) – recommended for older children at 9 and 12 months†
  – 1st booster 3 years after primary series and additional boosters every 5 years

HPV9 Vaccine – Gardasil-9 by Merck

• December 10, 2014 The FDA approved nine-valent HPV vaccine (V503) Gardasil-9 that includes coverage for 6, 11, 16, and 18—just like HPV4—but also for five additional high cancer-risk strains: 31, 33, 45, 52, and 58.

  – What might it offer vs. the current vaccines?
    • Additional 25% CIN 2 or cervical lesions
    • Additional 18% vaginal cancer cases
    • Additional 15% cervical cancer cases
    • Additional 4% of oropharyngeal cancer cases
    • The FDA has stated that “Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.”
Gardasil-9

• Gardasil-9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:
  – Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.
  – Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  – And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
    • Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS).
    • Cervical intraepithelial neoplasia (CIN) grade 1.
    • Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
    • Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.
    • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Gardasil-9

• Gardasil 9 is indicated in boys 9 through 15 years of age for the prevention of the following diseases:
  – Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
  – Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  – And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
    • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

ACIP Meeting Feb 26, 2015

• Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices (ACIP) voted to include GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) in the recommendations for use of HPV vaccines. GARDASIL 9 has been added to the routine recommendations for vaccination of 11- and 12-year-old females and males.
  – The vaccination series can be started at age nine. Vaccination is also recommended for females aged 13 to 26 and for males aged 13 to 21 who have not been vaccinated previously or have not completed the 3-dose series. GARDASIL 9 is not approved by the FDA for use in males 16 years of age and above.
  – GARDASIL 9 has been added to the CDC’s Vaccines for Children (VFC) program for both boys and girls.
ACIP Meeting Feb 26, 2015

- Same age recommendation
  - Males 9-21 years even though not FDA recommended in 16 to 21 year olds (off label)
- If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to HPV9, for protection against HPV16 or 18:
  - Any HPV product may be used to continue or complete the series for females;
  - HPV4 or HPV9 may be used to compete the series in males.
  - If HPV4 series is completed, currently not recommended to revaccinate with HPV9 but it may be done with 3 doses with benefit largely limited to female pts. (ACIP 6-2015)
  - HPV9 will continue to be available until mid 2016 until the HPV9 vaccine is FDA approved for males 16-26 y/o and then for an additional 6 months.(ACIP 6-2015)

HPV Vaccines

- We may also see a reduction in the number of doses of HPV 2, 4 and 9 Vaccines from 3 doses at 0,2 and 6 mo to 2 doses at 0 and 6 mo which is now an approved dosage regimen in Europe but only in children ages 9-13 y/o. (ACIP may act on this in Oct. 2015?)
- Should previously vaccinated patients be given the new vaccine?
  - Dr Sandra Fryhofer, Medscape 11-19-2014

Valsartan/Sacubitril - Entresto Previously LCZ696 by Novartis

- LCZ696 (Valsartan/sacubitril) is a first-in-class dual inhibitor of the angiotensin II receptor (AT II receptor) and neprilysin (NEP); a novel single fused molecule comprising molecular moieties of valsartan and NEP inhibitor prodrug AHU377 (1:1 ratio). Described as a dual-acting angiotensin receptor-neprilysin inhibitor (ARNI)
  - LCZ696 leads to increases in cyclic 3’,5’-guanosine monophosphate, as well as in levels of renin, angiotensin II, and plasma renin activity. The clinical relevance of the changes in neurohormone concentrations is not clear, although a relationship between baseline plasma renin and reduction in mean diastolic blood pressure (DBP) was observed.
Valsartan/Sacubitril – Entresto by Novartis

- Sacubitril (AHU377) is a prodrug of LBQ657, a neprilysin inhibitor
- Neprilysin is an enzyme expressed in the kidney that is responsible for the degradation of several endogenous substances, including C-type natriuretic peptide, atrial natriuretic peptide, B-type natriuretic peptide (BNP), endothelin-1, kinin peptides, opioid peptides, substance P, amyloid beta protein, gastrin, and angiotensin I.
- Natriuretic peptides (type A and B) promote vasodilation and natriuresis, inhibit abnormal growth of the ventricles, suppress the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, inhibit the release and action of vasopressin, and augment the parasympathetic nervous system.

Valsartan/Sacubitril - Entresto

- FDA approved 7-8-2015 indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.
- It is usually administered in conjunction with other heart failure therapies including an evidence based beta blocker and when appropriate an aldosterone antagonist, and replaces the ACE inhibitor or other ARB.
  - Film-coated tablets (sacubitril/valsartan): 24/26 mg; 49/51 mg; 97/103 mg for BID dosing
  - Cost: $12.50 per day or $375.00/mo (WAC)

Valsartan/Sacubitril - Entresto

- If switching from an ACE inhibitor to (sacubitril/valsartan) allow a washout period of 36 hours between administration of the two drugs
- The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice-daily.
- Double the dose of after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.
- Reduce the starting dose to 24/26 mg (sacubitril/valsartan) twice-daily for:
  - patients not currently taking an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents
  - patients with severe renal impairment
  - patients with moderate hepatic impairment
Valsartan/Sacubitril - Entresto

- Mean half-life of each compound was 8.9 to 16.6 hours for valsartan, 1.1 to 3.6 hours for sacubitril, and 9.9 to 11.1 hours for LBQ657.
- Bioavailability of valsartan following oral administration of LCZ696 400 mg is similar to valsartan 320 mg delivered by a single-agent tablet.

Valsartan/Sacubitril - Entresto

- Box Warning: Fetal toxicity - d/c with pregnancy
- Contraindications:
  - History of angioedema related to previous ACE inhibitor or ARB therapy.
  - Concomitant use with ACE inhibitors.
  - Concomitant use with aliskiren in patients with diabetes.
- Warnings/Precautions:
  - Observe for signs and symptoms of angioedema and hypotension.
  - Monitor renal function and potassium in susceptible patients.

Valsartan/Sacubitril - Entresto

- In the double-blind period of PARADIGM-HF, 0.5% of patients treated with (valsartan/sacubitril) and 0.2% of patients treated with enalapril had angioedema.
  - associated with a higher rate of angioedema in Black than in non-Black patients
- In the double-blind period of PARADIGM-HF, 18% of patients treated with (valsartan/sacubitril) and 12% of patients treated with enalapril reported hypotension as an adverse event
Valsartan/Sacubitril - Entresto

- In the double-blind period of PARADIGM-HF, 5% of patients in both the (valsartan/sacubitril) and enalapril groups reported renal failure as an adverse event.
- In the double-blind period of PARADIGM-HF, 12% of patients treated with (valsartan/sacubitril) and 14% of patients treated with enalapril reported hyperkalemia as an adverse event.
- Cough was reported in 9% of (valsartan/sacubitril) and 13% of enalapril treated patients.

PARADIGM-HF Trial

- Compared the angiotensin-neprilysin inhibitor LCZ696 (200 mg BID) with the angiotensin converting enzyme inhibitor enalapril (10 mg BID) in 8399 patients with heart failure and reduced ejection fraction (<35%, NYHA Class II-IV) able to tolerate ACEI or ARB and also on stable doses of beta blocker/mineralocorticoid antagonist unless not tolerated, in a double-blind trial. (NOTE only 5% of pts were black and <10% from North America)
- 200 mg of LCZ696 delivers the equivalent of 160 mg of valsartan (evidence-based dose of valsartan in HF and post MI)

- DOI: 10.1161/CIRCULATIONAHA.114.013748

PARADIGM-HF Trial

- After a mean of 27 months follow up the LCZ696-treated patients as compared to the enalapril treated patients required:
  - Less intensification of medical treatment for heart failure (520 versus 604; hazard ratio, 0.84; 95% confidence interval, 0.74–0.94; P=0.003)
  - Fewer emergency department visit for worsening heart failure (hazard ratio, 0.66; 95% confidence interval, 0.52–0.85; P=0.001).
  - Fewer hospitalizations for worsening heart failure (851 versus 1079; 23% reduction P=0.001)
  - Less hospitalisation for any cause; annualized rates of 30.3% and 26.3% respectively. These differences reflected a 12.6% RRR; ARR 4.0%; NNT 25 with LCZ696 instead of enalapril (hazard ratio, 0.87; 95% CI, 0.82–0.93; P=0.001).
  - Less likely to require intensive care (768 versus 879; 18% reduction, P=0.005).
  - All cause mortality: 835 patients in the enalapril group and 711 in the LCZ696 group, corresponding to annualized rates of 7.5% and 6.0%, respectively. HR 0.84 (95% CI 0.76–0.93 p=0.0009); RRR 16%; ARR 1.5%; NNT 67

- DOI: 10.1161/CIRCULATIONAHA.114.013748
### PARADIGM-HF: cause/mode of death

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<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>LCZ696</th>
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<tbody>
<tr>
<td>All causes</td>
<td>635</td>
<td>711</td>
</tr>
<tr>
<td>CV causes</td>
<td>683</td>
<td>558</td>
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<tr>
<td>Sudden</td>
<td>311</td>
<td>250</td>
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<td>WHF</td>
<td>184</td>
<td>147</td>
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Number

<table>
<thead>
<tr>
<th>HR</th>
<th>p =</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.84</td>
<td>&lt; 0.001</td>
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<tr>
<td>0.80</td>
<td>0.008</td>
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<td>0.80</td>
<td>0.008</td>
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</tr>
<tr>
<td>0.79</td>
<td>0.04</td>
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</tr>
</tbody>
</table>

### PARADIGM-HF: Percentage of patients with at least 5 points deterioration in KCCQ (Kansas City Cardiomyopathy Questionnaire) scores at month 8

- **Physical limitation**
- **Symptom stability**
- **Symptom burden**
- **Total symptom score**
- **Self efficacy**
- **Quality of life**
- **Social limitation**
- **Overall summary score**
- **Clinical summary score**

Clinical summary score based on the physical limitation and total symptom score domains. Death imputed as zero. The analysis included all patients with at least one KCCQ data point.

### Valsartan/Sacubitril – Entresto in PARADIGM - HF

- Mean daily doses achieved were LCZ696 375 mg and enalapril 18.9 mg; 76% and 75% of LCZ696 and enalapril patients, respectively, maintained the target dose through the end of the study.
- Incidence of symptomatic hypotension was 14% with LCZ696 and 9.2% with enalapril (P < 0.001); number needed to harm (NNH) with LCZ696 was 20.8.
- Incidence of serum creatinine elevated to at least 2.5 mg/dL was 3.3% with LCZ696 and 4.5% with enalapril (P = 0.007); NNH with enalapril was 83.3.
- Incidence of serum potassium greater than 6 mmol/L was 4.3% with LCZ696 and 5.6% with enalapril (P = 0.007); NNH with enalapril was 76.9.
- Incidence of cough was 11.3% with LCZ696 and 14.3% with enalapril (P < 0.001); NNH with enalapril was 33.3.
Angioedema?

- Omapatrilat, the most extensively studied vasopeptidase inhibitor, has shown greater lowering of blood pressure and vasculoprotective effects than have other therapeutic classes, including ACE inhibitors and calcium-channel blockers. However, omapatrilat treatment was associated with angio-oedema, probably due to concomitant inhibition of three enzymes (ACE, aminopeptidase P, and neprilysin) that participate in the breakdown of bradykinin, the putative mediator of angio-oedema induced by ACE inhibitors.

Ivabradine – Corlanor by Amgen

- April 15, 2015 The FDA approved ivabradine (Corlanor, Amgen) for reducing the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or less, who are in sinus rhythm with resting heart rate of 70 bpm or more, and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use. The drug acts by blocking the hyperpolarization-activated cyclic nucleotide–gated channel responsible for the cardiac pacemaker.
Ivabradine – Corlanor

• FDA granted Ivabradine expedited approval and did not hold an FDA Cardiovascular Advisory Committee Meeting.
• The drug has been available for several years in Europe, where it is sold by Servier under the brand names of Corlentor and Procoralan.

Ivabradine – Corlanor

• Ivabradine causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in subjects with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. Analysis of heart rate reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily.
• Ivabradine slows the rate of the heart by inhibiting the so-called “funny” current within the heart’s natural pacemaker, the sinoatrial node.
• Ivabradine does not have negative inotropic effects.

Ivabradine – Corlanor

Metabolism and Excretion
• The pharmacokinetics of ivabradine are linear over an oral dose range of 0.5 mg to 24 mg. Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation.
  – The major metabolite is the N-desmethyld derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethyld derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours.
  – ~4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine.
Ivabradine – Corlanor

Drug Interactions:
• Ivabradine is primarily metabolized by CYP3A4. Concomitant use of CYP3A4 inhibitors increases ivabradine plasma concentrations, and use of CYP3A4 inducers decreases them. Increased plasma concentrations may exacerbate bradycardia and conduction disturbances.
  – Strong CYP3A4 inhibitors are contraindicated (azole antifungals, macrolides, protease inhibitors and nefazodone)
  – Moderate 3A4 inhibitors should be avoided (diltiazem, verapamil and grapefruit juice)
  – 3A4 inducers should also be avoided (St John’s wort, rifampin, phenytoin and barbiturates)

Ivabradine – Corlanor

Contraindications:
• Acute decompensated heart failure
• Blood pressure less than 90/50 mmHg
• Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
• Resting heart rate less than 60 bpm prior to treatment
• Severe hepatic impairment
• Pacemaker dependence (heart rate maintained exclusively by the pacemaker)

Ivabradine can cause harm to fetuses and that women should not become pregnant while taking it.

Ivabradine – Corlanor

SHIFT Trial
• The Systolic Heart failure treatment with the If Inhibitor Ivabradine Trial (SHIFT) was a randomized, double-blind trial comparing Ivabradine and placebo in 6558 adult patients with stable NYHA class II to IV (primarily II and III) heart failure, left ventricular ejection fraction ≤ 35%, and resting heart rate ≥ 70 bpm. Patients had to have been clinically stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics, with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry.
Ivabradine – Corlanor

- All subjects were initiated on ivabradine 5 mg (or matching placebo) twice daily and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain the resting heart rate between 50 and 60 bpm, as tolerated.

