Stir-up

Tablets / Oral Drops

(Memantine Hydrochloride USP)

اسٹیر۔اپ

گولیاں / اورل ڈراپس

(میمنٹائین ھائیڈروکلورائیڈ)

COMPOSITION:

Each film coated tablet contains:
Memantine Hydrochloride USP … 10mg.
[USP Specs.]

Each g of solution contains:
Memantine Hydrochloride USP … 10mg
(20 Drops) [NQ's Specs.]

INDICATIONS: Stir-up (Memantine Hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRA-INDICATIONS: Hypersensitivity to the active substance or to any of the excipients.

PHARMACODYNAMICS: Mechanism of action: Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine Hydrochloride is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that Memantine Hydrochloride prevents or slows neurodegeneration in patients with Alzheimer's disease. Memantine Hydrochloride showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca2+, Na+ or K+ channels. Memantine Hydrochloride also showed antagonistic effects at the 5HT3 receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

PHARMACOKINETICS: Absorption: Following oral administration Memantine Hydrochloride is highly absorbed with peak concentrations reached in about 3-7 hours. Memantine Hydrochloride has linear pharmacokinetics over the therapeutic dose range. Food has no effect on the absorption of Memantine Hydrochloride.
Distribution: The mean volume of distribution of Memantine Hydrochloride is 9-11L/kg and the plasma protein binding is low (45%).
Metabolism: Memantine Hydrochloride undergoes partial hepatic metabolism. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of Memantine.
Elimination: Memantine Hydrochloride is excreted predominantly (about 48%) unchanged in urine and has a terminal elimination half- life of about 60-80 hours. The remainder is converted primarily to three polar metabolites which possess minimal NMDA receptor antagonistic activity: the N-glucuronide conjugate, 6-hydroxy memantine, and 1-nitrosodeaminated Memantine. A total of 74% of the administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

DOSAGE AND ADMINISTRATION:
STIR-UP TABLETS: The recommended starting dose of **Stir-up** is 5mg once daily. The dose should be increased in 5mg increments to 10mg/day (5mg twice daily), 15mg/day (5mg and 10mg as separate doses), and 20mg/day (10mg twice daily). The minimum recommended interval between dose increases is one week.

STIR-UP ORAL DROPS: Adults: The recommended starting dose of Memantine Hydrochloride is 5mg once daily and the maximum daily dose is 20mg once daily. In order to reduce the risk of undesirable effects, the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:
Week 1 (day 1-7): The patient should take 0.5ml solution (5mg) per day for 7 days.
Week 2 (day 8-14): The patient should take 1ml solution (10mg) per day for 7 days.
Week 3 (day 15-21): The patient should take 1.5ml solution (15mg) per day for 7 days.
From Week 4 on: The patient should take 2ml solution (20mg) once a day
Maintenance dose: The recommended maintenance dose is 20mg per day.
Elderly: The recommended dose for patients over the age of 65 years is 20mg per day (2ml solution), as described above.
Children and adolescents: Memantine Hydrochloride Oral Drops Solution is not recommended for use in children below 18 years.
Renal Impairment: A target dose of 5mg twice daily is recommended in patients with severe renal impairment (creatinine clearance of 5-29ml/min based on the Cockroft-Gault equation).
Hepatic Impairment: Stir-up should be administered with caution to patients with severe hepatic impairment.
Method of Administration: Stir-up can be taken with or without food. If a patient misses a single dose of **Stir-up**, that patient should not double up on the next dose.

INSTRUCTIONS FOR USE:
Each 0.5ml on the syringe mark = 5mg of Memantine Hydrochloride
Each one ml on the syring mark = 10mg of Memantine Hydrochloride
- Open the bottle: press the cap and turn it anticlockwise (Figure 1).
- Insert the syringe adaptor into the bottle neck (Figure 2).
- Take the syringe and put it in the adaptor opening (Figure 3).
- Turn the bottle upside down (Figure 4).
- Fill the syringe with a small amount of solution by pulling the piston down (Figure 4A). Then push the piston upward in order to remove any possible bubbles (Figure 4B). Finally, pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor. The top flat edge of the piston should be in line with the graduation mark you are measuring to (Figure 4C).
- Turn the bottle the right way up (Figure 5A).
- Remove the syringe from the adaptor (Figure 5B).
- Put the end of the syringe into your mouth and push the piston slowly back in to take the medicine. Alternatively, dispense the solution onto a spoon or into a small glass of water and take your medicine straight away.

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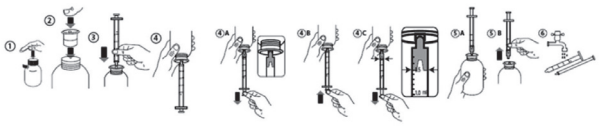
- Wash the syringe with water and let it dry before you use it again (Figure 6).
- Close the bottle with the plastic screw cap - leave the syringe adaptor in the bottle.



Week	Measured Amount on Syringe	Amount of Memantine
1	0.5ml/0.5g	5mg
2	1ml/1g	10mg
3	1.5ml/1.5g	15mg
4 Onwards	2ml/2g	20mg

SIDEEFFECTS: In general, the observed side effects are mild to moderate. **Common:** Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity **Uncommon:** Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

FERTILITY, PREGNANCY AND LACTATION:
Pregnancy: Pregnancy Category B; Memantine Hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether Memantine Hydrochloride is excreted in human breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking Memantine Hydrochloride should not breast-feed. **Fertility:** No adverse reactions of Memantine Hydrochloride were noted on male and female fertility.

OVERDOSAGE: Signs and symptoms most, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of Memantine Hydrochloride worldwide was 2.0g in a patient who took Memantine Hydrochloride in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered. Fatal outcome has been very rarely reported with Memantine Hydrochloride, and the relationship to Memantine Hydrochloride was unclear. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of Memantine Hydrochloride can be enhanced by acidification of urine.

WARNING & PRECAUTION: • Conditions that raise urine pH may decrease the urinary elimination of Memantine Hydrochloride resulting in increased plasma levels of Memantine Hydrochloride. • Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy. • Patients with conditions like myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension should be closely supervised.

INTERACTION: • The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of Memantine Hydrochloride with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dose adjustment may be necessary. • Concomitant use of Memantine Hydrochloride with amantadine or ketamine and dextromethorphan, or phenytoin should be avoided, owing to the risk of pharmacotoxic psychosis. • Other active substances such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with Memantine Hydrochloride leading to a potential risk of increased plasma levels. • There may be a possibility of reduced serum level of hydrochlorothiazide (HCT) when Memantine Hydrochloride is co-administered with HCT or any combination with HCT. • Isolated cases with international normalized ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants. • Memantine Hydrochloride did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin containing monooxygenase, epoxide hydrolase or sulphation.
Drugs that make the Urine Alkaline: The clearance of Memantine Hydrochloride was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, Memantine Hydrochloride should be used with caution under these conditions.
Use with Other N-methyl-D-aspartate (NMDA) Antagonists: The combined use of Memantine Hydrochloride with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

INSTRUCTIONS: Store below 30°C. Protect from heat and light. Keep out of the reach of children.

PRESENTATION: Stir-up 10mg tablets are available in Alu Alu blister pack of 10'sx2. **Stir-up 10mg/g Oral Drops** is available in pack size of 20g.

Manufactured by:
NABIQASIM INDUSTRIES (PVT.) LTD.
17/24, Korangi Industrial Area,
Karachi-Pakistan.
PHARMA

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

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