Reminyl™

NAME OF THE MEDICINAL PRODUCT
REMINYL (galantamine hydrobromide) Tablets and Oral Solution

QUALITATIVE AND QUANTITATIVE COMPOSITION
REMINYL tablets contain galantamine hydrobromide, equivalent to respectively 4, 8 and 12 mg galantamine base.
REMINYL oral solution contains galantamine hydrobromide, equivalent to 4 mg/ml galantamine base.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Film-Coated Tablets for Oral Use
- 4 mg galantamine as off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;
- 8 mg galantamine as pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;
- 12 mg galantamine as orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.

Oral Solution 4 mg/ml
Clear, colourless solution.

CLINICAL PARTICULARS
Therapeutic Indications
REMINYL is indicated for the treatment of mild to moderately severe dementia of the Alzheimer type.
Posology and Method of Administration
Adults
REMINYL should be administered twice a day, preferably with morning and evening meals. Ensure adequate fluid intake during treatment.
Starting Dose
The recommended starting dose is 8 mg/day (4 mg twice a day) for 4 weeks.
Maintenance Dose
- The initial maintenance dose is 16 mg/day (8 mg twice a day) and patients should be maintained on 16 mg/day for at least 4 weeks.
- An increase to the maximum recommended maintenance dose of 24 mg/day (12 mg twice a day) should be considered after appropriate assessment including evaluation of clinical benefit and tolerability.
- There is no rebound effect after abrupt discontinuation of treatment (e.g. in preparation for surgery).