- The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.
  - 89% of patients were taking beta-blockers, with 26% on guideline-defined target daily doses. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension (45% of patients not at target), fatigue (32%), dyspnea (14%), dizziness (12%), history of cardiac decompensation (9%), and bradycardia (6%).
  - 91% of patients were taking either an ACEI or ARB
  - 83% of patients were taking diuretics and 60% aldosterone antagonists

### Endpoint N=3241

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N=3241</th>
<th>%</th>
<th>N=3264</th>
<th>%</th>
<th>HR 95% CI</th>
<th>P-value</th>
<th>ARR/NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite of time to first hospitalization for HF and CV death</td>
<td>793</td>
<td>24.5%</td>
<td>937</td>
<td>28.7%</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
<td>4.2%/24</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>505</td>
<td>15.6%</td>
<td>660</td>
<td>20.2%</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
<td>4.6%/24</td>
</tr>
<tr>
<td>CV death as first event</td>
<td>288</td>
<td>8.9%</td>
<td>277</td>
<td>8.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean follow-up 23 months. Ivabradine’s benefit on the primary endpoint in SHIFT appeared to decrease as the dose of beta-blockers increased, with little if any benefit demonstrated in patients taking guideline-defined target doses of beta-blockers.

### Adverse Effects from SHIFT Trial:

<table>
<thead>
<tr>
<th>Effect</th>
<th>N=3241</th>
<th>%</th>
<th>N=3264</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>2.2%</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>8.9%</td>
<td>7.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>8.3%</td>
<td>6.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphenes, visual brightness*</td>
<td>2.8%</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency).

Postmarketing reports: syncope, hypotension, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment.
Ivabradine – Corlanor

BEAUTIFUL Trial:
- A randomized, double-blind, placebo-controlled trial in 10,917 adult patients with coronary artery disease, impaired left ventricular systolic function (EF < 40%) and resting heart rate ≥ 60 bpm. Patients had stable symptoms of heart failure and/or angina for at least 3 months, and were receiving conventional cardiovascular medications at stable doses for at least 1 month. Beta-blocker therapy was not required, nor was there a protocol mandate to achieve any specific dosing targets for patients who were taking beta-blockers. Patients were randomized 1:1 to ivabradine or placebo at an initial dose of 5 mg BID with the dose increased to 7.5 mg BID depending on resting heart rate and tolerability. The primary endpoint was the composite of time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure. Most patients were NYHA class II (61.4%) or class III (23.2%) - none were class IV. Through a median follow-up of 19 months, ivabradine did not significantly affect the primary composite endpoint (HR 1.00, 95% CI = 0.91, 1.10).

Ivabradine – Corlanor

SIGNIFY Trial:
- A randomized, double-blind trial administering Ivabradine or placebo to 19,102 adult patients with stable coronary artery disease but without clinically evident heart failure (NYHA class I). Beta blocker therapy was not required. Ivabradine was initiated at a dose of 7.5 mg BID and the dose could be increased to as high as 10 mg BID or down-titrated to 5.0 mg BID to achieve a target heart rate of 55 to 60 bpm. The primary endpoint was a composite of the first occurrence of either cardiovascular death or myocardial infarction. Through a median follow-up of 24.1 months, Ivabradine did not significantly affect the primary composite endpoint (HR 1.08, 95% CI = 0.96, 1.20).

Ivabradine – Corlanor

DOSAGE AND ADMINISTRATION:
- The recommended starting dose of Ivabradine is 5 mg twice daily with meals. Assess patient after two weeks and adjust dose to achieve a resting heart rate between 50 and 60 beats per minute (bpm) as shown in Table 1. Thereafter, adjust dose as needed based on resting heart rate and tolerability.
  - The maximum dose is 7.5 mg twice daily.
  - In patients with a history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg twice daily before increasing the dose based on heart rate.
Ivabradine – Corlanor

Dosage Adjustment Table

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 BPM</td>
<td>Increase dose by 2.5 mg BID up to a maximum dose of 7.5 mg BID</td>
</tr>
<tr>
<td>50-60 BPM</td>
<td>Maintain the dose</td>
</tr>
<tr>
<td>&lt; 50 BPM</td>
<td>Decrease the dose by 2.5 mg BID, if current dose is 2.5 mg BID discontinue therapy</td>
</tr>
</tbody>
</table>

Available as a scored 5 mg tablet and 7.5 mg unscored tablet
Cost is reported to be ~$375.00 per month wholesale

Ivabradine – Corlanor

• Role in therapy?
• Appears to reduce hospitalization for worsening heart failure but not mortality?
• Probably limited to those patients who have reduced EF HF and do not tolerate a beta blocker or are not able to reach the recommended dosage levels of one of the three recommended beta blocking agents and still have a resting heart rate of >/= 70 BPM

Standards of Medical Care in Diabetes—2015: Summary of Revisions

• The physical activity section was revised to reflect evidence that all individuals, including those with diabetes, should be encouraged to limit the amount of time they spend being sedentary by breaking up extended amounts of time (>90 min) spent sitting.
• Standards were updated to make clear that e-cigarettes are not supported as an alternative to smoking or to facilitate smoking cessation.
• Immunization recommendations were revised to reflect recent Centers for Disease Control and Prevention guidelines regarding PCV13 and PPSV23 vaccinations in older adults.
— Diabetes Care January 2015 vol. 38 no. Supplement 1 S4
Prolonged Sitting and Outcomes

• In this meta-analysis of 47 studies, sedentary lifestyle was linked to a hazard ratio (HR) for: all-cause mortality of 1.240 (95% CI, 1.090 - 1.410); an increase in cardiovascular disease mortality (HR, 1.179; 95% CI, 1.106 - 1.257); cardiovascular disease incidence (HR, 1.143; 95% CI, 1.002 - 1.729); cancer mortality (HR, 1.173; 95% CI, 1.108 - 1.242); cancer incidence (HR, 1.130; 95% CI, 1.053 - 1.213); and type 2 diabetes incidence (HR, 1.910; 95% CI, 1.642 - 2.222).

Prolonged Sitting and Outcomes

• The increased risk for all-cause mortality was most pronounced among people with lower levels of physical activity. The relative risk for sedentary behavior for all-cause mortality among those with high levels of physical activity was 30% lower than for those with low levels of physical activity. The hazard ratio for those who exercised frequently was 1.16 (95% CI, 0.84 - 1.59) compared with a HR of 1.46 (95% CI, 1.22 - 1.75) for those who did not.
• An editorial that accompanied the recent meta-analysis said research about sedentary behavior still has not led to specific guidelines about how to best modify sitting practices.

Standards of Medical Care in Diabetes—2015: Summary of Revisions

• The ADA now recommends a pre-meal blood glucose target of 80–130 mg/dL, rather than 70–130 mg/dL, to better reflect new data comparing actual average glucose levels with A1C targets.
• The type 2 diabetes management algorithm was updated to reflect all of the currently available therapies for diabetes management.
• The goal for diastolic blood pressure was changed from 80 mmHg to 90 mmHg for most people with diabetes and hypertension to better reflect evidence from randomized clinical trials. Lower diastolic targets may still be appropriate for certain individuals.
  – Diabetes Care January 2015 vol. 38 no. Supplement 1 S4
Standards of Medical Care in Diabetes—2015: Summary of Revisions

- Recommendations for statin treatment and lipid monitoring were revised after consideration of 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol. Treatment initiation (and initial statin dose) is now driven primarily by risk status rather than LDL cholesterol level.
- To reflect new evidence regarding the risks and benefits of tight glycemic control in children and adolescents with diabetes, the Standards now recommend a target A1C of <7.5% for all pediatric age groups; however, individualization is still encouraged.
- A new section was added to the Standards to provide recommendations related to pregnancy and diabetes, including recommendations regarding preconception counseling, medications, blood glucose targets, and monitoring.

Prevention or Delay of Type 2 Diabetes

Recommendations

- Patients with impaired glucose tolerance (IGT) A, impaired fasting glucose (IFG) E, or an A1C 5.7–6.4% E should be referred to an intensive diet and physical activity behavioral counseling program targeting loss of 7% of body weight and increasing moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.
- Follow-up counseling may be important for success. B
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. B
- Metformin therapy for prevention of type 2 diabetes may be considered in
  - those with IGT A, IFG E, or an A1C 5.7–6.4% E, especially for those with BMI >35 kg/m2, aged >60 years, and women with prior gestational diabetes mellitus (GDM). A

– Diabetes Care January 2015 vol. 38 no. Supplement 1 S4

– Diabetes Care 2015;38(Suppl. 1):S31–S32
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
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<th>CVD</th>
<th>Mortality</th>
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<tr>
<td>DCCT / EDIC*</td>
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<tr>
<td>VADT</td>
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</tbody>
</table>

Kendall DM, Bergenstal RM. © International Diabetes Center 2009


VADT Update

- After the conclusion of the 5.6 year VADT Trial, we followed participants, using central databases to identify procedures, hospitalizations, and deaths (complete cohort, with follow-up data for 92.4% of the 1791 veteran participants).
- The difference in glycated hemoglobin levels between the intensive-therapy group and the standard-therapy group averaged 1.5 percentage points during the trial (median level, 6.9% vs. 8.4%) and declined to 0.2 to 0.3 percentage points by 3 years after the trial ended.
- Primary outcome: time to the first major cardiovascular event (heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or cardiovascular-related death).
  

VADT Update

- Over a median follow-up of 9.8 years, the intensive-therapy group had a significantly lower risk of the primary outcome than did the standard-therapy group (hazard ratio, 0.83; 95% confidence interval [CI], 0.70 to 0.99; P=0.04), with an absolute reduction in risk of 8.6 major cardiovascular events per 1000 person-years, but did not have reduced cardiovascular mortality (hazard ratio, 0.88; 95% CI, 0.64 to 1.20; P=0.42). No reduction in total mortality was evident (hazard ratio in the intensive-therapy group, 1.05; 95% CI, 0.89 to 1.25; P=0.54; median follow-up, 11.8 years).
  
ADA Guidelines

- “Growing evidence suggests that there is an association between increase in sleep-time blood pressure and incidence of CVD events. A recent RCT of 448 participants with type 2 diabetes and hypertension demonstrated reduced cardiovascular events and mortality with median follow-up of 5.4 years if at least one antihypertensive medication was given at bedtime.”
- Results: major events (cardiovascular death, myocardial infarction, and stroke) were reduced by 75%; \( P = 0.003 \) NNT 15
- “Administer one or more antihypertensive medications at bedtime. (A)
— Diabetes Care 2012;35: S11-S63

ACE Inhibitors vs. ARB’s on Outcomes in Patients with Diabetes

- Twenty-three trials compared ACEIs with placebo or active drugs (32 827 patients) and 13 compared ARBs with no therapy (controls) (23 867 patients). When compared with controls (placebo/active treatment), ACEIs significantly reduced the risk of all-cause mortality by 13% (RR, 0.87; 95% CI, 0.78-0.98), CV deaths by 17% (0.83; 0.70-0.99), and major CV events by 14% (0.86; 0.77-0.95), including myocardial infarction by 21% (0.79; 0.65-0.95) and heart failure by 19% (0.81; 0.71-0.93).

ACE Inhibitors vs. ARB’s on Outcomes in Patients with Diabetes

- Treatment with ARBs did not significantly affect all-cause mortality (RR, 0.94; 95% CI, 0.82-1.08), CV death rate (1.21; 0.81-1.80), and major CV events (0.24; 0.85-1.01) with the exception of heart failure (0.76; 0.59-0.92).
- Both ACEIs and ARBs were not associated with a decrease in the risk for stroke in patients with DM.
- Meta-regression analysis showed that the ACEI treatment effect on all-cause mortality and CV death did not vary significantly with the starting baseline blood pressure and proteinuria of the trial participants and the type of ACEI and DM.
- Conclusion: ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population.
Empagliflozin – Jardiance by Boehringer Ingelheim and Lilly

- August 1, 2014 FDA approved sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- The FDA is requiring four post marketing studies:
  - Completion of an ongoing 7,000 pt. cardiovascular outcomes trial (EMPA-REG Outcome Trial)
  - A pediatric pharmacokinetic/pharmacodynamic study.
  - A pediatric safety and efficacy study. As part of the safety and efficacy study, the effect on bone health and development will be evaluated.
  - A nonclinical (animal) juvenile toxicity study with a particular focus on renal development, bone development, and growth.

Empagliflozin – Jardiance

- Aug. 20, 2015 Boehringer Ingelheim and Eli Lilly and Company announced positive top-line results from EMPA-REG OUTCOME®. This is a long-term clinical trial investigating cardiovascular (CV) outcomes for empagliflozin in more than 7,000 adults with type 2 diabetes (T2D) at high risk for CV events. EMPA-REG OUTCOME met its primary endpoint and demonstrated superiority of empagliflozin, when added to standard of care, in CV risk reduction. The primary endpoint was defined as time to first occurrence of either CV death, or non-fatal myocardial infarction or non-fatal stroke.
Empagliflozin – Jardiance

- EMPA-REG OUTCOME was a multicenter, randomized, double-blind, placebo-controlled trial in more than 7,000 individuals from 42 countries for a median duration of 3.1 years. The study evaluated the effect of empagliflozin (10mg or 25mg once daily) added to standard of care compared with placebo added to standard of care on CV events in adults with T2D at high risk of CV events and with less than optimized blood glucose control. The study was designed to first test for non-inferiority and then for superiority.
  - Standard of care was comprised of glucose lowering agents and cardiovascular drugs (including antihypertensive and lipid lowering agents).

EMPA-REG OUTCOME Trial

- Detailed study results will be presented on September 17 at the 51st European Association for the Study of Diabetes Annual Meeting in Stockholm, Sweden.
  - NEJM on-line 9-17-2015
- The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group.

