ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**INN**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	Organon GesmbH Siebenbrunnengasse 21/D/IV A-1050 Wien Austria	Mirtazapine	Remeron SolTab 15 mg Schmelztabletten	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab 30 mg Schmelztabletten	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab 45 mg Schmelztabletten	45 mg	Orodispersible tablets	Oral use	
Belgium	Organon Europe B.V., Kloosterstraat 6, 5349AB Oss, The Netherlands Delegation of power: Organon België n.v., Terhulpsesteenweg 166, 1170 Brussels , Belgium	Mirtazapine	Remergon	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergon	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergon	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergon SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergon SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergon SolTab	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergon	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
Cyprus	C.A.Papaellinas & Co Ltd 179 Yiannos Kranidiotis Avenue, 2235 Latsia, Nicosia, Cyprus	Mirtazapine	Remeron	30 mg	Film-coated Tablets	Oral use	
Czech Republic	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	REMERON 15 MG	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	REMERON 30 MG	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	REMERON 45 MG	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	REMERON SOLTAB 15 MG	15 mg	Orodispersible tablets	Oral use	

Member State	**Marketing Authorisation Holder**	**INN**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		Mirtazapine	REMERON SOLTAB 30 MG	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	REMERON SOLTAB 45 MG	45 mg	Orodispersible tablets	Oral use	
Denmark	IMI Pharma AS, Literbuen 9, DK- 2740 Skovlunde, Denmark	Mirtazapine	Mitazon Smelt	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mitazon Smelt	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mitazon Smelt	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mitazon	30 mg	Film-coated tablets	Oral use	
	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron Smelt	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Smelt	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Smelt	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
Estonia	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	45 mg	Orodispersible tablets	Oral use	
Finland	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron Soltab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Soltab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Soltab	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	15 mg/ml	Oral Solution	Oral use	990 mg/66 ml
	Oy Organon Ab	Mirtazapine	Mirtazon	30 mg	Film-coated tablets	Oral use	

Member State	Marketing Authorisation Holder	INN	Invented Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
	Maistraatinportti 2 00240 Helsinki, Finland	Mirtazapine	Mirtazon Smelt	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazon Smelt	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazon Smelt	45 mg	Orodispersible tablets	Oral use	
France	Organon S.A. Immeuble Optima 10 rue Godefroy 92821 PUTEAUX Cedex France	Mirtazapine	Norset	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Norset	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Norset	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Norset	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Norset	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Norset	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
Germany	Organon GmbH Mittenheimer Straße 62 85764 Oberschleißheim Germany	Mirtazapine	Remergil	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergil	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergil	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergil SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergil SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergil SolTab	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergil	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
	STADApharm GmbH Stadastraße 2-18 61118 Bad Vilbel Germany	Mirtazapine	Mirtazapin STADA	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapin STADA	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapin STADA	45 mg	Orodispersible tablets	Oral use	

Member State	**Marketing Authorisation Holder**	**INN**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Greece	Organon Hellas S.A. 122, Vouliagmenis Av. Helliniko 167 77 Athens, Greece	Mirtazapine	Remeron	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron	15 mg	Oral Solution	Oral use	
Hungary	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	45 mg	Orodispersible tablets	Oral use	
Iceland	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron Smelt	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Smelt	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Smelt	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron 15 mg/ml	15 mg/ml	Oral Solution	Oral use	990 mg/66 ml
Ireland	Organon Laboratories Ltd, Cambridge Science Park, Milton Road, CB4 0FL, United Kingdom	Mirtazapine	Zispin® film-coated tablets	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Zispin® film-coated tablets	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Zispin® film-coated tablets	45 mg	Film-coated tablets	Oral use	
	Organon (Ireland) Limited, PO Box 2857,	Mirtazapine	Zispin® Soltab® orodispersible tablets	15 mg	Orodispersible tablets	Oral use	

Member State	**Marketing Authorisation Holder**	**INN**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	Drynam Road, Swords, Co. Dublin, Ireland	Mirtazapine	Zispin® Soltab® orodispersible tablets	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Zispin® Soltab® orodispersible tablets	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Zispin® oral solution	15 mg/ml	Oral Solution	Oral use	990 mg/66 ml
Italy	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	mirtazapine	Remeron	15 mg	Film-coated tablets	Oral use	
		mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
		Mirtazapine	Remeron	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapina Organon	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapina Organon	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapina Organon	45 mg	Orodispersible tablets	Oral use	
Latvia	N.V. Organon, Kloosterstraat 6, P.O. Box 20, NL 5340 AB Oss, The Netherlands	Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	45 mg	Orodispersible tablets	Oral use	
Lithuania	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron Sol Tab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Sol Tab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron Sol Tab	45 mg	Orodispersible tablets	Oral use	

Member State	Marketing Authorisation Holder	INN	Invented Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Luxembourg	Organon Europe B.V. Kloosterstraat 6, 5349AB Oss, The Netherlands Delegation of power: Organon België n.v., Terhulpsesteenweg 166, 1170 Brussels , Belgium	Mirtazapine	Remergon	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergon	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergon	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remergon SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergon SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergon SolTab	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remergon	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
Netherlands	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron drank	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
		Mirtazapine	Remeron SolTab	15 mg	Orodispersible Tablets	Oral use	15 mg per tablet
		Mirtazapine	Remeron SolTab	30 mg	Orodispersible Tablets	Oral use	30 mg per tablet
		Mirtazapine	Remeron SolTab	45 mg	Orodispersible Tablets	Oral use	45 mg per tablet
		Mirtazapine	Mirtazapine orodispergeerbare tabletten	15 mg	Orodispersible Tablets	Oral use	15 mg per tablet
		Mirtazapine	Mirtazapine orodispergeerbare tabletten	30 mg	Orodispersible Tablets	Oral use	30 mg per tablet
		Mirtazapine	Mirtazapine orodispergeerbare tabletten	45 mg	Orodispersible Tablets	Oral use	45 mg per tablet
Norway	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss,	Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	30 mg per tablet
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	45 mg per tablet
		Mirtazapine	Remeron-S smeltetabletter	15 mg	Orodispersible tablets	Oral use	15 mg per tablet

