

ADVANCES IN PHARMACOTHERAPY

NEW THERAPEUTIC OPTIONS

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New Approvals 2007-2009

	2008	2009	2010
● New molecular entities	23	23	7
● New biologics	2	4	4
● Oral	10	13	5
● Injection	14	8	6
● Ophthalmic	1	2	
● Inhalation	0	0	
● Topical	1	0	
● Intranasal	0	0	

FDA Ratings New Molecular Entities

	2008	2009	2010
● P = Priority	7	8	3
● S = Standard	16	12	4
● BLA= Biologic	0	5	4

Dalfampridine (Ampyra)

- Increase walking distance in MS
- Potassium channel blocker
- Increases conduction of action potential
- 10 mg BID (12 hrs), SR take whole
- Do not make up the missed dose
- Avoid with seizure hx, CrCl < 50 ml/min/1.73m²

Dalfampridine

Adverse reaction	Dalfampridine	Placebo
UTI	12	8
Insomnia	9	4
Dizziness	7	4
Headache	7	4
Nausea	7	3
Asthenia	7	4
Back pain	5	2
Balance disorder	5	1

Dalfampridine

- 2 trials N = 540, MS 13 years, EDSS 6, must walk 25 feet in 8-45 sec
- 2-week placebo → 14-week double blind → 4-week placebo
- Responder analysis must walk faster on drug versus placebo on 3 of 4 visits
- 35 to 43% respond versus 8.3 to 9.3%

Dalfampridine

Percent Increase in Walking Speed	Dalfampridine	Placebo
≥ 0	83	65
≥ 10	55	33
≥ 20	34	13
≥ 30	17	4
≥ 40	7	3
≥ 50	2	1
≥ 60	1	1

Everolimus (Zortress)

- Prophylaxis of kidney graft rejection in adults with low-risk immunogenic factors
 - ABO blood type compatible
 - Anti-HLA Class I PRA , 20% or 50%
 - Negative T-cell cross match
- Blocks antigenic and IL-2, IL-15 activation and proliferation of T and B cells
- Used with basiliximab for induction and in combination with corticosteroids and reduced-dose cyclosporine

Everolimus

- Initiate dose at 0.75 mg twice daily
- Take whole every 12 hours with cyclosporine
- Adjust to trough concentrations of 3 to 8 ng/ml every 4 to 5 days
- Reduce dose by 50% in moderate hepatic impairment and by (?) with moderate 3A4 inhibitors
- May need dose adjustment with cyclosporine dose changes

Everolimus

- Do not use with strong 3A4 inhibitors or inducers
- Caution with P-g-P substrates
 - No grapefruit
- Everolimus inhibits 3A4 and 2D6

Everolimus

Warnings and Cautions

- Increased risk of infection, malignancy, and renal graft thrombosis
- Angioedema (ACEI), increased cholesterol and triglycerides, proteinuria, polyoma (BK virus) nephropathy, pneumonitis, diabetes, azospermia, oligospermia
- Do not use live vaccines
- Avoid prolonged sunlight, UV exposure

Everolimus

- ADRs > 20%: peripheral edema, HTN, constipation, nausea, anemia, UTI, hyperlipidemia

Adverse Rxn	Everolimus %	Mycophenolic Acid %
Serious ADR	57	52
Discontinuation	30	22
Infection	20	25
Peripheral edema	45	40
Hyperlipidemia	21	16
Stomatitis / Mouth Ulcer	8	3

Everolimus

Outcome	Everolimus %	Mycophenolic Acid %
Acute rejection	16.2	17
Graft loss	4.3	3.2
Death	2.5	2.2
Lost to follow-up	4.3	3.2

Estradiol valerate / Dienogest (EVD) (Natazia)

- Estrogen / Progestin oral contraceptive
- Decreases ovulation, alters mucus viscosity, inhibits implantation
- Do not use 35 y.o. and smoker, risk of thromboembolic event, undiagnosed genital bleeding, hormone sensitive cancer, liver tumor/disease, pregnancy
- BMI > 30 kg/m² unknown