EMPA-REG OUTCOME Trial

- The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority).
  - ARR = 1.6%, NNT 63
  - No significant differences in rates of MI or CVA
  - No significant difference with 10 vs. 25 mg doses.
  - Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46

- NEJM on-line 9-17-2015
EMPA-REG OUTCOME Trial

- Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction)
- Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).
- Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events.
  – NEJM on-line 9-17-2015

EMPA-REG OUTCOME Trial

- Unanswered questions:
  – What might explain the CV benefit seen in this short term trial when it has not been seen previously and both groups of patients were treated with evidence-based therapeutics to reduce CV risk (IE statins, RAST blockers, BB and aspirin)?
  - Hypothesis? Dr. Gerstein, McMaster University. speculates that the strikingly early separation of the event curves suggests that the effect of the study drug was likely not mediated through glucose or blood pressure. Instead, he felt that the osmotic diuretic aspect to this agent may have resulted in a better hemodynamic status, perhaps treating early heart failure or preventing heart failure.
  – Yale CME 2015 EASD Newsletter - Issue three

EMPA-REG OUTCOME Trial

- The proportions of patients with confirmed hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events consistent with volume depletion were similar in the two study groups. Urosepsis was reported in 0.4% of patients in the empagliflozin group and 0.1% of those in the placebo group, but there was no imbalance in overall rates of urinary tract infection, complicated urinary tract infection, or pyelonephritis.
- About 25% of empagliflozin treated patients discontinued therapy during the trial.
  – NEJM on-line 9-17-2015
Empagliflozin – Jardiance

• In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg once daily.

• In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on day 1 and 135 mL on day 5 of empagliflozin 25 mg once daily treatment.

Empagliflozin– Jardiance

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Empagliflozin</th>
<th>N</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dl)</th>
<th>Weight (Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>10mg</td>
<td>224</td>
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<td>-2.5</td>
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<td>-17.9</td>
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</table>

Trials are for 24 weeks with one exception and all values are placebo subtracted and mean baseline A1C was 8%.

Empagliflozin– Jardiance

<table>
<thead>
<tr>
<th>Adverse Effects from Controlled Trials</th>
<th>Placebo N=995</th>
<th>Empagliflozin 10 mg N=999</th>
<th>Empagliflozin 25 mg N=977</th>
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<tr>
<td>Urinary tract infection</td>
<td>7.6%</td>
<td>9.3%</td>
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<tr>
<td>Female genital mycotic infections (N=420-481)</td>
<td>1.5%</td>
<td>5.4%</td>
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<td>Upper respiratory tract infections</td>
<td>3.8%</td>
<td>3.1%</td>
<td>4.0%</td>
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<tr>
<td>Increased urination</td>
<td>1.0%</td>
<td>3.4%</td>
<td>3.2%</td>
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<td>Dyslipidemia</td>
<td>3.4%</td>
<td>3.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.2%</td>
<td>2.4%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Male genital mycotic infections (N=514-557)</td>
<td>0.4%</td>
<td>3.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.4%</td>
<td>2.3%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
Empagliflozin – Jardiance

Renal Effects:

• Empagliflozin may increase serum creatinine and decrease eGFR (the risk of impaired renal function is increased in elderly patients and patients with moderate renal impairment).
• The glucose lowering benefit of 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Empagliflozin – Jardiance

• The recommended dose is 10 mg once daily in the morning, taken with or without food. In patients tolerating empagliflozin, the dose may be increased to 25 mg.
  – In patients with volume depletion, correcting this condition prior to initiation of empagliflozin is recommended.
  – Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m² and should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m².
  – Cost ~ $354.50/ 30 tabs both strengths GoodRx.com

Empagliflozin/Linagliptin-Glyxambi (Boehringer Ingelheim/Eli Lilly)

• 2-2-2015 the FDA approved the empagliflozin/linagliptin combination Glyxambi (Boehringer Ingelheim/Eli Lilly) as adjunctive treatment to diet and exercise for adults with type 2 diabetes.
• The once-daily tablet is the first in the US to combine a sodium glucose cotransporter 2 (SGLT2) inhibitor (empagliflozin) with a dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin). The tablets contain 10 or 25 mg of empagliflozin and 5 mg of linagliptin.
  – Cost: $492.90/30 GoodRx.com
Empagliflozin/Linagliptin-Glyxambi

- The Phase III trial enrolled 686 adults with type 2 diabetes who had baseline hemoglobin A1c (HbA1c) levels between 7.0% and 10.5% despite taking high-dose metformin (mean daily dose 1889 mg).
  - Results at 24 weeks, those receiving empagliflozin/linagliptin achieved mean HbA1c levels of 6.9% with the 10/5 mg dose and 6.7% with the 25/5 mg dose, compared with 7.3% and 7.4% with empagliflozin 10 and 25 mg, respectively, and 7.3% with linagliptin 5 mg. (difference of 0.4 to 0.7%)
  - Diabetes Care 1-12-2015 on-line

Empagliflozin/Metformin – Synjardy by BI/Lilly

- FDA approved 8-27-2015
- Dosed twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.
- Available as:
  - 5 mg empagliflozin/500 mg metformin hydrochloride
  - 5 mg empagliflozin/1000 mg metformin hydrochloride
  - 12.5 mg empagliflozin/500 mg metformin hydrochloride
  - 12.5 mg empagliflozin/1000 mg metformin hydrochloride

Empagliflozin/Metformin – Synjardy

- In a 24 week trial in 637 patients on metformin at least 1500 mg/day randomized to empagliflozin 10 or 25 mg/day vs. placebo, the reductions in A1c placebo subtracted were -0.6 with both doses with a mean baseline A1c of 7.9% as well as a reduction in FPG of 26 and 29 mg/dl. The weight loss was -2.0 Kg and -2.5 Kg with the two doses of empagliflozin vs. metformin plus placebo. Systolic BP was also reduced by -4.1 mmHg and -4.8 mmHg vs. metformin plus placebo.
SGLT-2 Inhibitors and Bone Fractures?

- In a study in people with moderate renal impairment, 9-4% (8/85) of patients treated with 10 mg and 6-0% (5/83) of patients treated with 5 mg dapagliflozin had bone fractures over 104 weeks of follow-up, whereas no fractures were reported in patients receiving placebo.
- A pooled analysis of 8 trials with canagliflozin with a mean duration of 68 weeks suggested an ~30% increase in fractures
  – The Lancet Diabetes and Endocrinology 2015; 3:8-10

SGLT-2 Inhibitors and Bone Fractures?

- It has also been reported that 300 mg of canagliflozin reduced bone mineral density in both the total hip and lumbar spine
- SGLT-2 inhibitors increase serum phosphate levels and may also increase serum PTH levels (7-9%) but up to 50% in a significant number of patients. 1-25 dihydroxyvitamin D levels are also decreased by about 12% in patients on canagliflozin. The mechanism is not well established but it does require further study.
  – The Lancet Diabetes and Endocrinology 2015; 3:8-10

FDA Safety Announcement

- [5-15-2015] The FDA is warning that the SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.
- Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness.
FDA Safety Announcement

• From March 2013 (approval of the first drug in the class) through June 6, 2014, and identified 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis were reported.
  – The median time to onset of symptoms following initiation of drug therapy was 2 weeks (range 1 to 175 days). DKA case presentations were atypical in that glucose levels were only mildly elevated at less than 200 mg/dL in some reports.
  – The FDA is continuing to investigate this safety issue.

New Pen Device for Bydureon (once weekly exenatide)

• March 3, 2014: U.S. FDA Approves Bydureon® Pen (exenatide extended-release for injectable suspension) for Once-Weekly Treatment of Adults with Type 2 Diabetes.
• Each pen contains the recommended weekly dose of 2 mg and replaces the weekly trays which required patients to mix and draw up the dose (the trays will continue to be available as well as the pens)
  – Now from Astra Zeneca

Dulaglutide – Trulicity by Lilly

• 9/18/2014 the FDA approved Trulicity (dulaglutide), a once-weekly subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonist injection to improve glycemic control (blood sugar levels), along with diet and exercise, in adults with type 2 diabetes.
• The elimination half-life is ~ 5 days
Dulaglutide – Trulicity

- Available in 0.75-mg and 1.5-mg single-dose pens which do not require mixing, measuring or needle attachment and can be administered any time of day.
  - Insert states that for added comfort patients may want to take the pen out of the refrigerator for ~30 min prior to administration (DO NOT microwave or run under hot water)
- Box of 4 pens (either dose) ~$510.00 retail (GoodRx.com)

Dulaglutide – Trulicity

- The AWARD-6 study, once-weekly dulaglutide 1.5 mg achieved the primary endpoint of non-inferiority to once-daily liraglutide 1.8 mg, as measured by the reduction of hemoglobin A1c (HbA1c) from baseline at 26 weeks in 599 patients. (to date the only GLP-1 agonist to demonstrate non-inferiority to liraglutide to date)

Dulaglutide – Trulicity

- At the primary endpoint of 26 weeks, once-weekly dulaglutide 1.5 mg and once-daily liraglutide 1.8 mg significantly reduced HbA1c levels from baseline (~1.42 percent and -1.36 percent, respectively), with dulaglutide demonstrating non-inferiority compared to liraglutide. A similar majority of patients in both treatment groups (68 percent) reached the American Diabetes Association’s recommended HbA1c target of less than 7 percent. Patients treated with once-weekly dulaglutide and once-daily liraglutide showed significant weight reductions from baseline (~2.9 kg, -3.6 kg, respectively). This weight reduction was statistically greater in the liraglutide treatment arm.
  - The Lancet, Early Online Publication, 11 July 2014
  doi:10.1016/S0140-6736(14)60976-4
Dulaglutide – Trulicity

- FDA Box Warning: (Same as for all members of the GLP-1 class of medications)
  - “Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.”
  - Symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).
- Additional Warnings and Precautions;
  - In clinical trials, acute pancreatitis has been reported in association with dulaglutide.
  - Consider other antidiabetic therapies in patients with a history of pancreatitis.

Dulaglutide – Trulicity

The FDA is requiring the following post-marketing studies for Trulicity:
- A clinical trial to evaluate dosing, efficacy, and safety in pediatric patients;
- A study to assess potential effects on sexual maturation, reproduction, and CNS development and function in immature rats;
- A medullary thyroid carcinoma (MTC) case registry of at least 15 years duration to identify any increase in MTC incidence related to Trulicity;
- A clinical trial comparing Trulicity with insulin glargine on glycemic control in patients with Type 2 diabetes and moderate or severe renal impairment; and
- A cardiovascular outcomes trial to evaluate the cardiovascular risk of Trulicity in patients with high baseline risk of cardiovascular disease.

ELIXA – a cardiovascular safety outcomes trial of lixisenatide

- Lixisenatide is NOT FDA approved, investigational!
- March 2015, Sanofi announced top-line results of the ELIXA outcome study, a Phase IIIb cardiovascular safety outcomes trial of lixisenatide (Lyxumia®) compared to placebo in 6,000 a high-risk (post ACS) population of adults with Type 2 diabetes for the evaluation of cardiovascular safety.
  - First CV safety trial for any of the GLP-1 Agonists to report out.
- The results from the study showed that lixisenatide was non-inferior, although not superior, to placebo for cardiovascular safety, and establish that there is no additional cardiovascular risk, in a high-risk patient, associated with treatment with lixisenatide, helping to support the existing consensus around the therapeutic benefits of lixisenatide.
  - Results to be presented at ADA in Boston on June 9, 2015
Under Late Stage Development

- LixiLan by Sanofi (combination of insulin glargine/Lantus plus lixisenatide/Lyxumia a once a day GLP-1 agonist)
  - Phase 3 data in 1170 pts over 3 months found lower A1c with the combo vs. either agent alone, a 4th quarter US FDA filing is expected.
- Xultophy (IDegLira) by Novo/Nordisk (combination of insulin degludec/Tresiba plus liraglutide/Victoza)
  - Recent data from the DUAL-V Phase 3b trial in 557 pts presented at EASD 9/2015 found that Xultophy produced greater A1c reductions (-1.8 vs -1.1%), greater weight loss (3.2 Kg difference), 57% less hypoglycemia and greater patient satisfaction than insulin glargine.
  - (Approved by the European Comm 9-2014)

AFREZZA®
(insulin human [rDNA origin]) Technosphere Insulin (TI) Inhalation Powder

- Users self-administer TI by oral inhalation using the Gen2 inhaler by MannKind, Corp/ Sanofi-Aventis
- The to-be-marketed cartridges contain either 0.35 mg (10 U) or 0.7 mg (20 U) of insulin. The 10 U cartridge approximates 4 units of sc injected insulin (and is labeled as “4 units”) and the 20 U cartridge approximates 8 units of sc injected insulin (and is labeled as “8 units”).
- The Gen2 inhaler is small, discrete, easy to use, and is discarded and replaced every 15 days.
patients should have repeat spirometry (FEV1) after 6 months and annually thereafter. Patients who demonstrate a 20% reduction or more in FEV1 over baseline should be considered for discontinuation of the drug. Patients with asthma 29% had acute bronchospasm when using the inhaler. NOT recommended for patients who smoke or have stopped smoking in the last 6 months.

Once loaded and the cover closed KEEP INHALER LEVEL! Cartridges left over in an opened strip must be used within 3 days. No cleaning is required. As a breath-powered inhaler, it relies on a person's inhalation effort to reproducibly deliver TI to the pulmonary tract. Replaced inhaler every 15 days.
There are two strengths of AFREZZA® cartridges:

- One blue cartridge approximates 4 units of injected insulin.
- One green cartridge approximates 8 units of injected insulin.

AFREZZA®
(insulin human [rDNA origin]) Inhalation Powder

Not In Use: Refrigerated Storage
Sealed Foil Packages
Store unopened drug in a refrigerator 36 – 46°F (2 – 8°C).

In Use: Room Temperature Storage
Opened Foil Packages
Once a strip package has been opened.

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<thead>
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<th>Unopened</th>
<th>Must be used within 10 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strips</td>
<td>Opened</td>
<td>Must be used within 3 Days</td>
</tr>
</tbody>
</table>

AFREZZA®
(insulin human [rDNA origin]) Inhalation Powder

To switch from injected mealtime insulin to AFREZZA...