Member State	Marketing Authorisation Holder	INN	Invented Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
	The Netherlands	Mirtazapine	Remeron-S smeltetabletter	30 mg	Orodispersible tablets	Oral use	30 mg per tablet
		Mirtazapine	Remeron-S smeltetabletter	45 mg	Orodispersible tablets	Oral use	45 mg per tablet
		Mirtazapine	Remeron mikstur, oppløsning	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
Poland	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	30 mg	Film-coated tablets	Oral use	30 mg per tablet
Portugal	Organon Portuguesa Produtos Químicos e Farmacêuticos, Lda Av. José Malhoa, 16-B -2º 1070-159 Lisboa Portugal	Mirtazapine	Mirtazapina Organon	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Mirtazapina Organon	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Remeron SolTab	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
	Aacifar Produtos Químicos e Farmacêuticos, Lda Av. José Malhoa, 16-B -2º 1070-159 Lisboa Portugal	Mirtazapine	Mirtazon	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazon	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazon	45 mg	Orodispersible tablets	Oral use	
Romania	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss,	Mirtazapine	Remeron SolTab 15 mg	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron SolTab 30 mg	30 mg	Orodispersible tablets	Oral use	

Member State	Marketing Authorisation Holder	INN	Invented Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
	The Netherlands	Mirtazapine	Remeron SolTab 45 mg	45 mg	Orodispersible tablets	Oral use	
Slovak Republic	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	REMERON 15 mg	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	REMERON 30 mg	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	REMERON 45 mg	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	REMERON Soltab 15 mg	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	REMERON Soltab 30 mg	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	REMERON Soltab 45 mg	45 mg	Orodispersible tablets	Oral use	
Spain	Organon Española, S.A. Ctra. De Hospitalet, 147-149 Cityparc Ronda de Dalt Edificio Amsterdam 08940 Cornellá de Llobregat Barcelona , Spain	Mirtazapine	Rexer	15 mg	Film coated tablets	Oral use	
		Mirtazapine	Rexer	30 mg	Film coated tablets	Oral use	
		Mirtazapine	Rexer	45 mg	Film coated tablets	Oral use	
		Mirtazapine	Rexer Flas	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Rexer Flas	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Rexer Flas	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Rexer	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
	N.V. Organon, Kloosterstraat 6, P.O. Box 20, 5340 BH Oss, The Netherlands	Mirtazapine	Mirtazapina Organon	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapina Organon	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapina Organon	45 mg	Orodispersible tablets	Oral use	
Sweden	N.V. Organon, P.O. Box 20, NL - 5340 BH Oss, The Netherlands	Mirtazapine	Remeron	15 mg	Tablets	Oral use	
		Mirtazapine	Remeron	30 mg	Tablets	Oral use	
		Mirtazapine	Remeron	45 mg	Tablets	Oral use	
		Mirtazapine	Remeron	15 mg/ml	Oral solution	Oral use	990 mg/66 ml
		Mirtazapine	Remeron-S	15 mg	Orodispersible tablets	Oral use	

Member State	**Marketing Authorisation Holder**	**INN**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		Mirtazapine	Remeron-S	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Remeron-S	45 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Mirtazapin Imi Pharma	15 mg	Tablets	Oral use	
		Mirtazapine	Mirtazapin Imi Pharma	30 mg	Tablets	Oral use	
		Mirtazapine	MirtazapinImi Pharma	45 mg	Tablets	Oral use	
United Kingdom	Organon Laboratories Ltd, Cambridge Science Park, Milton Road, Cambridge, CB4 0FL United Kingdom	Mirtazapine	Mirtazapine 15mg Tablets	15 mg	Film-coated tablets	Oral use	
		Mirtazapine	Mirtazapine 30mg Tablets	30 mg	Film-coated tablets	Oral use	
		Mirtazapine	Mirtazapine 45mg Tablets	45 mg	Film-coated tablets	Oral use	
		Mirtazapine	Mirtazapine 15mg/ml Oral Solution	15 mg	Oral Solution	Oral use	990 mg/66 ml
		Mirtazapine	Zispin SolTab 15mg orodispersible tablet	15 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Zispin SolTab 30mg orodispersible tablet	30 mg	Orodispersible tablets	Oral use	
		Mirtazapine	Zispin SolTab 45mg orodispersible tablet	45 mg	Orodispersible tablets	Oral use	45 mg per tablet

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF REMERON AND ASSOCIATED NAMES (SEE ANNEX I)

Remeron (mirtazapine) has been referred for the harmonisation of Summary of Product Characteristics, in accordance with Article 30 (1) of Directive 2001/83/EC. Mirtazapine is indicated for episodes of major depression. The referral was triggered by the applicant and aims to harmonise major areas of discrepancy between the EU member states, with regard to the Summary of Product Characteristics (SPCs), Package Leaflets (PLs), labelling and Module 3 of the following products containing the active substance mirtazapine:

Remeron tablets 15, 30 and 45 mg
Remeron orodispersible tablets 15, 30 and 45 mg
Remeron oral solution 15 mg/ml

On 14 February 2007 a combined renewal via MRP was concluded for Remeron film-coated tablets 45 mg, Remeron 15, 30, 45 mg, Remeron oral solution 15 mg/ml, Mirtazapine orodispersible tablets 15, 30, 45 mg., involving in total 8 Member States, including the Reference Member State (RMS). The SPC proposals by the company were mainly based upon this MRP. Further the recommendations by the Pharmacovigilance Working Party with respect to the core SPC for antidepressants were implemented. Finally, the referral SPCs were revised in accordance with the European Commission (EC) Guideline on SPC, October 2005. The following sections of the Product Information were addressed during this harmonisation procedure.

SPC Section 4.1 Therapeutic Indications

In section 4.1 Therapeutic Indications of the SPC, the CHMP considered that the indication should be amended to: Episodes of major depression (or treatment of episodes of major depression) in accordance with the wording agreed for this indication for other products of which the SPC is harmonised in Europe. The CHMP considered that the addition of “in adults” was not acceptable. This proposal was adopted by the applicant/MAH and the issue was resolved.

SPC Section 4.2 Posology and Method of Administration

In Section 4.2 Posology and method of administration of the SPC, the CHMP considered that the sentence “Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months” should be replaced by “Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.” (in accordance with the wording of other antidepressants). The proposal was adopted by the applicant/MAH and the issue was resolved.

Additionally, the CHMP considered that the clearance of mirtazapine may be decreased in patients with moderate to severe renal impairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing Remeron to this category of patients (see section 4.4). The applicant/MAH was therefore asked to provide support for the cut-off at 40 ml/min as the range is normally defined as 30- 50 ml/min (moderate renal impairment).

To investigate the impact of renal impairment on the pharmacokinetics of mirtazapine, the applicant/MAH made reference to a clinical trial that was designed specifically for that purpose (trial 22503). In this study, subjects were divided into 4 categories using the following cut-off values:
Group 1 Normal healthy controls with a glomerular filtration rate (GFR) of >80 ml/min/1.73 m2
Group 2 Mild renal insufficiency with a GFR of 40-79 ml/min/1.73 m2
Group 3 Moderate/marked renal insufficiency with a GFR 10-39 ml/min/1.73 m2
Group 4 Severe renal insufficiency with a GFR <10 ml/min/1.73 m2
In each subgroup 10 subjects were included.