Children
Use of REMINYL in children is not recommended. No data on the use of REMINYL in pediatric patients are available.
Hepatic and Renal Impairment
Galantamine plasma levels may be increased in patients with moderate to severe hepatic or renal impairment. In patients with moderately impaired hepatic function, based on pharmacokinetic modeling, dosing could begin with 4 mg once daily, preferably taken in the morning for at least one week. Thereafter, patients should proceed with 4 mg b.i.d. for at least four weeks. In these patients, daily doses should not exceed 8 mg b.i.d.
In patients with severe hepatic impairment, the use of REMINYL is not recommended.
For patients with a creatinine clearance greater than 9 ml/min, no dosage adjustment is required.
In patients with severe renal impairment (creatinine clearance less than 9 ml/min), the use of REMINYL is not recommended since no data are available.
Concomitant Treatment
In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered (see: Interactions with Other Medicinal Products and Other Forms of Interaction).
Contraindications
REMINYL should not be administered to patients with a known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulations.
Special Warnings and Special Precautions for Use
REMINYL is indicated for patients with mild to moderately severe dementia of the Alzheimer's type. The benefit of REMINYL in patients with other types of dementia or other types of memory impairment has not been demonstrated.
Patients with Alzheimer's disease lose weight. Treatment with cholinesterase inhibitors, including galantamine, has been associated with weight loss in these patients. During therapy, patient's weight should be monitored.
As with other cholinomimetics, REMINYL should be given with caution in the following conditions:
Cardiovascular Conditions: because of their pharmacological action, cholinomimetics may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction disturbances or who use drugs that significantly reduce heart rate concomitantly, such as digoxin and beta-blockers. In clinical trials, use of REMINYL has been associated with syncope and rarely with severe bradycardia.
Gastrointestinal Conditions: patients at increased risk of developing peptic ulcers, e.g. those with a history of ulcer disease or those predisposed to these conditions, including those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS), should be monitored for symptoms. However, clinical studies with REMINYL showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. The use of REMINYL is not recommended in patients with gastrointestinal obstruction or recovering from gastrointestinal surgery.
Neurological Conditions: Although cholinomimetics are believed to have some potential to cause seizures, seizure activity may also be a manifestation of Alzheimer's disease.
Pulmonary Conditions: because of their cholinomimetic actions, cholinomimetics should be prescribed with care for patients with a history of severe asthma or obstructive pulmonary disease.
Genitourinary: the use of REMINYL is not recommended in patients with urinary outflow obstruction or recovering from bladder surgery.
Safety in Subjects With Mild Cognitive Impairment (MCI)
REMINYL is not indicated for individuals with mild cognitive impairment (MCI), i.e., those who demonstrate isolated memory impairment greater than expected for their age and education, but do not meet criteria for Alzheimer's disease.
Two, 2-year controlled trials in subjects with MCI did not meet dual primary efficacy outcomes. Although mortality in both treatment arms was low, more deaths were initially recorded in subjects randomized to galantamine than to placebo, but the incidence of serious adverse events was identical between treatment groups. The deaths were due to various causes that are not unexpected in an elderly population. When data retrieved from the large proportion of patients who discontinued prior to completion of the double-blind period was included, there was no evidence of an increasing risk of death in REMINYL-treated subjects over time. More subjects from the placebo than the galantamine group discontinued prior to death, which may account for the difference in mortality initially recorded.
The MCI study results are discrepant from those observed in studies of Alzheimer's disease. In pooled studies in Alzheimer's disease (n=4614), the mortality rate was numerically higher in the placebo than the REMINYL group.
Interactions With Other Medicinal Products and Other Forms of Interaction
Pharmacodynamic Interactions
Because of its mechanism of action, galantamine should not be given concomitantly with other cholinomimetics. Galantamine antagonises the effect of anticholinergic medication. As expected with cholinomimetics, a pharmacodynamic interaction is possible with drugs that significantly reduce the heart rate (e.g. digoxin and beta blockers).
Galantamine, as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.
Pharmacokinetic Interactions
Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine.
Inhibition of gastric acid secretion will not impair the absorption of galantamine.
Other Drugs Affecting the Metabolism of Galantamine
Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC only increased approximately 10%. Population PK analysis for patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline, fluoxetine, fluvoxamine, paroxetine and quinidine, known inhibitors of CYP2D6.
Therefore, during initiation of treatment with potent inhibitors of CYP2D6 or CYP3A4 patients may experience an increased incidence of cholinergic side effects, predominantly nausea and vomiting. Under these circumstances, based on tolerability, a reduction of the galantamine maintenance dose can be considered (see: Posology and Method of Administration).
Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, at a dose of 10 mg/daily for 2 days followed by 10 mg BID for 12 days had no effect on the pharmacokinetics of galantamine 16 mg/day at steady state.
Effect of Galantamine on the Metabolism of Other Drugs
Therapeutic doses of galantamine (12 mg b.i.d.) had no effect on the kinetics of digoxin and warfarin. Galantamine did not affect the increased prothrombin time induced by warfarin.
In vitro studies indicated that the inhibition potential of galantamine with respect to the major forms of human cytochrome P450 is very low.
Pregnancy and Lactation
Use During Pregnancy
Reproduction studies conducted in pregnant rats at doses up to 16 mg/kg (or about 25 times the human therapeutic dose) and in pregnant rabbits up to 40 mg/kg (or about 63 times the human therapeutic dose) did not show any evidence of a teratogenic potential. A non-significant increase in the incidence of minor skeletal abnormalities was noted at a dose of 16 mg/kg in rats.
No studies are available on the use of REMINYL in pregnant women. REMINYL should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Use During Lactation
It is not known whether REMINYL is excreted in human breast milk and there are no studies in lactating women. Therefore, women on REMINYL should not breast-feed.
Effects on Ability to Drive and Use Machines
Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, like other cholinomimetics, REMINYL may cause dizziness and somnolence, which could affect the ability to drive or use machines, especially during the first weeks after initiation of treatment.
Undesirable Effects
Clinical Trial Data
Double-Blind Data – Adverse Drug Reactions Reported at ≥1% Frequency
The safety of REMINYL was evaluated in 4457 subjects with mild to moderately severe dementia of the Alzheimer's type who participated in 7 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.
Adverse Drug Reactions (ADRs) reported by ≥1% of REMINYL-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of REMINYL-Treated Subjects in 7 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Reaction	REMINYL (n=2932) %	Placebo (n=1525) %
Metabolism and Nutrition Disorders		
Decreased appetite	5.2	1.4
Anorexia	3.8	1.0
Psychiatric Disorders		
Depression	4.2	2.9
Nervous System Disorders		
Dizziness	8.9	4.6
Headache	7.6	5.4
Tremor	2.0	0.8
Syncope	1.8	0.7
Lethargy	1.7	0.7
Somnolence	1.7	0.8
Cardiac Disorders		
Bradycardia	1.2	0.3
Gastrointestinal Disorders		
Nausea	25.0	7.6
Vomiting	12.8	3.1
Diarrhea	9.0	6.3
Abdominal pain	2.4	0.9
Abdominal pain upper	2.0	1.4
Dyspepsia	1.8	1.3
Stomach discomfort	1.6	0.6
Abdominal discomfort	1.0	0.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	1.2	0.7
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	1.5	0.8
General Disorders and Administration Site Conditions		
Fatigue	4.0	2.2
Asthenia	2.3	1.7
Malaise	1.4	0.7
Investigations		
Weight decreased	5.1	1.4