Find your injected insulin dose in the chart.
AFREZZA®
(insulin human [rDNA origin]) Inhalation Powder

• How supplied:
  – 60 – 4 unit cartridges and 2 inhalers
  – 90 – 4 unit cartridges and 2 inhalers ($269.00 CVS)
  – 90 – 8 unit cartridges and 2 inhalers
  – 90 cartridges; 60 – 4 unit cartridges and 30 – 8 unit cartridges and 2 inhalers ($302.80 RiteAid)
  – 90 cartridges; 30 – 4 unit cartridges and 60 – 8 unit cartridges and 2 inhalers ($334.31 RiteAid)
  – 180 cartridges; 90 -4 unit cartridges and 90 – 8 unit cartridges and 2 inhalers

AFREZZA®
(insulin human [rDNA origin]) Inhalation Powder
The FDA is requiring the following post-marketing studies for Afrezza:
  – a clinical trial to evaluate pharmacokinetics, safety and efficacy in pediatric patients;
  – a clinical trial to evaluate the potential risk of pulmonary malignancy with Afrezza (this trial will also assess cardiovascular risk and the long-term effect of Afrezza on pulmonary function);
  – two pharmacokinetic-pharmacodynamic euglycemic glucose-clamp clinical trials, one to characterize dose-response and one to characterize within-subject variability.

Toujeo – Insulin glargine U-300 by Sanofi
• Feb 25, 2015 FDA approved a new higher concentration U-300 insulin glargine - Toujeo available in the Solostar pen device only with 1.5ml (450U)/pen in boxes of 3 or 5 pens
• When compared head to head in multiple 26 weeks studies the efficacy was similar (noninferior) but the daily doses of Toujeo (U-300) were typically 10-20% higher than with Lantus (U-100)
• The data also suggest that the duration of action is slightly longer with a tail of ~30 hours.
Insulin Degludec- Tresiba
by Novo Nordisk

• September 25, 2015 FDA approved Tresiba (insulin degludec) a once-daily new-generation basal insulin analogue with a half-life of 25 hours and a duration of action of at least 42 hours. (expected launch date early 2016)
  – indicated for use alone, or in combination with oral antidiabetic medicines or bolus insulin, and is approved for glycemic control in adults with type 1 and type 2 diabetes.
  – Will only be available in the Flex Touch Pen in both U100 and U200/ml 3 ml pens which can be administered at anytime during the day.

Insulin Degludec- Tresiba

• Insulin degludec forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot.
• The protracted time action profile of TRESIBA is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.

Insulin Degludec- Tresiba

• Resubmissions are based on interim analysis of data from the DEVOTE trial, which is looking at the cardiovascular effects of the long-acting insulins and is expected to complete in the second half of 2016.
  – In the meantime, to preserve the integrity of the trial, only a small team within the company has access to the data, Novo said.
  – While approved in Japan and Europe, Tresiba was rejected by the US Food and Drug Administration in February 2013 on heart safety concerns.
Insulin Degludec- Tresiba

Starting Dose in Insulin Naïve Patients

• Type 1 Diabetes Mellitus: The recommended starting dose of TRESIBA in insulin naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short-acting insulin and divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Insulin Degludec- Tresiba

• Type 2 Diabetes Mellitus: The recommended starting dose of TRESIBA in insulin naïve patients with type 2 diabetes mellitus is 10 units once daily.

Starting Dose in Patients Already on Insulin Therapy

• Type 1 and Type 2 Diabetes Mellitus: Start TRESIBA at the same unit dose as the total daily long or intermediate-acting insulin unit dose.

Insulin Degludec- Tresiba

• Two replicate trials in patients with Type 1 diabetes evaluated degludec vs. glargine both with insulin aspart. (52 and 26 weeks duration).
  – The reductions in A1c were similar and both met non-inferiority with differences in A1c of 0.01 and 0.09, they also were similar in % with A1c < 7.0% as well as mean daily doses of basal insulin.
**Insulin Degludec- Tresiba**

- In the 52 week (BEGIN Basal-Bolus Type 1) trial the rates of overall confirmed hypoglycemia (plasma glucose <56 mg/dl or severe) were similar in the insulin degludec and insulin glargine groups (42·54 vs 40·18 episodes per patient-year of exposure; estimated rate ratio [degludec to glargine] 1·07 [0·89 to 1·28]; p=0·48).
- The rate of nocturnal confirmed hypoglycemia was 25% lower with degludec than with glargine (4·41 vs 5·86 episodes per patient-year of exposure; 0·75 [0·59 to 0·96]; p=0·021).
  
  — Lancet 2012; 379: 1489–97

**Insulin Degludec- Tresiba**

- The 52-week randomized BEGIN Once Long Trial was an open-label, multicenter trial that enrolled 1030 insulin naive patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling.
  
  — Metformin alone (82.5%) or in combination with a DPP-4 inhibitor (17.5%) was used as background therapy in both treatment arms.
  
  • Diabetes Care 35:2464–2471, 2012

**Insulin Degludec- Tresiba**

- At week 52 (BEGIN Once Long) Trial, the difference in HbA1c reduction from baseline between TRESIBA and insulin glargine U-100 was 0.09% with a 95% confidence interval of [-0.04%; 0.22%] and met the prespecified non-inferiority margin (0.4%).
  
  — A similar % of patients achieved an A1c of <7.0% and the mean daily dose of basal insulin was also similar.
  
  • Diabetes Care 35:2464–2471, 2012
Insulin Degludec- Tresiba

• Overall rates of confirmed hypoglycemia (PG <56 mg/dl or severe episodes requiring assistance) were similar, with degludec and glargine at 1.52 versus 1.85 episodes/patient-year of exposure (PYE).

• There were few episodes of nocturnal confirmed hypoglycemia in the overall population, and these occurred at a lower rate with degludec versus glargine (0.25 vs. 0.39 episodes/PYE; P = 0.038).

– Diabetes Care 35:2464–2471, 2012

Insulin Degludec- Tresiba

• The efficacy of insulin degludec U-200 was evaluated in a 26-week randomized, open-label, multicenter BEGIN LOW VOLUME trial in 457 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to insulin degludec U-200 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling.

  – Both treatment arms were receiving metformin alone (84%) or in combination with a DPP-4 inhibitor (16%) as background therapy.

  – Diabetes Care September 2013 vol. 36 no. 9 2536-2542

Insulin Degludec- Tresiba

• At week 26, the difference in HbA1c reduction from baseline between insulin degludec U-200 and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.11%; 0.19%] and met the pre-specified non-inferiority margin (0.4%).

  – A similar % of patients achieved an A1c of <7.0% and the mean daily dose of basal insulin was also similar.

  – Diabetes Care September 2013 vol. 36 no. 9 2536-2542
Insulin Degludec- Tresiba
• By 26 weeks, mean observed FPG reductions were significantly greater with iDeg than iGlar (–67 vs. –61 mg/dL; estimated treatment difference, P = 0.02). Despite this difference, rates of overall confirmed hypoglycemia were not higher with iDeg than with iGlar (1.22 and 1.42 episodes/patient-year, respectively), as were rates of nocturnal confirmed hypoglycemia (0.18 and 0.28 episodes/patient-year, respectively). Mean daily basal insulin dose was significantly lower by 11% with iDeg 200 units/mL compared with iGlar.
— Diabetes Care September 2013 vol. 36 no. 9 2536-2542

Insulin Degludec- Tresiba
• U-100 FlexTouch - 3 mL 100 units/mL - 300 Units/pen – max dose 80 Units in 1 Unit increments – available 5 pens/pack
• U-200 FlexTouch - 3 mL 200 units/mL - 600 Units/pen – max dose 160 Units in 2 Unit increments - available 3 pens/pack
• Keep under refrigeration (NOT frozen) but stable for 56 days (8 weeks) at room temperature once taken out of refrigeration.

Insulin Degludec/Aspart 70/30 – Ryzodeg by Novo Nordisk
• The FDA also approved Ryzodeg 70/30 contains insulin degludec in a soluble co-formulation with insulin aspart, and can be administered once or twice daily with any main meal.
Insulin Lispro - Humalog U-200
KwikPen by Lilly

- The first concentrated mealtime insulin analog to receive FDA approval, the Humalog U-200 KwikPen delivers the same dose as Lilly’s Humalog U-100 KwikPen in half the volume. Compared with the 300 units of insulin held by the U-100 formulation, the U-200 KwikPen holds 600 units, allowing diabetics to change their pens less frequently.
- The FDA based its approval on data that demonstrated the bioequivalence of Humalog U-200 relative to Humalog U-100 in a pharmacokinetic/pharmacodynamic study.
- Be careful in calculating the days supply with both of these new more concentrated insulins and be glad that they are not available in a vial!

SAVOR-TIMI 53 Trial

- 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.


SAVOR-TIMI 53 Trial

- A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively).
- More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007). NNH=143

SAVOR-TIMI 53 Trial

- Pancreatitis occurred infrequently, and the number of patients with acute or chronic pancreatitis was similar in the two groups (24 patients [0.3%] in the saxagliptin group and 21 patients [0.3%] in the placebo group, P=0.77).
- A1c reductions were modest at best ~ (0.3-0.4%)

FDA Advisory Committee

- April 14, 2015: 14 of 15 panelists from the Endocrinologic and Metabolic Drugs Advisory Committee voted to update the label for saxagliptin, primarily on the increased risk for heart failure. They also wanted to see information on the trend toward higher all-cause mortality. One panel member voted to withdraw the drug from the US market.

EXAMINE Trial

- Randomly assigned 5380 patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy for ~ 18 months.
- A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; P<0.001 for noninferiority & P = 0.32 for superiority).
EXAMINE Trial

- The incidences of acute and chronic pancreatitis were similar in the two groups; no cases were fatal.
- There were no significant between-group differences in the incidence of cancer, and there were no reports of pancreatic cancer.
- A1c reductions were also modest at best ~ 0.36%.

FDA Advisory Comm Meeting

- The FDA Advisory Comm is being asked by the FDA to review the data from the EXAMINE Trial specifically as it relates to the US/Canada subset of patients.
  - Results from the U.S. (plus Canada) sub-group were somewhat divergent from results in the entire study population. For that specific sub-group, the estimated HR suggested an increased risk for MACE (HR 1.28, 95% CI [0.89, 1.84]). Analyses stratified by baseline CV-risk factors were unable to fully explain the observed regional differences.

FDA Advisory Comm Meeting

- In the placebo arm of EXAMINE 89 subjects experienced at least one hHF event versus 106 subjects in the alogliptin arm (HR 1.19, 95% CI [0.90, 1.58]). Although the FDA does not find this estimate to be particularly reassuring,
- The FDA would like the Committee to opine on the relevance of the observed imbalance in hHF in EXAMINE.
FDA Advisory Committee

- April 14, 2015: The committee was not as concerned about the safety of alogliptin, but, still, 13 voted to add new data to the label, while three said there should be no change. The new safety information should focus on heart failure, said the majority, despite a lack of a real signal with that drug. Even so, some felt that heart failure could be a class-wide problem.

Sitagliptin Cardiovascular Outcome Study (TECOS)

- Type 2 Diabetes Mellitus, HbA1c is between 6.5% and 8.0% on stable dose(s) of antihyperglycemic agent(s), including insulin. Enrolled 14,724 patients age >/= 50 y/o with preexisting cardiovascular disease. (3 year follow-up)
- Primary Outcome Measures: Time to first confirmed cardiovascular (CV) event (a composite defined as CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization).

**TECOS Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sitagliptin (n=7382)</th>
<th>Placebo (n=7339)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>11.4%</td>
<td>11.6%</td>
<td>0.98 (0.89-1.08)</td>
</tr>
<tr>
<td>CV Death, non-fatal MI, non-fatal CVA</td>
<td>10.2%</td>
<td>10.2%</td>
<td>0.99 (0.89-1.10)</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.2%</td>
<td>5.0%</td>
<td>1.03 (0.89-1.19)</td>
</tr>
<tr>
<td>Hospitalization unstable angina</td>
<td>1.8%</td>
<td>1.8%</td>
<td>0.90 (0.70-1.16)</td>
</tr>
<tr>
<td>Fatal or non-fatal MI</td>
<td>4.1%</td>
<td>4.3%</td>
<td>0.95 (0.81-1.11)</td>
</tr>
<tr>
<td>Fatal or non-fatal CVA</td>
<td>2.4%</td>
<td>2.5%</td>
<td>0.97 (0.79-1.19)</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>3.1%</td>
<td>3.1%</td>
<td>1.00 (0.83-1.20)</td>
</tr>
<tr>
<td>Hospitalization for HF or CV Death</td>
<td>7.3%</td>
<td>7.2%</td>
<td>1.02 (0.90-1.15)</td>
</tr>
</tbody>
</table>

NEJM: on-line June 8, 2015
FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- 8-28-15 FDA is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling.
- The FDA found 33 patients and all experienced arthralgia that resulted in a substantial reduction in their prior level of activity, including 10 patients who were hospitalized due to disabling joint pain.

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- In 22 cases, symptoms appeared within 1 month of initiation of treatment with a DPP-4 inhibitor. In 20 of the 33 cases, the DPP-4 inhibitor was suspected as a possible cause of arthralgia and was discontinued within a month following the onset of symptoms. However, 8 of the remaining 13 cases reported a period of 44 days to 1 year between the onset of symptoms and discontinuation of the DPP-4 inhibitor. In 23 of the 33 cases, symptoms resolved less than 1 month after discontinuation of the drug.
  - eight of the 33 cases documented a positive rechallenge with the same or other drug in the class

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- Ten of the 33 cases reported fever and chills, rash, and swelling, which are suggestive of an immunological reaction. Of the 13 cases with available results of laboratory assays for systemic autoimmune disorders, 8 reported a negative or normal test result. Five cases reported positive test results: antinuclear antibody (n=2), erythrocyte sedimentation rate (n=1), C-reactive protein (n=1), and antinuclear cytoplasmic antibody (n=1). However, none of these tests are specific for a particular autoimmune condition that can cause severe joint pain.
Digoxin and Outcomes?