EVD

- Warnings and Cautions: stop 2 weeks before and 4 weeks after surgery, uncontrolled HTN, diabetes, hyperlipidemia, headache, abnormal uterine bleeding, 3A4 inducers
- ADR > 2%: HA (13%), uterine bleeding (8%), breast tenderness (6.6%), nausea / vomiting (6.5%), acne (3.9%), weight gain (2.8%)

EVD

- Take same time each day (within 12 hours)
- Take in order on blister pack
- Multiple starting recommendations

Color	Number of Tablets	Ingredients
Dark Yellow	2	3 mg EV
Medium Red	5	2 mg EV, 2 mg Dienogest
Light Yellow	17	2 mg EV, 3 mg Dienogest
Dark Red	2	1 mg EV
White	2	Inert

EVD

Outcome	Study 1	Study 2
Pearl Index	1.64	1.04
Failure Rate 1 year	0.016	0.010
Pregnancies	5/3,969	9/11,275

Liraglutide (Victoza)

- Type II diabetes
- Glucagon-Like Receptor-1 (GLP-1) agonist
- Not recommended as first-line therapy
- Thyroid C-cell tumors in rodents
- Contraindicated with hx of medullary thyroid cancer or multiple endocrine syndrome neoplasia syndrome type 2
- Pancreatitis 2.2 per 1000 patient years

Liraglutide

- Dose 0.6 mg daily (anytime) for one week then 1.2 mg daily, increase to 1.8 mg if needed
- Consider reducing sulfonylurea dose 50% to reduce hypoglycemia
- Discontinuation most frequently due to GI adverse effects

Liraglutide

Adverse Reaction	Liraglutide %	Glimepiride %
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
URI	9.5	5.6
Influenza	7.4	3.6
Anti-liraglutide antibodies	8.6	
Anti-GLP-1 antibodies	6.9	
Neutralizing antibodies	2.3	

Liraglutide

- Hypoglycemia 7.5 to 27%
- Highest with sulfonylurea
- Lower than sulfonylurea monotherapy
- Not greater than other non-sulfonylurea comparator agents

Liraglutide

- Multiple clinical trials: monotherapy, add on to metformin, glimepiride, metformin and glimepiride, metformin and rosiglitazone

Combined Trial Data	Change in A1C	Change in FPG	Weight Change
	(-) 0.8 – 1.5 %	(-) 15 – 44 mg/dl	(-) 1.6 – 2.8 kg (+) 0.2 – 0.3 with sulfonylurea

Denosumab (Prolia)

- RANK ligand inhibitor (Receptor Activator of Nuclear factor Kappa-B Ligand)
- Effects formation, function and survival of osteoclasts
- Postmenopausal women with osteoporosis and increased risk of fracture
 - History of fracture
 - Multiple risk factors
 - Failure or intolerance to other treatments

Denosumab

- 60 mg Q 6 months SC. Administered by healthcare professional only
- Patients must take 1000 mg Ca⁺⁺ and 400 IU daily
- Contraindications
 - Latex
 - Hypocalcaemia: nadir day 10, 0.4 to 1.7% below 8.5 mg/dl, greater with renal dysfunction

Denosumab

- Warnings and Cautions
 - Serious infection including skin, hypocalcaemia, dermatitis, rash, eczema, osteonecrosis, increased pancreatitis (?), malignancy (?)
- ADRs > 5%: back pain, extremity pain, hypercholesterolemia, musculoskeletal pain, cystitis
- Active Safety Surveillance Program
www.proliasafety.com

Denosumab

Treatment Outcome	Denosumab	Placebo
New Vertebral Fx	7.2%	2.3%
New Hip Fx	1.2%	0.7%
New Non-vertebral Fx	8.0%	6.5%

Denosumab

Absolute Change in Bone Mineral Density vs. Placebo	Percent
Spine	8.8
Hip	6.4
Femoral Neck	5.2

Cabazitaxel (Jevtana)

- Microtubular stabilizer
- Refractory metastatic, hormone refractory prostate cancer, previously treated with docetaxil, in combination with prednisone (10 mg daily)
- 25 mg/m² every 3 weeks in a one hour infusion
- Pretreat with antihistamine, corticosteroid, and H₂ antagonist