In a randomized, double-blind, placebo-controlled clinical trial, the safety profile of once-daily treatment with REMINYL prolonged release capsules was similar in frequency and nature to that seen with tablets.
Nausea and vomiting, the most frequent adverse drug reactions, occurred mainly during titration periods, lasted less than a week in most cases and the majority of patients had one episode. Prescription of antiemetics and ensuring adequate fluid intake may be useful in these instances.
Open-Label Data – Adverse Drug Reactions Reported at ≥1% Frequency
The safety of REMINYL was evaluated in 1454 subjects with mild to moderately severe dementia of the Alzheimer's type who participated in 5 open-label clinical trials. The information presented in this section was derived from pooled data.
Adverse Drug Reactions (ADRs) reported by ≥1% of REMINYL-treated subjects in these trials and not listed in Table 1 included Fall, which occurred at a rate of 6.5% in open-label trials.
Double Blind and Open-Label Data – Adverse Drug Reactions Reported at <1% Frequency
Additional ADRs that occurred in <1% of REMINYL-treated subjects in the double-blind and open-label clinical datasets are listed in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of REMINYL-Treated Subjects in Either Double-Blind or Open-Label Clinical Trials
Metabolism and Nutrition Disorders
Dehydration
Nervous System Disorders
Dysgeusia, Hypersomnia, Paresthesia
Eye Disorders
Vision blurred
Cardiac Disorders
Atrioventricular block first degree, Palpitations, Sinus bradycardia, Supraventricular extrasystoles
Vascular Disorders
Flushing, Hypotension
Gastrointestinal Disorders
Retching
Musculoskeletal and Connective Tissue Disorders
Muscular weakness

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates.
In Table 4, ADRs are presented by frequency category based on incidence in clinical trials, when known.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with REMINYL by Frequency Category Estimated from Spontaneous Reporting Rates
Psychiatric Disorders
Very rare – Hallucination, Hallucination visual, Hallucination auditory
Ear and Labyrinth Disorders
Very rare – Tinnitus
Vascular Disorders
Very *rare* - Hypertension
Hepatobiliary Disorders
Very rare - Hepatitis
Investigations
Very *rare* – Hepatic enzyme increased

Table 4. Adverse Drug Reactions Identified During Postmarketing Experience with REMINYL by Frequency Category Estimated from Clinical Trials
Psychiatric Disorders
Common – Hallucination
Uncommon - Hallucination visual, Hallucination auditory
Ear and Labyrinth Disorders
Uncommon – Tinnitus
Vascular disorders
Common - Hypertension
Hepatobiliary Disorders
Rare - Hepatitis
Investigations
Uncommon – Hepatic enzyme increased

