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Savella (Milnacipran)

1. Indications
   Management of Fibromyalgia

2. Warnings
   Increased risk of suicide up to age 24
   Not approved for pediatric patients

3. Dosage and Administration
   Improved tolerability with food
   Recommended dose: 100mg/day (50mg BID)
   Maximum dose: 200mg/day
   Initial titration:

Day 1:	12.5 mg
Day 2-3:	12.5 mg twice daily
Day 4-7:	25 mg twice daily
After Day 7:	50 mg twice daily

   do not abruptly discontinue

how supplied:	
12.5mg	#60
25mg	#60 & #180
50mg	#60 & #180
100mg	#60 & #180
4 week titration pack	

   Renal insufficiency
      Caution with moderate renal impairment
      If severe (creatine clearance of 5-29 ml/min) decrease dose by 50%
   Hepatic insufficiency: no dosage adjustment necessary
   MAOI- Discontinue 14 days before initiation of Savella, wait 5 days after stopping Savella to initiate MAOI

4. Contraindications
   Monoamine oxidase inhibitors
   Uncontrolled narrow- angle Glaucoma

5. Warnings and Precautions
   Suicide Risk
      Suicidal ideation: 0.5% placebo; 0%
      Savella 100mg/day; 1.3% Savella 200mg/day
   Serotonin Syndrome
      clinical: mental status: agitation, hallucinations, coma;
      autonomic instability: tachycardia, labile BP, hyperthermia;
      neuromuscular: hyperreflexia, incoordination;
      GI: nausea, vomiting, diarrhea
      Occurs potentially with any drugs elevating, serotonin levels
         i.e. triptans, tramadol, SSRIs, tryptophan
   Cardiovascular
      Use with caution in pre-existing hypertension or cardiac disease monitor BP/P before and after treatment
      - 12% increase risk of becoming hypertensive vs. placebo
      - 7% - >15 mm Hg increase in SBP
      - Increase pulse rate 7-8 beats/minute vs. placebo

Seizures

Use cautiously with Hx seizure
None reported in studies

Hepatotoxicity

Caution with Hx of substantial alcohol use or chronic liver disease
3-4% increase mild LFTs elevations (1-3x)
Rare severe liver injury with underlying liver diseases or polypharmacy

Hyponatremia

Rare cases
Cautious with elderly, concomitant diuretics

Abnormal Bleeding

Clinical ecchymosis, hematomas, epistaxis, petechiae, life threatening hemorrhages
Caution with other drugs that affect coagulation i.e. NSAIDs, aspirin

Activation of Mania

Cautious with Hx of mania

Hx Dysuria

1% incidence of dysuria
Cautious with BPH, prostatitis

6. Adverse Reactions
   - Nausea
     17% vs. placebo occurred early in course at treatment for 7-10 days and resolved spontaneously
   - Greater than or equal to 5% incidence and 2x placebo
     Constipation, hot flash, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, hypertension

7. Drug Interactions

Unlikely involved in clinically significant drug interactions due to minimal CYP450 related metabolism, and low binding to plasma proteins (13%)

Lithium- Increase serotonin syndrome
Epinephrine/Norepinephrine- Hypertension, arrhythmia
Serotonergic Drugs- Hypertension, coronary artery vasoconstriction
IV Digoxin- Hypotension, tachycardia
Clonidine- Inhibit its antihypertensive effect
Clomipramine- Euphoria, postural hypotension

8. Specific Populations

Pregnancy- Category C; use only if potential benefits justify fetal risks
Neonatal Serotonin Syndrome
Not recommended while nursing
No known abuse potential
No fatal cases up to 1000mg acute ingestion

9. Clinical Pharmacology
    - Potent inhibitor of neuronal norepinephrine and serotonin reuptake; 3:1
    - No significant effect on other receptors
    - Excreted predominately unchanged in urine 55%
    - Elimination ½ life: 6-8 hours
    - Steady state levels: 36-48 hours
    - Maximum concentration (Cmax): 2-4 hours; not affected by food
    - Plasma protein binding : 13%
    - No dosage adjustment with age unless renal function is severely impaired
    - No significant effect on CYP450 hepatic system
        i.e. in-vivo studies; carbamazepine, clomipramine, digoxin, fluoxetine, lithium, lorazepam, warfarin

10. Clinical Studies

Two double-blind, placebo-controlled, multicenter studies in FM adults

Mease et al (N=888) 6 months

Clauw et al (N=1190) 3 months

A larger proportion of patients treated with Savella than with placebo experienced a simultaneous:

1. Reduction in pain from baseline of at least 30% (VAS)
2. Improved or very much improved on the patient global assessment (PGIC)
3. Greater than or equal to 6-point improvement from baseline in physical function as measured by the medical outcome study short form 36 (SF-36).

Primary Efficacy Endpoints

1. For treatment of FM, 3 measure composite Response (MCR) must be met
   i.e. VAS, PGIC, SF-36

2. For treatment of pain in FM, 2 MCR must be met
   i.e. VAS, PGIC

At 3 months, still on meds

Mease	Placebo/ 3 MCR	Placebo/2MCR
FM 5.6 yrs	17% / 33%	27% / 45%
Clauw		
FM 9.8 yrs	13% / 25%	25% / 42%