Cabazitaxel

- Dose adjust to 20 mg/m² for
 - Grade 3 neutropenia for more than 3 weeks despite GCSF
 - Febrile neutropenia
 - Grade 3 diarrhea despite drug therapy
- Grade 3-4 ADRs > 5%: neutropenia, leucopenia, anemia, febrile neutropenia, diarrhea, fatigue, asthenia
- Cannot use with hepatic impairment

Cabazitaxel

- ADRs and grade > 10%: hematuria, back pain, peripheral neuropathy, pyrexia, dyspnea, dysguesia, cough, arthralgia, alopecia, abdominal pain
- 18% discontinue do to an ADR
- 12% require a dose decrease
- 28% require a dose delay
- CBC weekly through first course then before each new course

Cabazitaxel

- Tumor progression by RECIST criteria or increased PSA, or new bony lesions

Outcome	Cabazitaxel	Mitoxantrone
Death	62%	74%
Median survival	15.1 mo (14.1-16.3)	12.7 mo (11.6-13.7)
HR	0.70 (0.59-0.83) p < 0.001	
Tumor response	14.4%	4.4%

Tocilizumab (Actemra)

- IL-6 receptor inhibitor both soluble and membrane bound
- Moderate to severely active RA in patients who failed at least one anti TNF agent
- Use with or without methotrexate
- Risk of serious infections; TB, fungal, bacterial, viral, opportunistic
- Cannot give live vaccines

Tocilizumab

- Dose 4 to 8 mg/kg every 4 weeks
- 60 min infusion, infusion reaction 7-8% (5% placebo)
- Do not start tx if ANC < 2000 mm², platelets < 100,000 mm² or ALT/AST x 1.5 ULN
- Hold dose and/or reduce dose for
 - Elevated LFTs
 - Neutropenia
 - Thrombocytopenia

Tocilizumab

Adverse Laboratory Changes	
ANC < 1000 mm ²	1.8 – 3.4%
Plt , 100,000 mm ²	1.3 – 1.7%
AST to 3 x ULN	22 – 41%
ALT to 3 x ULN	36 – 48%
ALT > 3 to 5 x ULN	1 – 5%
LDL-C increase	13 – 25 mg/dl
Anti-mab antibody (neutralizing)	2% (1%)

Tocilizumab New RA

Monotherapy	8 mg/kg %	MTX up to 20 mg per week %
ACR 20 at 24 weeks	70	53
ACR 50	44	34
ACR 70	28	15

Tocilizumab Failed Methotrexate

With MTX	Placebo %	4 mg/kg %	8 mg/kg %
ACR 20 at 24 weeks	27	48 - 51	56 - 59
ACR 50	11	25 - 32	32 - 44
ACR 70	2	11 - 12	13 - 22

Tocilizumab Failed Previous DMARD

With DMARD	Placebo %	8 mg/kg %
ACR 20 at 24 weeks	25	61
ACR 50	9	38
ACR 70	3	21

Tocilizumab Failed TNF

With Methotrexate	Placebo %	4 mg/kg %	8 mg/kg
ACR 20 at 24 weeks	10	20	50
ACR 50	4	17	29
ACR 70	1	5	12

Alglucosidase (Lumizyme)

- Pompe disease, acid alpha glucosidase (GAA) deficiency
- 8 years and older, non-infantile onset disease, without cardiac hypertrophy
- Intravenous infusion of 20 mg/kg every 2 weeks
- 4-hour infusion titrated to adverse infusion reactions

Alglucosidase

- ADRs > 5%: anaphylaxis, urticaria, diarrhea, vomiting, dyspnea, pruritis, rash/erythema, pharyngolaryngeal pain, neck pain, flushing, feeling hot, chest discomfort
- Acute cardio-respiratory failure
- Delayed infusion Rxn up to 48 hours: urticaria, dizziness, musculoskeletal pain, stiffness, weakness, pharyngolaryngeal pain

Alglucosidase

- Systemic immune complex-mediated skin and organ toxicity several weeks to three years
- Fever, ↑ESR, inflammatory arthropathy
- Anti-rH GAA antibodies
- Check antibodies every 3 months for 2 years then annually
- Up to 100% of patients have IgG antibodies by 3 months