Overdose
Symptoms
Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the signs of a cholinergic crisis may develop: severe nausea, vomiting, gastro-intestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, collapse and convulsions. Increasing muscle weakness together with tracheal hypersecretions and bronchospasm, may lead to vital airway compromise.
There have been post-marketing reports of Torsade de Pointes, QT prolongation, bradycardia, ventricular tachycardia and brief loss of consciousness in association with inadvertent overdoses of galantamine. In one case where the dose was known, eight 4 mg tablets (32 mg total) were ingested on a single day. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting) resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day of oral solution, inadvertently ingested 160 mg (40 mL) and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.
Treatment
As in any case of overdose, general supportive measures should be used. In severe cases, anticholinergics such as atropine can be used as a general antidote for cholinomimetics. An initial dose of 0.5 to 1.0 mg i.v. is recommended, with subsequent doses based on the clinical response.
Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control centre to determine the latest recommendations for the management of an overdose.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Galantamine, a tertiary alkaloid is a selective, competitive and reversible inhibitor of acetylcholinesterase. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. As a consequence, an increased activity in the cholinergic system associated with improved cognitive function can be achieved in patients with dementia of the Alzheimer type.
Clinical Studies
The dosages of REMINYL shown to be effective in controlled clinical trials in Alzheimer's disease were 16, 24 and 32 mg/day. Of these doses, 16 and 24 mg/day were determined to have the best benefit/risk relationship and are the recommended doses. Galantamine's efficacy has been studied using four specific outcome measures: the ADAS-cog (a performance based measure of cognition), the CIBIC-plus (a global assessment by an independent physician based on a clinical interview with the patient and caregiver), several measurements of the activities of daily living and the Neuropsychiatric Inventory (NPI, a scale that measures behavioural disturbances).
In clinical studies, performance of galantamine treated patients on the ADAS-Cog (see Figure) and CIBIC-plus was consistently statistically significantly better than that of patients who were on placebo. Patients who were treated for 6 months with galantamine had ADAS-cog scores that were significantly improved compared to their baseline scores. Compared to the untreated patients there was a substantial and sustained benefit in cognitive functioning. Galantamine treatment also significantly preserved the activities of daily living, such as dressing, hygiene, meal preparation. These were assessed using the Disability Assessment in Dementia (the DAD) and the Alzheimer's Disease Cooperative Study (ADCS)-ADL-Inventory, caregiver-rated assessments. Galantamine doses of 16 and 24 mg daily maintained the NPI score throughout the observation period whereas the score of the placebo patients clearly deteriorated, as a result of the emergence of behavioural disturbances.
See figure 1 and 2.
Long-term treatment (combination of 6 months double-blind followed by 6 months open treatment) suggested that patients' cognitive and functional performance was maintained for a full year.
Alzheimer's Disease With Cerebrovascular Disease (AD+CVD)
The efficacy and safety of galantamine in subjects with Alzheimer's disease and significant cerebrovascular disease (AD+CVD) was investigated in a double-blind, placebo-controlled study. There were 282 subjects, 48% of the total study population (N=592), who met criteria for AD+CVD. Although the clinical trial was not powered for subgroup analyses, galantamine-treated subjects experienced a statistically significant improvement, compared to placebo-treated subjects on both primary outcomes [(cognition: ADAS-cog/11 [p<0.001]; global clinical assessment: CIBIC-plus [p<0.001] and on a measure of activities of daily living (DAD [p=0.003]). Overall, the safety and tolerability of galantamine in subjects with AD+CVD was similar to that seen in previous studies of galantamine in Alzheimer's disease. The most frequently reported adverse event in subjects was nausea (19% of galantamine and 11% of placebo subjects). Other events, occurring in >5% of AD+CVD subjects and reported more frequently in the galantamine than the placebo group, were dizziness, vomiting, abdominal pain, diarrhea, and fatigue. The incidence of "cerebrovascular disorders" (e.g., stroke) was higher in the placebo group (placebo, 5/96 [5%] subjects; galantamine, 2/186 [1%] subjects).
Overall, the safety profile in AD+CVD was consistent with that observed in studies of galantamine in subjects with Alzheimer's disease.
Mild Cognitive Impairment (MCI)
Two, 2-year controlled trials in subjects with MCI did not meet dual primary efficacy outcomes. Although mortality was low (0.7%), more deaths were initially recorded in subjects randomized to galantamine (13/1026) than to placebo (1/1022), but the incidence of serious adverse events was identical (19%) between treatment groups.