- New digoxin use and risks of death and HF hospitalization, controlling for medical history, laboratory results, medications, HF disease severity, and the propensity for digoxin use. We also conducted analyses stratified by sex and concurrent β-blocker use. Among 2891 newly diagnosed patients with systolic HF, 529 (18%) received digoxin.
- During a median 2.5 years of follow-up, incident digoxin use was associated with higher rates of death (14.2 versus 11.3 per 100 person-years) and HF hospitalization (28.2 versus 24.4 per 100 person-years). In multivariable analysis, incident digoxin use was associated with higher mortality (hazard ratio, 1.72; 95% confidence interval, 1.25–2.36) but no significant difference in the risk of HF hospitalization (hazard ratio, 1.05; 95% confidence interval, 0.82–1.34). Results were similar in analyses stratified by sex and β-blocker use.


Digoxin after 230 years?

- The Editorial by Dr. Opie entitled “Digitalis, Yesterday and Today, But Not Forever” concludes: “This conclusion is the opposite of what the earlier studies favoring digoxin use in the bygone era of imperfect therapy for HF had found, with the new conclusion that therapy for HF that includes β-blockade and full angiotensin-II modulation dispenses with the need for taking the risks of adding digoxin therapy. The data at our disposal, taking into account the current study, allow us to seriously question the advice on digoxin given by both the current and influential guidelines, European and American.”


TREAT-AF Trial

- Researchers identified 122,465 outpatients in the VA health system who were seen for newly diagnosed, nonvalvular AF during VA fiscal years 2004 through 2008 (23.4% received digoxin). Cumulative mortality rates were significantly higher for digoxin-treated patients than for untreated patients (95 vs. 67 per 1000 person-years). Digoxin use was independently associated with mortality after multivariate adjustment and propensity matching, even after adjustment for drug adherence.

- Propensity matching HR: 1.21, 95% CI: 1.17 to 1.25, p < 0.001

- J Am Coll Cardiol. 2014;64(7):660-668
Digoxin in A. Fib?

- Nov. 21, 2014 a report in Circulation: Arrhythmia and Electrophysiology from Kaiser Permanente in California details a trial that followed nearly 15,000 newly diagnosed patients with A Fib and over 3 years 4800 were treated with digoxin.
- Patients who took digoxin had a 71 percent higher risk of death and a 63 percent higher risk of hospitalization than those who did not take the drug.

Rocket-AF Trial and Digoxin

- In 14,171 randomly assigned patients in the Rocket-AF Trial, digoxin was used at baseline in 5,239 (37%). Patients given digoxin were more likely to be female and have a history of heart failure, diabetes, and persistent A Fib. After adjustment, digoxin was associated with:
  - increased all-cause mortality (5.41 vs 4.30 events per 100 patient-years; hazard ratio 1.77, 95% CI 1.04–1.52; p=0.0093),
  - vascular death (3.65 vs 2.69 per 100 patient-years; 1.9; 1.03–1.39, p=0.0201),
  - sudden death (1.68 vs 1.12 events per 100 patient-years; 1.36; 1.08–1.70, p=0.0076).

Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

- May 10, 2013 The Food and Drug Administration today approved Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.
  - Developed by GlaxoSmithKline, in collaboration with Theravance.
Fluticasone furoate /Vilanterol inhalation powder –Breo Ellipta

• Maintenance treatment of COPD: 1 inhalation of Breo Ellipta 100 mcg/25 mcg (fluticasone furoate /vilanterol inhalation powder) once daily.
• Cost ~$300.00 Goodrx.com
• The plasma half-life of the components is ~24 hours and 21 hours respectively
• FEV1 improvement 214 ml at peak and 144 ml at trough
• FDA Box Warning as with all other LABA containing medications Asthma Related Deaths but NOT indicated for patients with asthma

Be careful, every time you move the cover you move to the next dose!
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

- March 19, 2015 the FDA Advisory Committees (Pulmonary, Allergy, Drug safety) voted 16 to 4 to recommend Breo Ellipta for adults 18 y/o and older with asthma but also voted 18-2 against approval for children ages 1-17 y/o.
- The panel also voted 17-3 that the data supported safety in adults but only one panel member voted that safety was supported in children.

Umeclidinium and Vilanterol – Anoro Ellipta Inhaler by GSK

- A combination of umeclidinium, an anticholinergic (LAMA), and vilanterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
- Not indicated for the relief of acute bronchospasm or for the treatment of asthma.
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

- Inhalation Powder. Inhaler containing 2 double-foil blister strips of powder formulation for oral inhalation. One strip contains umecclidinium 62.5 mcg per blister and the other contains vilanterol 25 mcg per blister.
  - The half-life of both components is about 11 hours
  - Dose is one inhalation once a day.
- FDA Box WARNING: ASTHMA-RELATED DEATH
  - Available as both a 30 dose and 7 dose institutional inhaler

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Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

- Improvements in the primary endpoint of mean change in trough forced expiratory volume in 1 second (FEV1) were significantly greater with combination therapy than with umecclidinium monotherapy and vilanterol monotherapy (FEV1 improvement 243 ml at peak and 171 ml at trough with combination), as were reductions in symptom scores and rescue albuterol use.
  - Risk for exacerbations was lower in all treatment groups compared with placebo, but was no lower with combination therapy than with monotherapy. Adverse events were similar in all groups.
  - Chest 2014 May; 145:981. (http://dx.doi.org/10.1378/chest.13-1579)

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Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

- GSK/Theravance announced 10-21-2014 the results of a trial in 905 patients with COPD were randomised 1:1 to UMEC/VI (Anoro) 62.5/25mcg inhalation powder or tiotropium (Spiriva)18mcg for 24 weeks.
- Results: At the end of the treatment period in the trial, UMEC/VI 62.5/25mcg showed a statistically significant improvement of 112ml compared with tiotropium 18mcg.
  - Respiratory Medicine. 2014.DOI:0.1016/j.rmed.2014.10.002
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

- **Drug Interactions:**
  - Vilanterol is a CYP 3A4 substrate so use caution when patients are taking strong 3A4 inhibitors (i.e. clarithromycin, protease inhibitors,azole antifungals)
  - Umeclidinium is a CYP 2D6 substrate (no significant interactions seen?)
  - MAO inhibitors and Tricyclics may increase QTc
  - Anticholinergics are likely additive to umclidinium, caution in males with BPH
  - Beta blockers?

Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

- Both components may increase CV risk?
  - A dose-dependent increase in heart rate was observed (~9-20 Beats per minute increase with higher than recommended doses)
- **Adverse Effects:**
  - Include pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain.
- **Cost:** ~$310.00/ 30 doses Goodrx.com

**CAUTION:** If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled.
Umeclidinium – Incruse Ellipta Inhaler

- INCRUSE™ ELLIPTA® 62.5 mcg/ dose is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- The effective half-life after once daily dosing is 11 hours.
- Trough FEV1 (mL) at Day 169: Difference From Placebo (95% CI) n = 280 115ml (76, 155)
- Cost ~ $240.00 Goodrx.com

Olodaterol - Striverdi Respimat

by Boehringer Ingelheim

- FDA approved July 31, 2014 - Olodaterol is a long-acting once a day beta-adrenergic agonist (LABA) for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema with airflow obstruction.
  - Each actuation from the mouthpiece contains 2.7 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. Two actuations equal one dose of 5 mcg at the same time each day.
Olodaterol – Striverdi Respimat

- STRIVERDI RESPIMAT is NOT indicated to treat acute deterioration of COPD
- STRIVERDI RESPIMAT is NOT indicated to treat asthma (Box Warning about Asthma Related Death as with all LABA’s)
- Available in a 60 spray Respimat inhaler (30 doses)
- Cost ~$170.00 Goodrx.com

Olodaterol – Striverdi Respimat

Tiotropium – Spiriva Respimat

- FDA approved 9-25-2014; indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).
- The delivered dose is 2.5 microgram tiotropium per puff (2 puffs/dose or 5 mcg) and is equivalent to 3.124 microgram tiotropium bromide monohydrate
- NOTE there are now two different inhalers!
- Cost ~ $315.00 Goodrx.com
Tiotropium – Spiriva Respimat

2.5 mcg/inhalation for COPD

- September 16, 2015 the FDA approved SPIRIVA RESPIMAT for the long-term, once-daily, prescription maintenance treatment of asthma in people ages 12 and older. SPIRIVA RESPIMAT is not a treatment for sudden asthma symptoms.
- SPIRIVA RESPIMAT, 1.25 µg/puff (2 puff/dose or 2.5 mcg) is a long-term, once-daily, prescription maintenance treatment of asthma for people 12 years and older.

Tiotropium – Spiriva Respimat

1.25 mcg/inhalation for Asthma

- Blue cap color is for patients with asthma!
Combination of Tiotropium and Olodaterol - Stiolto Respimat

- 5/21/2015 the FDA approved Boehringer Ingelheims Fixed-Dose Combination Tiotropium Plus Olodaterol – Stiolto for Patients with COPD. (LAMA + LABA)

- The NDA submission for tiotropium + olodaterol FDC is based on results from three global Phase III trials – the 52-week replicate TONADO® 1&2 studies and the 6-week cross-over VIVACITO® dose finding study.

  - The phase III clinical trial program (TOviTO®) for tiotropium + olodaterol includes more than 7,000 people living with varying severities of COPD worldwide.

Tiotropium and Olodaterol - Stiolto Respimat

- Each actuation from the mouthpiece contains 3.124 mcg tiotropium bromide monohydrate, equivalent to 2.5 mcg tiotropium, and 2.736 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. (Each dose is two actuations once a day)

- Label also contains the LABA class Box Warning – Asthma Related Death.
Tiotropium and Olodaterol - Stiolto Respimat

- Do not initiate Stioloto Respimat in acutely deteriorating COPD patients.
- **Do not use for relief of acute symptoms.** Concomitant short-acting beta-2 agonists can be used as needed for acute relief.
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or sensitivity to sympathomimetic drugs.
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs.

Tiotropium and Olodaterol - Stiolto Respimat

- **Drug Interactions:**
  - Other adrenergic drugs may potentiate effect. Use with caution.
  - Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution.
  - MAO inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution.
  - Beta-blockers may decrease effectiveness. Use with caution and only when medically necessary
Tiotropium and Olodaterol - Stiolto Respimat

• Recommended Dosing: is two inhalations once-daily at the same time of the day. Do not use Stiolto Respimat more than two inhalations every 24 hours.
  – Stiolto Respimat Inhalation Spray is available as:
    • Stiolto Respimat Inhalation Spray: 60 metered actuations (NDC 0597-0155-61)
    • Stiolto Respimat Inhalation Spray: 28 metered actuations (NDC 0597-0155-31) (institutional pack)

Tiotropium and Olodaterol - Stiolto Respimat

• Prior to first use, the Stiolto Respimat cartridge is inserted into the Respimat inhaler and the unit is primed.
  – When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use.
  – If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use.
  – If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use.

Global Strategy for Diagnosis, Management and Prevention of COPD
Therapeutic Options: Bronchodilators

• Long-acting inhaled bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.
• Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.
• Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

© 2013 Global Initiative for Chronic Obstructive Lung Disease
Regular treatment with inhaled corticosteroids improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV$_1$ < 60% predicted.

Inhaled corticosteroid therapy is associated with an increased risk of pneumonia.

Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients.

An inhaled corticosteroid combined with a long-acting beta$_2$-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.

Combination therapy is associated with an increased risk of pneumonia.

Addition of a long-acting beta$_2$-agonist/inhaled glucocorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended First choice</th>
<th>Alternative choice</th>
<th>Other Possible Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA pm or SABA pm</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LABA and LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Arnuity Ellipta (fluticasone furoate inhalation powder) by GSK/Theravance

- FDA approved August 20, 2014 ARNUITY ELLIPTA is a corticosteroid indicated for: once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Not indicated for relief of acute bronchospasm.
  - Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

Arnuity Ellipta (fluticasone furoate inhalation powder)

- In a 343 patient placebo controlled trial 100 mcg fluticasone furoate QD was similar to 250 mcg of fluticasone propionate BID
- Available in 100 and 200 mcg/inhalation Ellipta 30 dose dry powder inhaler
- Cost ~ $145.00 per 100 mcg and ~$190.00/200 mcg Goodrx.com
- Also available in 14 blisters (institutional pack).
Arnuity Ellipta (fluticasone furoate inhalation powder)

PROAIR RESPICLICK (albuterol sulfate) inhalation powder by Teva

- FDA approved 4-1-2015 for treatment (1-2 inhalations up to every 4-6 hours) or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm (15-30 min before exercise) in patients 12 years of age and older.
- DO NOT USE with a spacer!

PROAIR RESPICLICK (albuterol sulfate) inhalation powder

- PROAIR RESPICLICK is a multi-dose breath-actuated dry powder inhaler that meters 117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) from the device reservoir and delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouth piece per actuation.
  - 200 actuations per device with a dose counter
  - No priming required!
  - Do Not wash or put any part of your inhaler in water
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

- Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.
- Store the inhaler at room temperature and to avoid exposure to extreme heat, cold, or humidity.
Replacing your PROAIR RESPICLICK inhaler

- The counter on the back of your inhaler shows how many doses you have left.
  - When there are '20' doses left, the dose counter will change to red and you should refill your prescription or ask your doctor for another prescription
- Do not open the cap unless you are taking a dose. Opening and closing the cap without inhaling a dose will waste the medicine and may damage your inhaler
Suvorexant - BELSOMRA® C-IV by Merck

• FDA approved 8-13-2014 the first of a new class of hypnotics, an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

• The mechanism by which suvorexant exerts its therapeutic effect in insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.