At that time, in 1989, the cut-off values for the level of renal impairment were in line with FDA draft Guidance for Industry on "Pharmacokinetics and Pharmacodynamics in patients with Impaired renal function: study design, data analysis, and impact on dosing and labelling". That is the reason for the cut-off value of 40 ml/min/1.73 m2. This FDA Guidance was superseded in 1998. In addition, the most recent EU Guideline was only established in 1994 (Note for Guidance on the evaluation on the pharmacokinetics of medicinal products in patients with impaired renal function, CHMP/EWP/225/02). Importantly, patients with renal impairment and their doctors should be aware of the fact that in subjects with impaired renal function exposure to mirtazapine may be increased and that there is a positive correlation between severity and exposure. The CHMP considered this explanation to be acceptable and the issue was resolved.

SPC Section 4.3 Contraindications

The applicant/MAH restricted the contra-indication to hypersensitivity only, in accordance with the EC Guideline on SPC, as only absolute contraindications should be mentioned and relative contra-indications should move to the warning section 4.3 or section. However, the CHMP did not consider this explanation acceptable and requested that the applicant/MAH should argue why these contra-indications are not absolute. The CHMP was of the opinion that Phenylketonuria, MAO inhibitors, and pathological alterations of blood count are considered absolute contra-indications.

Phenylketonuria
The applicant/MAH argued that, according to the Guideline on SPC (October 2005) contraindications "arising from the presence of certain excipients (under reference to the Guideline on excipients in the label and package leaflet of medicinal products for human use)" should be included. The Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006) and the above mentioned guideline (CHMP/463/00) indicate which excipients and information should appear in the labelling. The Annex explicitly mentions those excipients that require to be mentioned as a contraindication (e.g. hypersensitivity to peanut or soya oil). These do not include hereditary deficiencies of amino acid (phenylalanine) metabolism, such as phenylketonuria. Since it is indicated in the Annex that aspartame, containing a source of phenylalanine may be harmful for people with phenylketonuria (and no comment is included in the Annex that a contraindication should be included in the SPC, such as done for peanut oil), this is not considered to be an absolute contraindication. The amount of phenylalanine is low in Remeron orodispersible tablets. Patients who are sensitive to phenylalanine are usually aiming for low phenylalanine levels (e.g. through diet), not complete abstinence of this source. The use of aspartame as presented in these amounts in Remeron orodispersible tablets is not an absolute contraindication. It is therefore proposed to keep this warning in the corresponding section, section 4.4. Aspartame may be/is considered contraindicated in infants, but mirtazapine is not to be used in this age category and, consequently, requires no further warning.

The CHMP considered that the explanations provided appear scientifically sound and justified, noting that the aspartame content of the product is adequately addressed in the proposed form

MAO-inhibitors
The applicant/MAH argues that it does not have data from clinical trials evaluating interactions between MAO inhibitors (MAO-Is) and mirtazapine. As explained in the referral application dossier, animal studies have shown that mirtazapine induces only a small and temporary increase in noradrenalin and serotonin levels in the hippocampus (data available on request). Since the mechanism of interaction is different for MAO-Is with mirtazapine compared to MAO-Is and SSRIs, it is unlikely that the risk of serotonin syndrome is as high as with other serotonergic antidepressants, such as SSRIs. MAO-inhibitors are therefore relatively contra-indicated with Remeron. The low number of post-marketing reports suggests that this interaction does not occur frequently and do not warrant any change to the location in the SPC where the warning for concomitant use of Remeron with MAO-Is is provided. The warning at section 4.5 seems sufficient for its purpose. Hence it is proposed not to include MAO-inhibitors as absolute contraindication in section 4.3.

The CHMP considered that a contraindication is acceptable, given the marginal influence on noradrenaline and serotonin levels and the post-marketing experience available to date.

Pathological alterations of blood count
The applicant/MAH stated that there are no data indicating that mirtazapine aggravates conditions where blood count is altered. Given the very low incidence of the most serious condition, i.e. agranulocytosis (independent from the question of causality or whether it surpasses the background incidence), this is not an absolute contraindication and should not be included in section 4.3

With regards to the pathological alterations of blood count, the CHMP considered that proposed wording is acceptable, based on the meta-analysis report provided in the applicant/MAH's responses.

SPC Section 4.5 Special Warnings and precautions for use

In Sections 4.3 (Contra-indications) and 4.5 (Interaction with other medicinal products and forms of interaction) of the SPC, the interaction with MAOIs concerns an absolute contra-indication in accordance with the SPCs for SSRIs and SNRIs. The CHMP considered that the arguments provided by the applicant/MAH were insufficient to justify that mirtazapine would act different from SSRIs and SNRIs (e.g. venlafaxine). Moreover, the CHMP was of the opinion that the mechanism of interaction with MAOIs with mirtazapine is different from SSRIs. The low number of post-marketing reports does not justify this either. Therefore, the addition of a cross reference to section 4.3 of the SPC in section 4.5 (after the wording related to the interaction with MAOIs) was recommended, in line with the harmonised SPC for SSRIs and in line with the SPC for venlafaxine - a SNRI.

As a conclusion to the discussion, the following text was subsequently agreed between the CHMP and the applicant/MAH to include the following: deletion of reference to section 4.3 for serotonin syndrome, deletion of "other" and the addition of "venlafaxine" in the text below. The applicant/ MAH also agreed to include the interaction with MAOIs in section 4.3 of the SPC:

Pharmacodynamic interactions
Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors (see section 4.3).
In addition, as with ~~other~~ SSRIs, co-administration with other serotonergic ~~drugs~~ active substances (L-tryptophan, triptans, tramadol, linezolid, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin ~~5-HT~~ associated effects (serotonin syndrome: see ~~Section 4.3 Contraindications and~~ section 4.4 ~~Special Warnings and Special Precautions for Use~~). Caution should be advised and a closer clinical monitoring is required when these drugs are combined with mirtazapine.

Therefore, the following wording on pharmacodynamic interactions for Section 4.5 of the SPC was recommended:

Pharmacodynamic interactions
- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors.
- In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects (serotonin syndrome: see section 4.4) Caution should be advised and a closer clinical monitoring is required when these drugs are combined with mirtazapine.

- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine.
- Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages while taking mirtazapine.
monitoring for signs of beginning serotonergic overstimulation maintained is warranted.
- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalized ratio (INR) in subjects treated with warfarin. As at a higher dose of mirtazapine a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Additionally in Section 4.5 of the SPC, the CHMP considered it sufficient to state that Lithium and mirtazapine showed no pharmacokinetic interactions (last paragraph section 4.5) without further specifications. The general wording on absence of interactions should not be included. Finally, the cimetidine interaction study should be included in section 4.5. Pharmacokinetic interactions. Therefore the following wording was recommended:

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40 % and 50 % respectively. ~~Caution should be exercised when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin or nefazodone.~~
- ***When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapin may increase more than 50 %. Caution should be exercised and the dose may have to be decreased when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.***
- ~~No significant pharmacokinetic interactions are expected between mirtazapine and other psychotropic active substances because most psychotropic active substances are metabolized by multiple cytochrome P450 (CYP) iso-enzymes and one metabolic pathway will compensate for the other in case of inhibition of one or more CYP iso-enzymes. Mirtazapine does not significantly inhibit or induce CYP iso-enzymes.~~
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptyline~~, *or*~~ risperidone **or lithium.** ~~A single dose of mirtazapine does not result in any acute effect on the pharmacokinetics of lithium at steady state.~~

SPC 4.8 Undesirable Effects

During the last PSUR period (01 Sep 2004 to 01 Sep 2007), 36 cases of hyponatraemia and 8 cases of SIADH were reported for mirtazapine (Remeron). Accordingly hyponatraemia and SIADH are already described under 4.4 Special warnings. For consistency, the CHMP considered that these undesirable effects should also be stated under 4.8 (Undesirable Effects). This proposal was adopted by the applicant/MAH and the issue was resolved.

Package Leaflet

The following amendments to the PIL were recommended, in line with the changes made to the SPC.

a. BEFORE YOU TAKE REMERON

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Limited experience with Remeron administration to pregnant women does not indicate an increased risk. However, caution should be exercised when used during pregnancy.
~~Do not take Remeron while you are pregnant. Despite this, in special cases your doctor may prescribe Remeron for you because it may be in the best interest of you and your child.~~
If you are taking Remeron and you become pregnant or you plan to get pregnant, ask your doctor whether you may continue taking Remeron.
Ask your doctor whether you can breast-feed, while taking Remeron.

b. BEFORE YOU TAKE REMERON
Take care when taking Remeron in combination with:

- **antidepressants such as SSRIs, venlafaxine and L-tryptophan or triptans** (used to treat migraine)**, tramadol** (a pain-killer)**, linezolid** (an antibiotic)**, lithium** (used to treat some psychiatric conditions) **and St. Johns Wort – Hypericum perforatum preparations** (a herbal remedy for depression**)**. In very rare cases Remeron alone or the combination of Remeron with these medicines, can lead to a so-called serotonin syndrome. Some of the symptoms of this syndrome are: inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness. If you get a combination of these symptoms, talk to your doctor immediately.

The CHMP considered that the proposed wording under bullet point **a** and **b** were acceptable. A warning concerning the use during pregnancy and the possible risk of withdrawal effects on the newborn were recommended to be included in the PIL.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling, package leaflet and Module 3.

- the Summaries of Products Characteristic, labelling, package leaflet and Module 3 proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Remeron and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg orodispersible tablets
Remeron and associated names (see Annex I) 30 mg orodispersible tablets
Remeron and associated names (see Annex I) 45 mg orodispersible tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Remeron 15 mg orodispersible tablet contains 15 mg of mirtazapine.
Each Remeron 30 mg orodispersible tablet contains 30 mg of mirtazapine.
Each Remeron 45 mg orodispersible tablet contains 45 mg of mirtazapine.

Excipients:
Each Remeron 15 mg orodispersible tablet contains 4.65 mg aspartame and 28 mg sucrose.
Each Remeron 30 mg orodispersible tablet contains 9.30 mg aspartame and 56 mg sucrose.
Each Remeron 45 mg orodispersible tablet contains 13.95 mg aspartame and 84 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

15 mg orodispersible tablet:
Round, white, standard bevelled-edge, coded with 'TZ/1' on one side.
30 mg orodispersible tablet:
Round, white, standard bevelled-edge, coded with 'TZ/2' on one side.
45 mg orodispersible tablet:
Round, white, standard bevelled-edge, coded with 'TZ/4' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of episodes of major depression.

4.2 Posology and method of administration

Adults
The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg. Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Elderly
The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children and adolescents under the age of 18 years
Remeron should not be used in children and adolescents under the age of 18 years (see section 4.4).

Renal impairment
The clearance of mirtazapine may be decreased in patients with moderate to severe renal impairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing Remeron to this category of patients (see section 4.4).

Hepatic impairment
The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into account when prescribing Remeron to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

Mirtazapine has an elimination half-life of 20-40 hours and therefore Remeron is suitable for once daily administration. It should be taken preferably as a single night-time dose before going to bed. Remeron may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).
The tablets should be taken orally. The tablet will rapidly disintegrate and can be swallowed without water.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with mirtazapine gradually to avoid withdrawal symptoms (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age
Remeron should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany therapy with antidepressants especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or

thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of Remeron orodispersible tablets should be given to the patient.

Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with Remeron. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with Remeron. In the postmarketing period with Remeron very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases mostly concerned patients with an age above 65. The physician should be alert for symptoms like fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken.

Jaundice
Treatment should be discontinued if jaundice occurs.

Conditions which need supervision
Careful dosing as well as regular and close monitoring is necessary in patients with:
- epilepsy and organic brain syndrome: Although clinical experience indicates that epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Remeron should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency
- hepatic impairment: Following a single 15 mg oral dose of mirtazapine, the clearance of mirtazapine was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine was about 55 % increased.
- renal impairment: Following a single 15 mg oral dose of mirtazapine, in patients with moderate (creatinine clearance < 40 ml/min) and severe (creatinine clearance ≤ 10 ml/min) renal impairment the clearance of mirtazapine was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 %increased respectively. No significant differences were found in patients with mild renal impairment (creatinine clearance < 80 ml/min) as compared to the control group.
- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarction, where normal precautions should be taken and concomitant medicines carefully administered.
- low blood pressure.
- diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Like with other antidepressants, the following should be taken into account:
- Worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.
- When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
- Although Remeron is not addictive, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to the underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.

– Care should be taken in patients with micturition disturbances like prostate hypertrophy and in patients with acute narrow-angle glaucoma and increased intra-ocular pressure (although there is little chance of problems with Remeron because of its very weak anticholinergic activity).
– Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported very rarely with the use of mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatraemia.

Serotonin syndrome
Interaction with serotonergic active substances: serotonin syndrome may occur when selective serotonin reuptake inhibitors (SSRIs) are used concomitantly with other serotonergic active substances (see section 4.5). Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with Remeron alone (see section 4.8).

Elderly patients
Elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with Remeron, undesirable effects have not been reported more often in elderly patients than in other age groups.

Sucrose
Remeron contains sugar spheres, containing sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Aspartame
Remeron contains aspartame, a source of phenylalanine. Each tablet with 15 mg, 30 mg and 45 mg mirtazapine corresponds to 2.6 mg, 5.2 mg and 7.8 mg phenylalanine, respectively. It may be harmful for patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors (see section 4.3).
  In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects (serotonin syndrome: see section 4.4). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine.
- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine.
- Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages while taking mirtazapine.

- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalized ratio (INR) in subjects treated with warfarin. As at a higher dose of mirtazapine a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Pharmacokinetic interactions
- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40 % and 50 % respectively.
- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapine may increase more than 50 %. Caution should be exercised and the dose may have to be decreased when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptyline, risperidone or lithium.

4.6 Pregnancy and lactation

Limited data of the use of mirtazapine in pregnant women do not indicate an increased risk for congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance, however developmental toxicity has been observed (see section 5.3). Caution should be exercised when prescribing to pregnant women. If Remeron is used until, or shortly before birth, postnatal monitoring of the newborn is recommended to account for possible discontinuation effects. Animal studies and limited human data have shown excretion of mirtazapine in breast milk only in very small amounts. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Remeron should be made taking into account the benefit of breast-feeding to the child and the benefit of Remeron therapy to the woman.

4.7 Effects on ability to drive and use machines

Remeron has minor or moderate influence on the ability to drive and use machines. Remeron may impair concentration and alertness (particularly in the initial phase of treatment). Patients should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

4.8 Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Remeron.

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with Remeron in randomized placebo-controlled trials (see below) are somnolence, sedation, dry mouth, weight increased, increase in appetite, dizziness and fatigue.

All randomized placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of Remeron. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1501 patients (134 person years) receiving doses of mirtazapine up to 60 mg and 850 patients (79 person years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorized incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with Remeron than with placebo, added with adverse reactions from spontaneous reporting. The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

Table 1. Adverse reactions of Remeron

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known
Investigations	▪ Weight increased[1]				
Blood and the lymphatic system disorders					▪ Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anemia thrombocytopenia) ▪ Eosinophilia
Nervous system disorders	▪ Somnolence[1, 4] ▪ Sedation[1, 4] ▪ Headache[2]	▪ Lethargy[1] ▪ Dizziness ▪ Tremor	▪ Paraesthesia[2] ▪ Restless legs ▪ Syncope	▪Myoclonus	▪ Convulsions (insults) ▪ Serotonin syndrome ▪ Oral paraesthesia
Gastrointestinal disorders	▪ Dry mouth	▪ Nausea[3] ▪ Diarrhea[2] ▪ Vomiting[2]	▪ Oral hypoaesthesia		▪ Mouth oedema
Skin and subcutaneous tissue disorders		▪ Exanthema[2]			
Musculoskeletal and connective tissue disorders		▪ Arthralgia ▪ Myalgia ▪ Back pain[1]			
Metabolism and nutrition disorders	▪ Increase in appetite[1]				▪ Hyponatraemia
Vascular disorders		▪ Orthostatic hypotension	▪ Hypotension[2]		
General disorders and administration site conditions		▪ Oedema peripheral[1] ▪ Fatigue			
Hepatobiliary disorders				▪ Elevations in serum transaminase activities	
Psychiatric disorders		▪ Abnormal dreams ▪ Confusion ▪ Anxiety[2, 5] ▪ Insomnia[3, 5]	▪ Nightmares[2] ▪ Mania ▪ Agitation[2] ▪ Hallucinations ▪ Psychomotor restlessness (incl. akathisia, hyperkinesia)		▪ Suicidal ideation[6] ▪ Suicidal behaviour[6]
Endocrine disorders					▪ Inappropriate antidiuretic hormone secretion

[1] In clinical trials these events occurred statistically significantly more frequently during treatment with Remeron than with placebo.
[2] In clinical trials these events occurred more frequently during treatment with placebo than with Remeron, however not statistically significantly more frequently.
[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with Remeron.
[4] N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy.

[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.
[6] Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).

In laboratory evaluations in clinical trials transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with Remeron than with placebo).

4.9 Overdose

Present experience concerning overdose with Remeron alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses.
Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. Activated charcoal or gastric lavage should also be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antidepressants, ATC code: N06AX11

Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.
The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 Pharmacokinetic properties

After oral administration of Remeron, the active substance mirtazapine is rapidly and well absorbed (bioavailability ≈ 50 %), reaching peak plasma levels after approx. two hours. Binding of mirtazapine to plasma proteins is approx. 85 %. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

Mirtazapine is extensively metabolized and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.
The clearance of mirtazapine may be decreased as a result of renal or hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity or genotoxicity.
In reproductive toxicity studies in rats and rabbits no teratogenic effects were observed. At two-fold systemic exposure compared to maximum human therapeutic exposure, there was an increase in post-implantation loss, decrease in the pup birth weights, and reduction in pup survival during the first three days of lactation in rats.
Mirtazapine was not genotoxic in a series of tests for gene mutation and chromosomal and DNA damage. Thyroid gland tumours found in a rat carcinogenicity study and hepatocellular neoplasms found in a mouse carcinogenicity study are considered to be species-specific, non-genotoxic responses associated with long-term treatment with high doses of hepatic enzyme inducers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sugar spheres
hypromellose
povidone K30
magnesium stearate
basic butylated methacrylate copolymer
aspartame (E951)
citric acid, anhydrous
crospovidone (type A)
mannitol (E421)
microcrystalline cellulose
natural and artificial orange flavour (No. SN027512)
sodium hydrogen carbonate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture

6.5 Nature and contents of container

Child-resistant, peel-to-open, rigid perforated unit dose blister, formed from a laminate of aluminum foil and plastic films sealed to a paper-based laminate of aluminum foil coated with a heat seal lacquer.
The plastic films contain: PVC (polyvinyl chloride), polyamide and polyester.

The blisters contain 6 orodispersible tablets each. The following pack sizes are available for each strength: 6 (1x6), 18 (3x6), 30 (5x6), 48 (8x6) and 96 (16x6) and 180 (10x18 (3x6)) orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton, 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 15 mg mirtazapine

3. LIST OF EXCIPIENTS

Sugar spheres (containing sucrose) and aspartame (E951)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

6 orodispersible tablets
18 orodispersible tablets
30 orodispersible tablets
48 orodispersible tablets
96 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Label on bundle pack, 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 15 mg mirtazapine

3. LIST OF EXCIPIENTS

Sugar spheres (containing sucrose) and aspartame (E951)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

180 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 15

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister, 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

TEAR

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton, 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 30 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 30 mg mirtazapine

3. LIST OF EXCIPIENTS

Sugar spheres (containing sucrose) and aspartame (E951)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

6 orodispersible tablets
18 orodispersible tablets
30 orodispersible tablets
48 orodispersible tablets
96 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 30

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Label on bundle pack, 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 30 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 30 mg mirtazapine

3. LIST OF EXCIPIENTS

Sugar spheres (containing sucrose) and aspartame (E951)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