When data retrieved from the large proportion of patients in both treatment groups who discontinued prior to completion of the double-blind period (GAL-COG-3002) were included, a total of 102 deaths were identified, 56 in the galantamine group and 46 in the placebo group (relative risk [95% CI] = 1.24 [0.84,1.83]; p = 0.274). The 24-month intent-to-treat analysis recorded 20 deaths among subjects randomised to placebo compared to 34 deaths recorded among subjects randomised to REMINYL (relative risk [95% CI] = 1.70 [1.00, 2.90]; p = 0.051). Of subjects who died within the protocol-specified period of 30 days of discontinuing double-blind study medication, there were 14 in the galantamine group and 3 in the placebo group (relative risk [95% CI] = 4.08 [1.57,10.57]; p = 0.004).
More placebo-treated than galantamine-treated subjects discontinued prior to death, which may account for the difference in mortality initially recorded. Thirteen deaths in the placebo group and 20 deaths in the galantamine group were found to be directly related to adverse events that occurred while the subjects were exposed to double-blind study drug (relative risk [95% CI] = 1.54 (0.78, 3.04); p = 0.218.
The deaths were due to various causes that are not unexpected in an elderly population. About half of the deaths in both placebo and active treatment groups were due to vascular causes. There was no evidence of an increasing risk of death in REMINYL-treated subjects over time. This pattern was consistently observed in all analyses of the data.
The MCI study results are discrepant from those observed in studies of Alzheimer's disease. In pooled studies in Alzheimer's disease (n=4614), the mortality rate was numerically higher in the placebo than the REMINYL group. There is no evidence of increased mortality due to REMINYL in Alzheimer's disease, including Alzheimer's dementia with cerebrovascular disease.
Pharmacokinetic Properties
Galantamine is a low-clearance drug (plasma clearance of approximately 300 ml/min) with a moderate volume of distribution (average Vd_{ss} of 175 l). The elimination of galantamine is bi-exponential, with a terminal half-life in the order of 7-8 h.
After oral intake of a single dose of 8 mg galantamine, absorption is rapid, with a peak plasma concentration of 43 ± 13 ng/ml, which is reached after 1.2 hours, and a mean AUC_∞ of 427 ± 102 ng.h/ml. The absolute oral bioavailability of galantamine is 88.5%. Oral intake of galantamine with food slows down its rate of absorption (C_{max} reduced by about 25%), but does not affect the extent to which it is absorbed (AUC).
After repeated oral dosing of 12 mg galantamine b.i.d., mean trough and peak plasma concentrations fluctuated between 30 and 90 ng/ml. The pharmacokinetics of galantamine are linear in the dose range 4-16 mg b.i.d.
Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 90-97% of the radioactivity was recovered in urine and 2.2-6.3% in the faeces. After i.v. and oral administration, 18-22% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 ml/min, which represents 20-25% of the total plasma clearance.
Major metabolic pathways were N-oxidation, N-demethylation, O-demethylation, glucuronidation and epimerization. O-demethylation was far more important in extensive metabolisers of CYP2D6. The levels of excretion of total radioactivity in urine and faeces were not different between poor and extensive metabolisers. *In vitro* studies confirmed that cytochrome P450 2D6 and 3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine.
In plasma from poor and extensive metabolisers, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In plasma from extensive metabolisers, the glucuronide of O-desmethylgalantamine was also important.
None of the active metabolites of galantamine (norgalantamine, O-desmethylgalantamine and O-desmethylnorgalantamine) could be detected in their unconjugated form in plasma from poor or extensive metabolisers after single dosing. Norgalantamine was detectable in plasma from patients after multiple dosing, but did not represent more than 10% of the galantamine levels.
Data from clinical trials in patients indicate that the plasma concentrations of galantamine in patients with Alzheimer's disease are 30-40% higher than in healthy young subjects.
The pharmacokinetics of galantamine in subjects with mild hepatic impairment (Child-Pugh score of 5-6) were comparable to those in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% (see: Posology and Method of Administration).
The disposition of galantamine was studied in young subjects with varying degrees of renal function. Elimination of galantamine decreased with decreasing creatinine clearance. Plasma concentrations of galantamine increased in subjects with impaired renal function by 38% in moderate (Cl_{CR}=52-104 ml/min) or 67% in severe renal impairment (Cl_{CR}=9-51 ml/min), compared to age and weight-matched healthy subjects (Cl_{CR}>=121 ml/min). A population pharmacokinetic analysis and simulations indicate that no dose-adjustments are needed in Alzheimer patients with renal impairment provided that the Cl_{CR} is at least 9 ml/min (see: Posology and Method of Administration) as the galantamine clearance is lower in the Alzheimer population.
Plasma protein binding: The plasma protein binding of galantamine is low: 17.7 ± 0.8%. In whole blood, galantamine is mainly distributed to blood cells (52.7%) and plasma water (39.0%), whereas the fraction of galantamine bound to plasma proteins in only 8.4%. The blood-to-plasma concentration ratio of galantamine is 1.17.
Preclinical Safety Data
All other preclinical safety data relevant to the prescriber have been included in the appropriate sections.