Alglucosidase

Outcome	Baseline	End of Study
Forced Vital Capacity		
Alglucosidase	55%	56.2%
Placebo	55%	52.8%
6 min walk test		
Alglucosidase	330 meters	355 meters
Placebo	330 meters	327 meters

Alglucosidase

Infantile 0.6 to 6 months	Survival 18 months	Survival 36 months
Alglucosidase	57%	37%
Historic Control	2%	2%

Velaglucerase (VPRIV)

- Treatment of Type 1 Gaucher disease age 4 and older
- Replacement enzyme for glucocerebrosidase in genetic autosomal recessive condition
- Excessive build up of glucocerebroside in spleen, liver, bone marrow
- Anemia, thrombocytopenia, organomegaly

Velaglucerase Dose-ranging study

Baseline Values	Change from Baseline 45 U/kg	Change from Baseline 60 U/kg	Significant Change from Baseline	Significant Difference Between Doses
Hb 10.6 gm/dl	2.4	2.4	No	No
Plts 90 x 10 ⁹ /L	41	51	Yes	No
Liver volume (%/BW)	-0.3	-0.84	No	No
Spleen Volume (%/BW)	-1.9	-1.9	Yes	No

Velaglucerase

- Comparative study versus imiglucerase no difference in primary endpoint, increase in Hb 1.6 gm/dl vs. 1.5 gm/dl
- Transfer from imiglucerase to velaglucerase; Hb declined 0.3 gm/dl and platelets increased 12 x 10⁹/L
- Dose from 15 U/kg to 60 U/kg every other week by infusion

Velaglucerase

- Infusion reactions 51.9% mild occur in first 6 months and decline over time (headache, dizziness, hypo or hypertension, nausea, fatigue, pyrexia)

Velaglucerase

Adverse Reactions > 10%	
Pyrexia	22.2%
Headache	35%
Dizziness	27.2%
Abdominal pain	18.5%
Nausea	5.6%
Back Pain	16.7%
Joint Pain	14.8%
URI	31.5%
Increased aPTT	11.1%
Fatigue/asthenia	13%

Carglumic Acid (Carbaglu)

- Carbamoyl phosphate synthetase activator
- Acute and maintenance treatment of hyperammonemia in patients with a deficiency of hepatic N-acetylglutamate synthase
- Adults and children
- Acute: 100 to 250 mg/kg/day
- Maintenance 100 mg/kg/day

Carglumic Acid

- Dosed to ammonia levels
- 2 to 4 doses per day
- Each tablet dissolved in a minimum of 2.5 ml of water (only) and taken immediately
- Rinse container and drink again
- Not taken whole or crushed

Carglumic Acid

- Refrigerate until opened, then keep at room temperature
- Discard one month after opening
- ADRs greater than 13% and greater than placebo: infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, headache

Collagenase Clostridium Histolyticum (CCH) (Xiaflex)

- Enzymatic destruction of collagen and collagen containing tissues
- Adults with Dupuytren's contracture with a palpable cord
- Direct injection into cord for contracture of metacarpophalangeal or proximal interphalangeal
- Followed by extension procedure (3 x per cord, every 4 weeks)

CCH Adverse Reactions

- Swelling of hand 73%
- Ecchymosis 78%
- Contusion 70%
- Hemorrhage 38%
- Injection site reaction 35%
- Pain in extremity 35%
- Allergic Reaction 15%

CCH

Outcome	CCH	Placebo
Extension 0-5 degrees of normal	44-66 %	5-7%
Extension achieved with one injection	27-39%	1-5%
Median improvement in range of motion	35-36 degrees	4-8 degrees

Polidocanol (Ascelra)

- Contact sclerosing agent
- Uncomplicated spider (< 1 mm) and reticular (1 – 3 mm) varicose veins in lower extremities
- Followed by compression and walking for 15-20 minutes
- Compression stockings at all times for 2-7 days and daytime only for up to 3 weeks

Polidocanol

- Mild injection site reactions 3%
- Anaphylaxis has occurred
- Do not use if recent acute thromboembolic event

Questions?