180 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 30

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister, 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 30 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

TEAR

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton, 45 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 45 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 45 mg mirtazapine

3. LIST OF EXCIPIENTS

Sugar spheres (containing sucrose) and aspartame (E951)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

6 orodispersible tablets
18 orodispersible tablets
30 orodispersible tablets
48 orodispersible tablets
96 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 45

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Label on bundle pack, 45 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 45 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 45 mg mirtazapine

3. LIST OF EXCIPIENTS

Sugar spheres (containing sucrose) and aspartame (E951)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

180 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 45

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister, 45 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and assoicated names (see Annex I) 45 mg orodispersible tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

TEAR

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Remeron and associated names (see Annex I) 15 mg orodispersible tablets
Remeron and associated names (see Annex I) 30 mg orodispersible tablets
Remeron and associated names (see Annex I) 45 mg orodispersible tablets

[See Annex I - To be completed nationally]

Mirtazapine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT REMERON IS AND WHAT IT IS USED FOR

Remeron is one of a group of medicines called **antidepressants**.
Remeron is used to treat depressive illness.

2. BEFORE YOU TAKE REMERON

Do not take Remeron
- if you are **allergic** (hypersensitive) to mirtazapine or any of the other ingredients of Remeron. If so, you must talk to your doctor as soon as you can before taking Remeron.
- if you are taking or have recently taken (within the last two weeks) medicines called monoamine oxidase inhibitors (MAO-Is).

Take special care with Remeron

Use in children and adolescents under 18 years of age
Remeron should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Remeron for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Remeron for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking

Remeron. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Remeron in this age group have not yet been demonstrated.

Thoughts of suicide and worsening of your depression
If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:

- if you have previously had thoughts about killing or harming yourself.
- if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

→ If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Also take special care with Remeron

- if you have, or have ever had one of the following conditions.
  → Tell your doctor about these conditions before taking Remeron, if not done previously.
  -**seizures** (epilepsy). If you develop seizures or your seizures become more frequent, stop taking Remeron and contact your doctor immediately;
  -**liver disease**, including jaundice. If jaundice occurs, stop taking Remeron and contact your doctor immediately;
  -**kidney disease**;
  -**heart disease**, or **low blood pressure**;
  -**schizophrenia**. If psychotic symptoms, such as paranoid thoughts become more frequent or severe, contact your doctor straight away;
  -**manic depression** (alternating periods of feeling elated/overactivity and depressed mood). If you start feeling elated or over-excited, stop taking Remeron and contact your doctor immediately;
  -**diabetes** (you may need to adjust your dose of insulin or other antidiabetic medicines);
  -**eye disease**, such as increased pressure in the eye (glaucoma);
  -**difficulty in passing water** (urinating), which might be caused by an enlarged prostate.
- if you develop signs of infection such as inexplicable high fever, sore throat and mouth ulcers.
  → Stop taking Remeron and consult your doctor immediately for a blood test.
  In rare cases these symptoms can be signs of disturbances in blood cell production in the bone marrow. While rare, these symptoms most commonly appear after 4-6 weeks of treatment.
- if you are an elderly person. You could be more sensitive to the side-effects of antidepressants.

Taking other medicines
Tell your doctor or pharmacist if you are taking (or plan to take) any of the medicines in the following list.
Please also tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not take Remeron in combination with:

- **monoamine oxidase inhibitors** (MAO inhibitors). Also, do not take Remeron during the two weeks after you have stopped taking MAO inhibitors. If you stop taking Remeron, do not take MAO inhibitors during the next two weeks either.
  Examples of MAO inhibitors are moclobemide, tranylcypromine (both are antidepressants) and selegiline (used for Parkinson's disease).

Take care when taking Remeron in combination with:

- **antidepressants such as SSRIs, venlafaxine and L-tryptophan, or triptans** (used to treat migraine)**, tramadol** (a pain-killer), **linezolid** (an antibiotic), **lithium** (used to treat some psychiatric conditions) **and St. John's Wort – Hypericum perforatum preparations** (a herbal remedy for depression). In very rare cases Remeron alone or the combination of Remeron with these medicines, can lead to a so-called serotonin syndrome. Some of the symptoms of this syndrome are: inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes, and unconsciousness. If you get a combination of these symptoms, talk to your doctor immediately.
- **the antidepressant nefazodone**. It can increase the amount of Remeron in your blood. Inform your doctor if you are using this medicine. It might be needed to lower the dose of Remeron, or when use of nefazodone is stopped, to increase the dose of Remeron again.
- **medicines for anxiety or insomnia** such as benzodiazepines;
  medicines for schizophrenia such as olanzapine;
  medicines for allergies such as cetirizine;
  medicines for severe pain such as morphine.
  In combination with these medicines Remeron can increase the drowsiness caused by these medicines.
- **medicines for infections;** medicines for bacterial infections (such as erythromycin); medicines for fungal infections (such as ketoconazole) and medicines for HIV/AIDS (such as HIV-protease inhibitors).
  In combination with Remeron these medicines can increase the amount of Remeron in your blood. Inform your doctor if you are using these medicines. It might be needed to lower the dose of Remeron, or when these medicines are stopped, to increase the dose of Remeron again.
- **medicines for epilepsy** such as carbamazepine and phenytoin;
  medicines for tuberculosis such as rifampicin.
  In combination with Remeron these medicines can reduce the amount of Remeron in your blood. Inform your doctor if you are using these medicines. It might be needed to increase the dose of Remeron, or when these medicines are stopped to lower the dose of Remeron again.
- **medicines to prevent blood clotting** such as warfarin.
  Remeron can increase the effects of warfarin on the blood. Inform your doctor if you are using this medicine. In case of combination it is advised that a doctor monitors your blood carefully.

Taking Remeron with food and drink
You may get drowsy if you drink alcohol while you are taking Remeron.
You are advised not to drink any alcohol.
You can take Remeron with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Limited experience with Remeron administration to pregnant women does not indicate an increased risk. However, caution should be exercised when used during pregnancy.
If you are taking Remeron and you become pregnant or you plan to get pregnant, ask your doctor whether you may continue taking Remeron. If you use Remeron until, or shortly before birth, your baby should be supervised for possible adverse effects.
Ask your doctor whether you can breast-feed, while taking Remeron.

Driving and using machines
Remeron can affect your concentration or alertness. Make sure these abilities are not affected before you drive or operate machinery.

Important information about some of the ingredients of Remeron
Remeron orodispersible tablets contain sugar spheres, containing sucrose. If you have been told by your doctor that you have an intolerance for some sugars, contact your doctor before taking this medicinal product.

Remeron orodispersible tablets contain aspartame, a source of phenylalanine. May be harmful for people with phenylketonuria.