PHARMACEUTICAL PARTICULARS
List of Excipients
Film-Coated Tablets
Tablet Core:
The inactive ingredients are colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate and microcrystalline cellulose.
Film-Coating:
The inactive ingredients are hypromellose *[hydroxypropyl methylcellulose]*, propylene glycol, talc and titanium dioxide.
The 4 mg tablets also contain yellow ferric oxide. The 8 mg tablets contain red ferric oxide. The 12 mg tablets contain red ferric oxide and orange yellow S aluminium lake.
Oral Solution
The inactive ingredients are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water.
Incompatibilities
Not applicable.
Shelf Life
Observe expiry date on the outer pack.
Special Precautions for Storage
REMINYL tablets: store between 15° and 30°C.
REMINYL oral solution: store between 15° and 30°C, protect from freezing, use within 3 months of first opening.
Keep out of reach of children.
Nature and Contents of Container
Tablets
The tablets are packaged in a PVC-PE-PVDC/Alu blister that holds 14 tablets. Blisters are packed in a cardboard box.
Oral Solution
The oral solution is packaged in a 100 ml amber glass bottle with a LDPE insert, a PP/LDPE child resistant closure and a HDPE/LDPE/PS pipette, calibrated in millilitres. The pipette has a minimum volume of 0.5 ml and a maximum volume of 4 ml.
Instructions for Use and Handling <and Disposal>
See figure 3
To open the bottle and use the pipette:
1: The bottle comes with a child-resistant cap, and should be opened as follows:
   - Push the plastic screw cap down while turning it counter clockwise.
   - Remove the unscrewed cap.
2: Insert the pipette into the bottle.
   While holding the bottom ring, pull the top ring up to the mark corresponding to the number of millilitres you need to give.
3: Holding the bottom ring, remove the entire pipette from the bottle.
   Empty the pipette into any non-alcoholic drink by sliding the upper ring down and drink it immediately.
   Close the bottle.
   Rinse the pipette with some water.

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JANSSEN-CILAG
Manufactured by: see outer pack
for Janssen Pharmaceutica N.V.,
Turnhoutseweg 30, B-2340 Beerse, Belgium