Suvorexant – BELSOMRA C-IV

• The recommended dose is 10 mg, taken no more than once per night and within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. (T1/2 ~ 12 hours)
5, 10, 15 and 20 mg tabs ~$280-300.00/30 tabs (GoodRx)

  – If the 10 mg dose is well-tolerated but not effective, the dose can be increased. The maximum recommended dose of is 20 mg once daily.

  – The recommended dose of is 5 mg when used with moderate CYP3A inhibitors and the dose generally should not exceed 10 mg in these patients. Suvorexant is not recommended for use with strong CYP3A inhibitors.

  – Food may delay the onset of action.

Suvorexant – BELSOMRA C-IV

• Polysomnographic Assessment of Time to Sleep Onset (2 trials) difference from placebo

  – Study 1 (15-20 mg doses) at 1 month – 10 min; and at 3 months – 8 min.

  – Study 2 (15-20 mg doses) at 1 month – 8 min; and at 3 months no difference.

• Polysomnographic Assessment of Sleep Maintenance (Wake After Sleep Onset)

  – Study 1 at 1 month – 26 min; and at 3 months – 17 min.

  – Study 2 at 1 month – 24 min; and at 3 months – 31 min.
**Suvorexant – BELSOMRA C-IV**

- Doses of 30 mg and 40 mg in the 3-month placebo-controlled trials (Study 1 and Study 2). The higher doses were found to have similar efficacy to lower doses, but significantly more adverse reactions were reported at the higher doses.

- **Daytime somnolence:** Risk of impaired alertness and motor coordination, including impaired driving; risk increases with dose; caution patients taking 20 mg against next-day driving and other activities requiring complete mental alertness.

- **Nighttime “sleep-driving” and other complex behaviors** while out of bed and not fully awake. Risk increases with dose, with use of CNS depressants, and with alcohol.

- **Depression:** Worsening of depression or suicidal thinking may occur. Risk increases with dose. Immediately evaluate any new behavioral changes.

- **Compromised respiratory function:** Effect on respiratory function should be considered.

- **Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms:** Risk increases with dose.

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**Naltrexone and Bupropion Extended-Release Tablets – Contrave** by Orexigen Therapeutics and Takeda

- FDA approved 9-10-2014, **Contrave is a combination of naltrexone, an opioid antagonist, and bupropion, an antidepressant, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:**
  - 30 kg/m2 or greater (obese) or
  - 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

- **Extended-Release Tablets:** 8 mg naltrexone HCl /90 mg bupropion HCl
Naltrexone and Bupropion Extended-Release Tablets – Contrave

• Response to therapy should be evaluated after 12 weeks at the maintenance dosage. If a patient has not lost at least 5% of baseline body weight, **discontinue Contrave**, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Naltrexone and Bupropion Extended-Release Tablets – Contrave

**BOX WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS**

• Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders.
• Monitor for worsening and emergence of suicidal thoughts and behaviors.
• Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation.

Naltrexone and Bupropion Extended-Release Tablets – Contrave

**Contrave is contraindicated in:**
- Uncontrolled hypertension
- Seizure disorder or a history of seizures
- Use of other bupropion-containing products (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, and APLENZIN)
- Bulimia or anorexia nervosa, which increase the risk for seizure
- Chronic opioid or opiate agonist (e.g., methadone) or partial agonists (e.g., buprenorphine) use, or acute opiate withdrawal
- Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- Concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with Contrave.

Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction observed with naltrexone exposure.
Naltrexone and Bupropion Extended-Release Tablets – Contrave

Adverse Effects:

<table>
<thead>
<tr>
<th></th>
<th>Contrave 32 mg/360 mg N=2545 %</th>
<th>Placebo N=1515 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea</td>
<td>32.5</td>
<td>6.7</td>
</tr>
<tr>
<td>• Constipation</td>
<td>19.2</td>
<td>7.2</td>
</tr>
<tr>
<td>• Headache</td>
<td>17.6</td>
<td>10.4</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>10.7</td>
<td>2.9</td>
</tr>
<tr>
<td>• Dizziness</td>
<td>9.9</td>
<td>3.4</td>
</tr>
<tr>
<td>• Insomnia</td>
<td>9.2</td>
<td>5.9</td>
</tr>
<tr>
<td>• Dry mouth</td>
<td>8.1</td>
<td>2.3</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>7.1</td>
<td>5.2</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>4.2</td>
<td>2.8</td>
</tr>
<tr>
<td>• Hot flush</td>
<td>4.2</td>
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<td>• Fatigue</td>
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<td>• Tremor</td>
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Naltrexone and Bupropion Extended-Release Tablets – Contrave

Table 2: Change in Weight in 58 Week Trial with CONTRAVE (STUDY 1)

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<tr>
<th></th>
<th>CONTRAVE 32 mg/360 mg</th>
<th>Placebo</th>
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Naltrexone and Bupropion Extended-Release Tablets – Contrave

Recommended Dosing

Contrave dosing should be escalated according to the following schedule:

<table>
<thead>
<tr>
<th>Morning Dose</th>
<th>Evening Dose</th>
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</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Week 2</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Week 3</td>
<td>2 tablets</td>
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<tr>
<td>Week 4 &amp; on</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

Taken by mouth in the morning and in the evening can be taken with food except avoid with high fat meal which increases bioavailability. The tablets should not be cut, chewed, or crushed. Total daily doses greater than 32 mg/360 mg per day (two tablets twice daily) are not recommended.

Cost: ~$220.00/120 tabs (GoodRx)
Liraglutide – Saxenda by Novo Nordisk

- Sept. 2014: Members of the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee voted 14-1 support approval of Saxenda (liraglutide 3 mg) as an adjunct to diet and exercise in adults with a BMI of 30 or more, or 27 or more with at least one weight-related comorbidity.
- Dec 23, 2014 FDA approval

Liraglutide – Saxenda

- FDA Advisory Committee panelists expressed concern about the lack of data beyond 1 year for liraglutide in obesity and a variety of safety issues — including gallbladder disease, pancreatitis, breast and thyroid cancers, and increased heart rate — but most said they were comfortable with those issues being addressed in postmarketing studies.

Liraglutide – Saxenda

- A majority of the panel agreed that the ongoing cardiovascular outcomes trial of the 1.8-mg diabetes dose, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, would be sufficient to characterize the cardiovascular risk of the 3.0-mg dose in terms of identifying any signals that would need to be followed. Results from that trial, for which data on neoplasms and other adverse events are also being collected, are due in 2016.
Liraglutide – Saxenda

- Saxenda is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of > 30 kg/m² or greater (obese) or > 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia).

Liraglutide – Saxenda

Dosing:
- Recommended dose of Saxenda is 3 mg daily. Administer at any time of day, without regard to the timing of meals.
  - Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached. Inject subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment.
  - Available in 3 ml pens 6 mg/ml in boxes of 5 pens (dosage on pen is 0.6, 1.2, 1.8, 2.4 and 3.0 mg)
  - Cost ~$1,100.00/ 5 pens (similar to cost per mg in Victoza pens ~$220.00/pen)

Liraglutide – Saxenda

- Trial 1839 (phase 3 trial in patients without type 2 diabetes): Main 56-week trial in 3731 patients
  - Mean placebo adjusted weight loss 5.39 Kg
- Trial 1922 (phase 3 trial in patients with type 2 diabetes) 623 patients at 56 weeks
  - Mean placebo adjusted weight loss 4.08 Kg
- Trial 1923 (phase 3 weight maintenance trial in patients without type 2 diabetes) 413 pts at 56 weeks
  - Mean placebo adjusted weight loss 5.86 Kg
- Trial 3970 (phase 3 trial in patients with obstructive sleep apnea) 359 patients at 32 weeks
  - Mean placebo adjusted weight loss 4.92 Kg

* Liraglutide 3.0 mg NDA 206321 Endocrinologic and Metabolic Drug Advisory Committee, 11 September 2014
Liraglutide – Saxenda

- In the trials, the most common adverse events with liraglutide 3.0 mg vs. placebo were nausea (39% vs. 14%), diarrhea (21% vs. 10%), vomiting (16% vs. 4%), and hypoglycemia when used in combination with sulfonylureas despite a halving of the sulfonylurea dose (15% vs. 6%).
- Serious adverse events included acute pancreatitis (7 patients with liraglutide vs. 1 with placebo) and acute gallstone disease (2.3% vs. 0.9%). Dr. Phillips attributed those events to weight loss, but FDA reviewer Julie Golden, MD, said there was not enough information to determine the mechanism.

Liraglutide – Saxenda

- The rate of neoplasms was not significantly greater with liraglutide 3.0 mg, but the incidence of thyroid neoplasm — 4 with liraglutide vs. 1 with placebo — was nearly 4 times greater than what would be expected in the general population.
- Female breast neoplasms were numerically greater with liraglutide — 12 vs. 2 with comparator drugs — but the difference was not significant.

Liraglutide – Saxenda

- Panelists expressed concern about the lack of data beyond 1 year for liraglutide in obesity and a variety of safety issues — including gallbladder disease, pancreatitis, breast and thyroid cancers, and increased heart rate — but most said they were comfortable with those issues being addressed in postmarketing studies.
Placebo adjusted weight loss at 1 year was 3.3 Kg in all studies.

Phentermine/Topiramate extended-release – Qsymia (C-IV)

Adverse Effects: (at the target dose 15/92 mg)
- Increased heart rate: >10 BPM in 56% of patients and >20 BPM in 20% of patients
- Paresthesia (tingling of face, hands and feet) in 20% of patients vs. 1.9% on placebo
- Metallic taste in 9.4% vs. 1.1% on placebo
- Mood/sleep disorder in 20.6% vs. 10.3% on placebo
- Anxiety in 7.9% vs. 2.6% on placebo
- Impaired cognition in 7.6% vs. 1.5% on placebo
- Metabolic acidosis: reduced bicarbonate (<21 mEq/L) in 12.8% vs. 2.1%
- Hypokalemia (<3.5 mEq/L) in 4.9% vs. 1.1%
- Elevated serum creatinine (monitor baseline and periodically)
- Nephrolithiasis in 1.1% vs. 0.3% on placebo
Endocrine Society Weight Loss Guidelines

- A key emphasis of the new US guidance is the recognition that weight-loss drugs do not "work on their own," but rather should be used to amplify the effects of behavioral changes to reduce caloric consumption.
  - "The addition of these medications to the lifestyle program will result in greater weight loss overall and better maintenance of the weight loss."
  - The panel notes that pharmacotherapy for obesity may reduce comorbid conditions and promote greater adherence to behavioral changes. In particular, weight loss may promote greater physical activity.

IMPROVE-IT: Results At Long Last

- The results of IMPROVE-IT (AHA 11/17/2014 Scientific Sessions). The study included more than 18,000 patients from 39 countries who were stable following ACS (<10 days). Patients were randomized to one of two treatment strategies: simvastatin 40 mg alone or simvastatin 40 mg plus ezetimibe 10 mg. They were followed for a minimum of 2.5 years or until the study investigators accrued 5,250 clinical events.
  - At baseline, the mean LDL-cholesterol level among the ACS patients was 95 mg/dL in both treatment arms. With simvastatin 40 mg, LDL-cholesterol levels were reduced to 69.9 mg/dL at 1 year. The addition of ezetimibe 10 mg to simvastatin further lowered LDL-cholesterol levels, to 53.2 mg/dL at 1 year. Over 7 years, there remained a significant difference between the two treatments in the achieved LDL-cholesterol levels.

<table>
<thead>
<tr>
<th>Primary End Point and Individual Components (7-Year Event Rates)</th>
<th>Simvastatin, n=9077 (%)</th>
<th>Ezetimibe/Simvastatin, n=9067 (%)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Primary end point (Cardiovascular death, MI, stroke, unstable angina, coronary revascularization)</td>
<td>34.7</td>
<td>32.7</td>
<td>0.016</td>
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<tr>
<td>All-cause death</td>
<td>15.3</td>
<td>15.4</td>
<td>0.782</td>
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<tr>
<td>MI</td>
<td>14.8</td>
<td>15.1</td>
<td>0.062</td>
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<tr>
<td>Stroke</td>
<td>4.0</td>
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<td>0.052</td>
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<tr>
<td>Ischemic stroke</td>
<td>4.1</td>
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<td>0.008</td>
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<tr>
<td>Unstable angina</td>
<td>1.9</td>
<td>2.1</td>
<td>0.018</td>
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<tr>
<td>Coronary revascularization</td>
<td>25.4</td>
<td>21.8</td>
<td>0.107</td>
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</table>

Primary combined endpoint at 7 years: RRR 6.4%; ARR 2.0%; NNT 50
MI at 7 years: ARR 1.7%; NNT 59
Ischemic stroke at 7 years: 0.7%; NNT 142

Primary Endpoint Over Time

![Image showing the primary endpoint over time graph.](image)

**High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;50%</td>
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<tr>
<td>Atorvastatin (80)-80 mg</td>
<td>Rosuvastatin (40)-10 mg</td>
<td>Simvastatin 10 mg</td>
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<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Pravastatin 40 (80) mg</td>
<td>Pravastatin 10 mg</td>
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<td>Lovastatin 40 mg</td>
<td>Fluvastatin 40 mg bid</td>
<td>Lovastatin 20 mg</td>
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<td>Pitavastatin 2-4 mg</td>
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<td>Fluvastatin XL 80 mg</td>
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</table>

Specific statins and doses are noted in bold that were evaluated in RCTs. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.

**Lilly’s CETP Inhibitor Evacetrapib Trial Stopped**

- **ACCELERATE**, conducted at 540 sites in 37 countries, had enrolled 12,095 patients with diabetes, a history of acute coronary syndrome, statin-resistant dyslipidemia, and other high-risk features. It was following them for the composite end point of CV death, MI, stroke, revascularization, or hospitalization for unstable angina. It had been scheduled to go on for another year.

- However, the trial’s data safety monitoring board recommended the trial be stopped based on a prespecified data review that “suggested there was a low probability the study would achieve its primary end point based on results to date,” according to Lilly.