3. HOW TO TAKE REMERON

Always take Remeron exactly as your doctor or pharmacist tells you to. You should check with your doctor or pharmacist if you are not sure.

How much to take
The usual starting dose is 15 or 30 mg every day. Your doctor may advise you to increase your dose after a few days to the amount that is best for you (between 15 and 45 mg per day). The dose is usually the same for all ages. However, if you are an elderly person or if you have renal or liver disease, your doctor may adapt the dose.

When to take Remeron
→ Take Remeron at the same time each day**.**
It is best to take Remeron as a single dose before you go to bed. However your doctor may suggest to split your dose of Remeron – once in the morning and once at night-time before you go to bed. The higher dose should be taken before you go to bed.

Take the orodispersible tablet as follows
Take your tablets orally.

1. **Do not crush the orodispersible tablet**
   In order to prevent crushing the orodispersible tablet, do not push against the tablet pocket (Figure A).

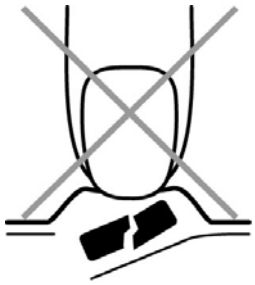


Fig. A.

2. **Tear off one tablet pocket**
   Each blister contains six tablet pockets, which are separated by perforations. Tear off one tablet pocket along the dotted lines (Figure 1).

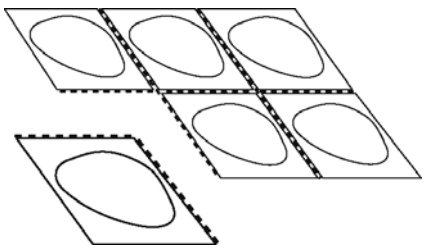


Fig. 1.

3. **Peel off the lid**
   Carefully peel off the lidding foil, starting in the corner indicated by the arrow (Figures 2 and 3).

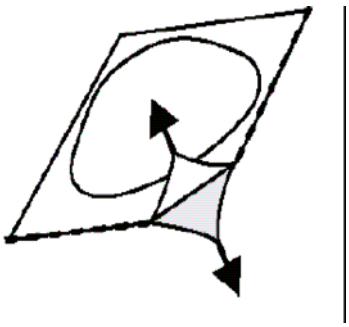


Fig. 2.

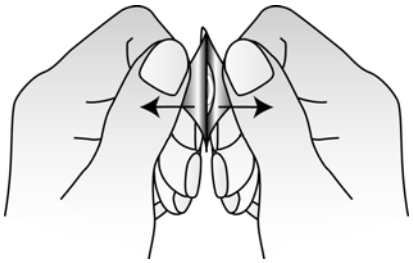


Fig. 3.

4. Take out the orodispersible tablet

Take out the orodispersible tablet with dry hands and place it on the tongue. (Figure 4).

Fig. 4.

It will rapidly disintegrate and can be swallowed without water.

When can you expect to start feeling better

Usually Remeron will start working after 1 to 2 weeks and after 2 to 4 weeks you may start to feel better.

It is important that, during the first few weeks of the treatment, you talk with your doctor about the effects of Remeron:

→ 2 to 4 weeks after you have started taking Remeron, talk to your doctor about how this medicine has affected you.

If you still don't feel better, your doctor may prescribe a higher dose. In that case, talk to your doctor again after another 2 to 4 weeks. Usually you will need to take Remeron until your symptoms of depression have disappeared for 4 to 6 months.

If you take more Remeron than you should

→ If you or someone else have taken too much Remeron, call a doctor straight away**.**

The most likely signs of an overdose of Remeron (without other medicines or alcohol) are **drowsiness**, **disorientation and increased heart rate**.

If you forget to take Remeron

If you are supposed to take your dose **once a day**

- If you have forgotten to take your dose of Remeron, do not take the missed dose. Just skip it. Take your next dose at the normal time.

If you are supposed to take your dose **twice a day**

- if you have forgotten to take your morning dose, simply take it together with your evening dose.
- if you have forgotten to take your evening dose, do not take it with the next morning dose; just skip it and continue with your normal morning and evening doses.
- if you have forgotten to take both doses, do not attempt to make up for the missed doses. Skip both doses and continue the next day with your normal morning and evening doses.

If you stop taking Remeron
→ Only stop taking Remeron in consultation with your doctor.
If you stop too early, your depression might come back. Once you are feeling better, talk to your doctor. Your doctor will decide when treatment can be stopped.
Do not suddenly stop taking Remeron, even when your depression has lifted. If you suddenly stop taking Remeron you may feel sick, dizzy, agitated or anxious, and have headaches. These symptoms can be avoided by stopping gradually. Your doctor will tell you how to decrease the dose gradually.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Remeron can cause side effects, although not everybody gets these side effects. Some side effects are more likely to occur than others. The possible side effects of Remeron are listed below and can be divided as:

- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: cannot be estimated from the available data

Very common:
- increase in appetite and weight gain
- drowsiness or sleepiness
- headache
- dry mouth

Common:
- lethargy
- dizziness
- shakiness or tremor
- nausea
- diarrhoea
- vomiting
- rash or skin eruptions (exanthema)
- pain in your joints (arthralgia) or muscles (myalgia)
- back pain
- feeling dizzy or faint when you stand up suddenly (orthostatic hypotension)
- swelling (typically in ankles or feet) caused by fluid retention (oedema)
- tiredness
- vivid dreams
- confusion
- feeling anxious
- sleeping problems

Uncommon:

- feeling elated or emotionally ‘high’ (mania)
  → Stop taking Remeron and tell your doctor straight away.
- abnormal sensation in the skin e.g. burning, stinging, tickling or tingling (paraesthesia)
- restless legs
- fainting (syncope)
- sensations of numbness in the mouth (oral hypoaesthesia)
- low blood pressure
- nightmares
- feeling agitated
- hallucinations
- urge to move

Rare:
- yellow colouring of eyes or skin; this may suggest disturbance in liver function (jaundice)
  → Stop taking Remeron and tell your doctor straight away.
- muscle twitching or contractions (myoclonus)

Not known:
- signs of infection such as sudden unexplainable high fever, sore throat and mouth ulcers (agranulocytosis)
  → Stop taking Remeron and contact your doctor straight away for a blood test.
  In rare cases Remeron can cause disturbances in the production of blood cells (bone marrow depression). Some people become less resistant to infection because Remeron can cause a temporary shortage of white blood cells (granulocytopenia). In rare cases Remeron can also cause a shortage of red and white blood cells, as well as blood platelets (aplastic anemia), a shortage of blood platelets (thrombocytopenia) or an increase in the number of white blood cells (eosinophilia).
- epileptic attack (convulsions)
  → Stop taking Remeron and tell your doctor straight away.
- a combination of symptoms such as inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness. In very rare cases these can be signs of serotonin syndrome.
  → Stop taking Remeron and tell your doctor straight away.
- thoughts of harming or killing yourself
  → Contact your doctor or go to a hospital straight away.
- abnormal sensations in the mouth (oral paraesthesia)
- swelling in the mouth (mouth oedema)
- hyponatraemia
- inappropriate anti-diuretic hormone secretion

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE REMERON

Keep out of the reach and sight of children.