  “The study is not being stopped for safety findings,” – Oct 12, 2015
**PCSK9 Loss-of-Function Mutations Resulted in Low LDL-C Levels and Reduced CHD Rates**

- **Black Subjects**
  - $P = .008$
  - Normal Subject: 9.7
  - Mutation Carrier: 1.2
  - $n = 3278$ (n = 85)

- **White Subjects**
  - $P = .005$
  - Normal Subject: 11.8
  - Mutation Carrier: 6.3
  - $n = 9228$ (n = 301)

- Wild-type PCSK9 degrades LDL receptors.
- Loss-of-function mutations increase hepatic LDLR expression, reducing LDL-C levels by 15%-40%.
- CHD was reduced 47%-87% in PCSK9 loss-of-function mutation carriers compared with normal individuals.

*References*


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**PCSK9 Regulates Surface LDLRs by Increasing Their Lysosomal Degradation**

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**Impact of PCSK9 Monoclonal Antibodies on LDL Receptor Surface Concentrations**
Alirocumab-Praluent by Sanofi/Regeneron

- July 24, 2015 the FDA approved alirocumab as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
- The effect of alirocumab on cardiovascular morbidity and mortality has not been determined.

Alirocumab-Praluent

- Alirocumab is a human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab is a PCSK9 inhibitor produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.
- Alirocumab is a human monoclonal antibody that binds to PCSK9 which binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.
Alirocumab-Praluent

- Supplied in single-dose pre-filled pens and single-dose pre-filled glass syringes. Each pre-filled pen or pre-filled syringe is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution. (available in cartons containing 1 or 2, pre-filled pens and 1 or 2, pre-filled syringes).
- Cost: $14,600.00/year

Alirocumab-Praluent

- The recommended starting dose of alirocumab is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.
- Measure LDL-C levels within 4 to 8 weeks of initiating or titrating alirocumab to assess response and adjust the dose, if needed. If a dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient’s original schedule.

Alirocumab-Praluent

- Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab at subcutaneous doses of 75 mg Q2W or 150 mg Q2W.
  - The median apparent half-life of alirocumab is reduced to 12 days when administered with a statin; however, this difference is not clinically meaningful and does not impact dosing recommendations.
### Alirocumab-Praluent

**Adverse reactions** led to discontinuation of treatment in 5.3% of patients treated with alirocumab and 5.1% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were allergic reactions (0.6% versus 0.2% for alirocumab and placebo, respectively) and elevated liver enzymes (0.3% versus < 0.1%).

**Allergic reactions** were reported more frequently in patients treated with alirocumab than in those treated with placebo (8.6% versus 7.8%). Serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported in patients using alirocumab.

**Local injection site reactions** including erythema/redness, itching, swelling, and pain/tenderness (7.2% versus 5.1% for alirocumab and placebo, respectively). Few patients discontinued treatment because of these reactions (0.2% versus 0.4%).

### Alirocumab-Praluent

**Low LDL-C Values**
- In a pool of both placebo- and active-controlled clinical trials, 796 alirocumab-treated patients had two consecutive calculated LDL-C values < 25 mg/dL, and 288 had two consecutive calculated LDL-C values < 15 mg/dL. Changes to background lipid-altering therapy (e.g., maximally tolerated statins) were not made in response to low LDL-C values, and alirocumab dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C are unknown.

### Alirocumab-Praluent

**Immunogenicity**
- As with all therapeutic proteins, there is a potential for immunogenicity with alirocumab. In a pool of ten placebo- and active-controlled trials, 4.8% of patients treated with alirocumab had anti-drug antibodies (ADA) newly detected after initiating treatment as compared with 0.6% of patients treated with control.
- Patients who developed ADA had a higher incidence of injection site reactions compared with patients who did not develop ADA (10.2% vs 5.9%).
- A total of 1.2% of patients treated with alirocumab developed neutralizing antibodies (NAb) on at least one occasion as compared with no patients treated with control, and 0.3% of patients both tested positive for NAb and exhibited transient or prolonged loss of efficacy. The long-term consequences of continuing treatment in the presence of persistent NAb are unknown.
**Alirocumab-Praluent**

- The efficacy of alirocumab was investigated in five double-blind placebo-controlled trials that enrolled 3499 patients; 36% were patients with heterozygous familial hypercholesterolemia (HeFH) and 54% were non-FH patients who had clinical atherosclerotic cardiovascular disease. Three of the five trials were conducted exclusively in patients with HeFH. All patients were receiving a maximally tolerated dose of a statin, with or without other lipid-modifying therapies.

**Alirocumab-Praluent**

- Study 1 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1553 patients to alirocumab 150 mg Q2W and 788 patients to placebo. All patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction.
  - The mean age was 61 years (range 18–89), 38% were women, 93% were Caucasian, 3% were Black, and 5% were Hispanic/Latino. Overall, 69% were non-FH patients with clinical atherosclerotic cardiovascular disease and 18% had HeFH. The average LDL-C at baseline was 122 mg/dL.
  - At 24 weeks the lipid levels alirocumab minus placebo were LDL-C -58%; TC -36%; Non HDL-C -50% and ApoB – 51%.

**Alirocumab-Praluent**

- Studies 3 and 4 were multicenter, double-blind, placebo-controlled trials that, combined, randomly assigned 490 patients to alirocumab and 245 to placebo. The trials were similar with regard to both design and eligibility criteria. All patients had HeFH, were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy, and required additional LDL-C reduction.
  - The mean age was 52 years (range 20–87), 45% were women, 94% were Caucasian, 1% were Black, and 3% were Hispanic/Latino. Overall, 45% of these patients with HeFH also had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 141 mg/dL.
Alirocumab-Praluent

- At week 12, the treatment difference between alirocumab 75 mg Q2W and placebo in mean LDL-C percent change was -48% (95% CI: -52%, -44%).
- At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, alirocumab was up-titrated to 150 mg Q2W for the remainder of the trials. At week 24, the mean treatment difference between alirocumab and placebo in mean LDL-C percent change from baseline was -54% (95% CI: -59%, -50%; p-value < 0.0001). The dose was up-titrated to 150 mg Q2W in 196 (42%) of 469 patients treated with alirocumab for at least 12 weeks. The LDL-C-lowering effect was sustained to week 52.

ODYSSEY-OUTCOMES Trial with Alirocumab-Praluent

- Sanofi/Regeneron have been asked by the FDA to study the potential for cognitive harm in long-term phase 3 trials, including ODYSSEY-OUTCOMES, their large-scale study of alirocumab in patients with acute coronary syndrome (ACS).
- In this study, which will include approximately 18,000 ACS patients, alirocumab will be compared with evidence-based medical therapy to determine whether alirocumab can further reduce the risk of cardiovascular events, including coronary heart disease death, MI, stroke, and coronary revascularization.

ODYSSEY Long Term Trial

- The, reported by Dr. Jennifer Robinson, University of Iowa, included 2,341 patients with hypercholesterolemia at very high risk, including patients with heterozygous FH (18%), who were on maximally tolerated statin therapy (44% on high-dose intensive statin therapy) with or without other lipid lowering treatment. Baseline LDL cholesterol was 122 mg/dL. All patients were randomized to double-blind treatment with alirocumab (150 mg every 2 weeks, n=1553) or placebo (n=788) every 2 weeks for up to 78 weeks. ESC Congress August 31, 2014
ODYSSEY Long Term Trial

• At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was −62 percentage points (P<0.001); the treatment effect remained consistent over a period of 78 weeks.

ODYSSEY Long Term Trial

• The alirocumab group, as compared with the placebo group, at 78 weeks had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%).
  – This could delay any FDA action as they may require completed trials to evaluate neurocognitive effects?

ODYSSEY Long Term Trial

• In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) at 78 weeks was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).
Evolocumab – Repatha by Amgen

- FDA approved 8-27-2015 a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and: for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
- Patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C when other LDL-C lowering therapies are not adequate (e.g., statins, ezetimibe, LDL apheresis).

Evolocumab – Repatha

- The effect of evolocumab on cardiovascular morbidity and mortality has not been determined.
- Available as:
  - Injection: 140 mg/mL in a single-use prefilled syringe
  - Injection: 140 mg/mL in a single-use prefilled SureClick ® autoinjector
  - Cost: $542.31/140 mg dose WAC or about $14,100.00/year for the every other week dosage.
  - (The company is planning on marketing a 420 mg syringe early next year but until then they say they will work with insurers to assure better pricing on the 3 x 140 mg once monthly dosage)
- Storage:
  - Keep in the refrigerator. Prior to use, allow to warm to room temperature for at least 30 minutes. Alternatively, for patients and caregivers, the drug can be kept at room temperature (up to 25°C [77°F]) in the original carton. However, under these conditions, the medication must be used within 30 days.

Evolocumab – Repatha

- Administer by subcutaneous injection
- Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH:
  - 140 mg every 2 weeks or 420 mg* once monthly in abdomen, thigh, or upper arm
- HoFH:
  - 420 mg* once monthly
  - *To administer 420 mg, give 3 x 140 mg injections consecutively within 30 minutes
Evolocumab – Repatha

• Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin kexin 9 (PCSK9).
• Evolocumab is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Evolocumab – Repatha

• Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.
• Evolocumab is estimated to have an effective half-life of 11 to 17 days.

Evolocumab – Repatha

• Potential Drug Interactions:
  – An approximately 20% decrease in the Cmax and AUC of evolocumab was observed in patients co-administered with a high-intensity statin regimen.
  – This difference is not clinically meaningful and does not impact dosing recommendations.
Familial Hypercholesterolemia

• HeFH is most commonly due to loss-of-function mutations in the LDL receptor gene.
• Current treatments (statins, ezetimibe, bile acid sequestrants, niacin) yield reductions in LDL-C of 50-65% in HeFH patients. However, many patients are still unable to achieve recommended LDL-C targets.

Evolocumab – Repatha

• Data in patients with heterozygous familial hypercholesterolemia (HeFH):
• A multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 329 patients with heterozygous familial hypercholesterolemia (HeFH) on statins with or without other lipid-lowering therapies. Patients were randomized to receive subcutaneous injections of evolocumab 140 mg every two weeks, 420 mg once monthly, or placebo.
  – HeFH was diagnosed by the Simon Broome criteria

Evolocumab – Repatha

• Characteristics of the HeFH patients included:
  – 38% of patients had clinical atherosclerotic cardiovascular disease. The mean age at baseline was 51 years (range, 19 to 79 years), 15% of the patients were ≥65 years old, 42% were women, 90% were White, 5% were Asian, and 1% were Black. The average LDL-C at baseline was 156 mg/dL with 76% of the patients on high-intensity statin therapy. 
Evolocumab – Repatha

• Results after 12 weeks:
  – In these patients with HeFH on statins with or without other lipid lowering therapies, the differences between evolocumab and placebo in mean percent change in LDL-C from baseline to Week 12 was -61% (95%CI: -67%, -55%; p < 0.0001) and -60% (95%CI: -68%, -52%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively.

Evolocumab – Repatha

• Data in patients with homozygous familial hypercholesterolemia (HoFH):
  • A multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with homozygous familial hypercholesterolemia (HoFH). In this trial, 33 patients received subcutaneous injections of 420 mg of evolocumab once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe).

Evolocumab – Repatha

• Characteristics of the HoFH patients included:
  – The mean age at baseline was 31 years, 49% were women, 90% White, 4% were Asian, and 6% other. The trial included 10 adolescents (ages 13 to 17 years), 7 of whom received evolocumab. The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents.
Evolocumab – Repatha

• Results after 12 weeks:
• In these patients with HoFH, the difference between evolocumab and placebo in mean percent change in LDL-C from baseline to Week 12 was -31% (95%CI: -44%, -18%; p < 0.0001).
• Patients known to have two LDL-receptor negative alleles (little to no residual function) did not respond to evolocumab.

Evolocumab – Repatha

• Patients with CVD who were unable to get to goal LDL-C on high intensity statin with or without ezetimibe:
• A multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 139 patients with atherosclerotic CVD who received protocol-determined background lipid-lowering therapy of atorvastatin 80 mg daily with or without ezetimibe 10 mg daily. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or evolocumab 420 mg administered subcutaneously once monthly.

Evolocumab – Repatha

• Characteristics of these high risk CVD patients:
  – The mean age at baseline was 59 years (range, 35 to 75 years), 25% were ≥ 65 years, 40% were women, 80% were White, 3% were Black, 5% were Asian, and < 1% were Hispanic or Latino. After stabilization on the assigned background therapy, the mean baseline LDL-C was 105 mg/dL.
Evolocumab – Repatha

- Results after 52 weeks of evolocumab added to baseline high intensity atorvastatin 80 mg with or without ezetimibe:
- In these high risk patients with CVD the difference between evolocumab 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -54% (95% CI: -65%, -42%; p <0.0001). Apo B levels were reduced by 40% (95% CI: -50%, -30%).

Evolocumab – Repatha

- In the 52 week trial adverse reactions led to discontinuation of treatment in 2.2% of evolocumab-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to evolocumab treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for evolocumab and placebo, respectively).

Evolocumab – Repatha

OSLER 1 & 2 Trials

- Amgen in two open-label, randomized trials, enrolled 4465 patients who had completed 1 of 12 phase 2 or 3 studies of evolocumab. Regardless of study-group assignments in the parent trials, eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 months with assessment of lipid levels, safety, and (as a prespecified exploratory analysis) adjudicated cardiovascular events including death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. Data from the two trials were combined.
Evolocumab – Repatha
OSLER 1 & 2 Trials

- Evolocumab reduced the level of LDL cholesterol by 61%, from a median of 120 mg per deciliter to 48 mg per deciliter (P<0.001). Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL cholesterol.

Evolocumab – Repatha
OSLER 1 & 2 Trials

- The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; P=0.003).

Evolocumab – Repatha

- Injection site reactions occurred in 3.2% and 3.0% of evolocumab-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising.
- In placebo-controlled trials, neurocognitive events were reported in less than or equal to 0.2% in evolocumab-treated and placebo-treated patients.
- Low LDL-C Levels: In a pool of placebo-and active-controlled trials, as well as open-label extension studies that followed them, a total of 1609 patients treated with evolocumab had at least one LDL-C value < 25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and evolocumab dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not seen in the trials we do not know for sure if this is associated with any adverse effects.
Evolocumab – Repatha

• Immunogenicity: There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of evolocumab, but the long-term consequences of continuing evolocumab treatment in the presence of anti-drug binding antibodies are unknown.

Flibanserin – Addyi by Sprout/Valeant

• August 18, 2015 Flibanserin (Addyi) was FDA approved for: Treatment of hypoactive sexual desire disorder in premenopausal women (HSDD)
  Dosing regimen: 100 mg tablet orally once daily at bedtime
  – administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (such as somnolence and sedation).
  – Discontinue flibanserin after 8 weeks if the patient does not report an improvement in her symptoms.

Sprout sold to Valeant for $1 billion

Flibanserin - Addyi

• June 4, 2015 the FDA Advisory Committees: Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee voted 18 to 6 to recommend FDA approval for the treatment of hypoactive sexual desire disorder in premenopausal women.
• Several committee members said they voted “yes” with great misgivings because of the drug’s modest benefit and possible side effects. “The unmet need seems to be so strong that even for a drug with rather modest benefit, I think approving the product with strong limitations seems to be the right step at this point,”
Flibanserin - Addyi

- Flibanserin is a new molecular entity that is an agonist at the 5 hydroxytryptamine (5HT) type 1A receptor and an antagonist at the 5HT type 2A receptor. Flibanserin is not approved in any country.
- First evaluated for the treatment of MDD based upon effects on 5HT but it was not found to be effective and the research switched to HSDD.

Flibanserin - Addyi

- Hypoactive sexual desire disorder (HSDD) is defined in the DSM IV as “Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician taking into account factors that affect sexual functioning, such as age and the context of the person’s life.”
  - Occurs in about 7% of premenopausal females.
  - The disturbance causes marked distress and interpersonal difficulty.
  - The sexual dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Flibanserin - Addyi

- This is the 3rd time the FDA has reviewed the NDA for this agent. The first two reviews failed to show sufficient efficacy and safety which resulted in additional data being required.
  - After the first review Boehringer Ingelheim transferred the NDA to Sprout Pharmaceuticals.
  - The results of the three efficacy trials are summarized in the next slide.
Flibanserin - Addyi

• The Applicant and the FDA agree that statistically significant differences between flibanserin and placebo have been demonstrated in three phase 3 trials for Satisfying Sexual Events (SSEs) a 3 question patient diary, sexual desire measured by the Female Sexual Function Index (FSFI) a 19 question 0-5 scale, and the Female Sexual Distress Scale-Revised (FSDS-R) a 13 question 0-4 scale. The findings are consistent across the three phase 3 trials, demonstrating a pharmacologic effect of flibanserin in the patients studied.

Flibanserin - Addyi

• The results are summarized below:
  • From a median baseline of about 2-3 SSEs per month, flibanserin resulted in a median placebo-corrected increase of about 0.5-1.0 SSEs per month.
  • From a mean baseline of about 1.8-1.9 on the FSFI desire score, flibanserin resulted in a placebo-corrected mean increase of 0.3-0.4 (the FSFI desire score range is 1.2-6.0).
  • From a mean baseline of 3.2-3.4 on the distress score, flibanserin resulted in a placebo corrected mean improvement of 0.3-0.4 (on a scale of 0-4).

Flibanserin - Addyi

• Across all endpoints, more flibanserin-treated patients are classified as responders compared to placebo-treated patients. The absolute difference in the percentage of responders with flibanserin and the percentage of responders with placebo is about 9-15%. Placebo response rates are high, ranging from 29%-49%.
• It appears that there may be limited efficacy by Week 4 of treatment and that it may take up to 8-16 weeks (not all the endpoints were assessed at Week 12) until the treatment effect plateaus.
• The fundamental question is whether these observed placebo-corrected treatment effects outweigh the risks associated with treatment.
Flibanserin - Addyi

Clinical safety concerns identified in the September 27, 2013, CR letter:

• Flibanserin causes central nervous system depression (e.g., fatigue, somnolence, and sedation) which is more pronounced in settings where flibanserin exposure is increased and when flibanserin is administered during the daytime rather than at bedtime. In addition, the long half-life of flibanserin (~12 hours) raises concern for residual next-day impairment even if flibanserin is dosed at bedtime.

• Concomitant administration of centrally-acting medications (e.g., serotonin norepinephrine reuptake inhibitors, alcohol, triptans) may adversely affect flibanserin tolerability.

• Concerns regarding the additive sedative and hypotensive effects of concomitant use of alcohol.

• Co-administration of flibanserin with drugs that are strong or moderate CYP3A4 inhibitors leads to a significant increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension, which may be severe, compared to flibanserin used alone.

• Central nervous system (CNS) adverse effects such as dizziness and fatigue appear to be more pronounced when flibanserin is administered with hormonal contraceptives (which are mild CYP3A4 inhibitors). This interaction may compromise the safety of flibanserin in young women, many of whom will likely be chronic users of hormonal contraceptives.

• Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events.

• A greater incidence of appendicitis among flibanserin users compared to placebo may represent a class effect of drugs with 5HT2A antagonism.

• It is unclear whether the increased incidence of mouse mammary tumors observed at flibanserin exposures approximately 4 and 13 times higher than those of women taking the recommended dose represents a clinical risk of breast cancer. The absence of a mammary tumor signal in rats does not completely exclude human risk.

Flibanserin - Addyi

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo (%) N=1905</th>
<th>Flibanserin 100 mg (%) N=1543</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Sedation</td>
<td>0.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Somnolence or sedation or fatigue (CNS depression)</td>
<td>7.9</td>
<td>20.6</td>
</tr>
</tbody>
</table>
Flibanserin - Addyi

• WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS
  ‒ Contraindicated with Alcohol The use of ADDYI and alcohol increases the risk of severe hypotension and syncope. Therefore, alcohol use is contraindicated in patients taking ADDYI. Before prescribing ADDYI, assess the likelihood of the patient abstaining from alcohol, taking into account the patient’s current and past drinking behavior, and other pertinent social and medical history. Counsel patients who are prescribed ADDYI about the importance of abstaining from alcohol use. Because of the increased risk of hypotension and syncope due to an interaction with alcohol, ADDYI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADDYI REMS Program.
  ‒ Contraindicated with Strong or Moderate CYP3A4 Inhibitors The concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore, the use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking ADDYI.
  ‒ Contraindicated in Patients with Hepatic Impairment The use of ADDYI in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope.

Flibanserin - Addyi

• ADDYI REMS Program ADDYI is available only through a restricted program under a REMS called the ADDYI REMS Program, because of the increased risk of severe hypotension and syncope due to an interaction between ADDYI and alcohol. Notable requirements of the ADDYI REMS Program include the following:
  ‒ Prescribers must be certified with the program by enrolling and completing training.
  ‒ Pharmacies must be certified with the program and must only dispense to patients pursuant to a prescription from a certified prescriber.

Flibanserin - Addyi

Drug Interactions:
  • Strong CYP3A4 inhibitors (e.g., ketoconazole) increase systemic exposure to flibanserin over 4-fold, and the combination of flibanserin with strong CYP3A4 inhibitors is poorly tolerated.
  • Fluconazole, which is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor, increases systemic exposure to flibanserin 7-fold. The combination of flibanserin with fluconazole is associated with an increased risk of syncope and hypotension which may result in serious injuries.
  • Adverse events exacerbated by concomitant use of flibanserin with an SS/NRI were anxiety, somnolence, fatigue, insomnia, and dizziness.
**Flibanserin - Addyi**

- In the phase 1 DDI study, alcohol, consumed over 10 minutes and combined with flibanserin, increased the incidence of somnolence, orthostatic hypotension and syncope.
  - The Applicant's proposed draft label includes a warning regarding the risks of CNS depression, hypotension and syncope associated with co-administration of flibanserin with alcohol.
- The incidences of somnolence, dizziness and fatigue were greater among flibanserin treated patients who were on HCs than those who were not. Concurrent use appears to increase flibanserin levels by ~40% and the applicant proposed label indicates an increased risk of these side effects.

**Ticagrelor – Brilinta by AZ**

- Updated Indication 9/2015 Ticagrelor is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel.
- Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS.
- Administer 90 mg twice daily during the first year after an ACS event. **After one year administer 60 mg twice daily (New Dosage)**

**Ticagrelor – Brilinta**

- PLATO was a randomized double-blind study comparing ticagrelor 180 mg LD and 90 mg BID (N=9333) to clopidogrel 300 mg LD and 75-100 mg/day (N=9291), both given in combination with aspirin and other standard therapy for 6-12 months, in patients with acute coronary syndromes (ACS), who presented within 24 hours of onset of the most recent episode of chest pain or symptoms.
Ticagrelor – Brilinta

Endpoint | Ticagrelor N=9333 | Clopidogrel N=9291 | Hazard Ratio (95% CI) | P-value | ARR/NNT
--- | --- | --- | --- | --- | ---
Primary Composite (CV death, MI, CVA) | 9.8% | 11.7% | 0.84 (0.77-0.92) | 0.0013 | 1.9%/53
Secondary Endpoints
CV death | 4.0% | 5.1% | 0.79 (0.69-0.91) | 0.0011 | 1.1%/53
MI | 5.8% | 6.9% | 0.84 (0.75-0.95) | 0.0045 | 1.1%/91
Stroke | 1.5% | 1.3% | 1.37 (0.91-2.52) | 0.22 | 
All cause mortality | 4.5% | 5.9% | 0.78 (0.59-0.99) | 0.0003 | 1.4%/72
In-stent thrombosis (11,289 pts with PCI/stenting) | 1.3% | 1.9% | 0.67 (0.50-0.91) | 0.0091 | 0.6%/167

PEGASUS-TIMI 54 Trial
• PEGASUS: Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
  — 21,162 patients randomized at 1161 sites in 31 countries
  — Stable pts with history of MI 1-3 yrs prior (median 1.7 yrs) + 21 additional atherothrombosis risk factor (53% history of STEMI, 41% NSTEMI and 6% unknown)
  — Planned treatment with ASA 75 – 150 mg/d & Standard background care (97.3% on 75-100 mg ASA; 93% on a statin; 82% on a BB and 80% on an ACEI/ARB)
  — Randomized to either ticagrelor 90 mg BID or 60 mg BID or to placebo all added to low dose aspirin and followed for median of 33 months.

PEGASUS-TIMI 54

<table>
<thead>
<tr>
<th>Outcome @ 3 years</th>
<th>T90</th>
<th>T60</th>
<th>P</th>
<th>HR T90/P</th>
<th>HR T60/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Death, MI, or Stroke</td>
<td>7.0</td>
<td>7.1</td>
<td>0.82</td>
<td>0.82 P=0.002</td>
<td>0.83 P=0.003</td>
</tr>
<tr>
<td>Coronary Death or MI</td>
<td>5.6</td>
<td>5.8</td>
<td>0.81</td>
<td>0.81 P=0.004</td>
<td>0.84 P=0.01</td>
</tr>
<tr>
<td>Coronary Death</td>
<td>1.5</td>
<td>1.7</td>
<td>0.73</td>
<td>0.73 P=0.02</td>
<td>0.80 P=0.09</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>5.2</td>
<td>4.7</td>
<td>1.00</td>
<td>1.00 P=0.99</td>
<td>0.89 P=0.14</td>
</tr>
</tbody>
</table>

For Coronary Death, MI, or Stroke:
T90/P ARR = 1.3%, NNT = 77
T60/P ARR = 1.2%, NNT = 83

Key:
• Ticagrelor 90 mg bid (N=7250) = T90
• Ticagrelor 60 mg bid (N=7045) = T60
• Placebo (N=7053) = P
• Ticagrelor 90 vs Placebo = T90/P
• Ticagrelor 60 vs Placebo = T60/P
PEGASUS-TIMI 54

Major TIMI Bleeding*
- Ticagrelor 90 mg BID/ASA = 2.6% (ARI 1.5%, NNH = 67)
  - HR vs. placebo/ASA = 2.69 (1.96–3.70) p<0.0001
- Ticagrelor 60 mg BID/ASA = 2.3% (ARI 1.2%, NNH = 83)
  - HR vs. placebo/ASA = 2.32 (1.68–3.21) p<0.0001
- Placebo/ASA BID = 1.1%
  - *Major TIMI Bleeding:
    - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
    - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit
    - Fatal bleeding (bleeding that directly results in death within 7 d)

PEGASUS-TIMI 54

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>T90</th>
<th>T60</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea AE</td>
<td>18.9%</td>
<td>15.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>(ARI = 12.5%, NNH = 8 T90/P and ARI = 9.4%, NNH = 11 T60/P)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leading to study drug d/c</td>
<td>6.5%</td>
<td>4.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>(ARI = 5.7%, NNH = 18 T90/P and ARI = 3.8%, NNH = 27 T60/P)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1.2%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001 for both doses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oxycodone – Oxaydo by Egalet

- OXAYDO™—the first and only immediate-release oxycodone that discourages intranasal abuse—has no generic equivalent.
  - Available in 5 and 7.5 mg tablets
- Formulated with an inactive ingredient that may cause nasal burning and throat irritation when snorted. Contains sodium lauryl sulfate, which is found in soap, shampoo, and other personal hygiene products.
- Dosing: Recommended starting dose for opioid-naive patients is 5 mg-15 mg every 4 to 6 hours.
  - OXAYDO must be swallowed whole.
  - Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.
  - OXAYDO is not amenable to crushing and dissolution. Do not administer OXAYDO via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.
Oxycodone – Oxaydo

• Six times more recreational users reported they would not take OXAYDO again (30% of subjects exposed to OXAYDO responded that they would not take the drug again compared to 5% of subjects exposed to immediate-release oxycodone).
  
  “The clinical significance of the difference in drug liking and difference in response to taking the drug again reported in this study has not yet been established. There is no evidence that OXAYDO has reduced abuse liability compared to immediate-release oxycodone.”