Do not use Remeron after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture

Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Remeron contains

- The active substance is mirtazapine.
  Remeron 15 mg orodispersible tablets contain 15 mg mirtazapine per orodispersible tablet.
  Remeron 30 mg orodispersible tablets contain 30 mg mirtazapine per orodispersible tablet.
  Remeron 45 mg orodispersible tablets contain 45 mg mirtazapine per orodispersible tablet.
- The other ingredients are sugar spheres, hypromellose, povidone K30, magnesium stearate, basic butylated methacrylate copolymer, aspartame (E951), anhydrous citric acid, crospovidone (type A), mannitol (E421), microcrystalline cellulose, natural and artificial orange flavour (No. SN027512) and sodium hydrogen carbonate.

What Remeron looks like and contents of the pack

Remeron are orodispersible tablets.
Remeron 15 mg orodispersible tablets are round, white, standard bevelled-edge tablets coded with 'TZ/1' on one side.
Remeron 30 mg orodispersible tablets are round, white, standard bevelled-edge tablets coded with 'TZ/2' on one side.
Remeron 45 mg orodispersible tablets are round, white, standard bevelled-edge tablets coded with 'TZ/4' on one side.
The orodispersible tablets are packed in a child-resistant perforated unit dose blister.

For Remeron 15, 30 and 45 mg orodispersible tablets the following pack sizes are available: 6, 18, 30, 48, 90, 96 and 180 orodispersible tablets (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names
[not applicable for art 30 referral]

This leaflet was last revised/approved in .

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg film-coated tablets
Remeron and associated names (see Annex I) 30 mg film-coated tablets
Remeron and associated names (see Annex I) 45 mg film-coated tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Remeron 15 mg film-coated tablet contains 15 mg of mirtazapine.
Each Remeron 30 mg film-coated tablet contains 30 mg of mirtazapine.
Each Remeron 45 mg film-coated tablet contains 45 mg of mirtazapine.

Excipients:
Each Remeron 15 mg film-coated tablet contains 109 mg lactose (as monohydrate).
Each Remeron 30 mg film-coated tablet contains 217 mg lactose (as monohydrate).
Each Remeron 45 mg film-coated tablet contains 325 mg lactose (as monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

15 mg film-coated tablet:
Oval, biconvex, yellow, scored and marked with ‘Organon’ on one side-and a code on the other side (TZ/3).
The tablet can be divided into equal halves.
30 mg film-coated tablet:
Oval, biconvex, red-brown, scored and marked with ‘Organon’ on one side-and a code on the other side (TZ/5).
The tablet can be divided into equal halves.
45 mg film-coated tablet:
Oval, biconvex, white and marked with ‘Organon’ on one side-and a code on the other side (TZ/7).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of episodes of major depression.

4.2 Posology and method of administration

Adults
The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg. Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Elderly

The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children and adolescents under the age of 18 years
Remeron should not be used in children and adolescents under the age of 18 years (see section 4.4).

Renal impairment
The clearance of mirtazapine may be decreased in patients with moderate to severe renalimpairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing Remeron to this category of patients (see section 4.4).

Hepatic impairment
The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into account when prescribing Remeron to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

Mirtazapine has an elimination half-life of 20-40 hours and therefore Remeron is suitable for once daily administration. It should be taken preferably as a single night-time dose before going to bed. Remeron may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).
The tablets should be taken orally, with fluid, and swallowed without chewing.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with mirtazapine gradually to avoid withdrawal symptoms (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age
Remeron should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an

increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany therapy with antidepressants especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of Remeron film-coated tablets should be given to the patient.

Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with Remeron. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with Remeron. In the postmarketing period with Remeron very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases mostly concerned patients with an age above 65. The physician should be alert for symptoms like fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken.

Jaundice
Treatment should be discontinued if jaundice occurs.

Conditions which need supervision
Careful dosing as well as regular and close monitoring is necessary in patients with:
- epilepsy and organic brain syndrome: Although clinical experience indicates that epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Remeron should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency.
- hepatic impairment: Following a single 15 mg oral dose of mirtazapine, the clearance of mirtazapine was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine was about 55 %increased.
- renal impairment: Following a single 15 mg oral dose of mirtazapine, in patients with moderate (creatinine clearance <40 ml/min) and severe (creatinine clearance ≤ 10 ml/min) renal impairment the clearance of mirtazapine was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 % increased respectively. No significant differences were found in patients with mild renal impairment (creatinine clearance <80 ml/min) as compared to the control group.
- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarction, where normal precautions should be taken and concomitant medicines carefully administered.
- low blood pressure.
- diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Like with other antidepressants, the following should be taken into account:
- Worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified
- When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
- Although Remeron is not addictive, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea are the most

frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to the underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.

– Care should be taken in patients with micturition disturbances like prostate hypertrophy and in patients with acute narrow-angle glaucoma and increased intra-ocular pressure (although there is little chance of problems with Remeron because of its very weak anticholinergic activity).
– Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported very rarely with the use of mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatraemia.

Serotonin syndrome
Interaction with serotonergic active substances: serotonin syndrome may occur when selective serotonin reuptake inhibitors (SSRIs) are used concomitantly with other serotonergic active substances (see section 4.5). Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with Remeron alone (see section 4.8).

Elderly patients
Elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with Remeron, undesirable effects have not been reported more often in elderly patients than in other age groups.

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors (see section 4.3).
  In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects (serotonin syndrome: see section 4.4). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine.
- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine.
- Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages while taking mirtazapine.
- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalized ratio (INR) in subjects treated with warfarin. As at a higher dose of

mirtazapine a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40% and 50% respectively.
- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapine may increase more than 50 %. Caution should be exercised and the dose may have to be decreased when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptyline, risperidone or lithium.

4.7 Pregnancy and lactation

Limited data of the use of mirtazapine in pregnant women do not indicate an increased risk for congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance, however developmental toxicity has been observed (see section 5.3). Caution should be exercised when prescribing to pregnant women. If Remeron is used until, or shortly before birth, postnatal monitoring of the newborn is recommended to account for possible discontinuation effects. Animal studies and limited human data have shown excretion of mirtazapine in breast milk only in very small amounts. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Remeron should be made taking into account the benefit of breast-feeding to the child and the benefit of Remeron therapy to the woman.

4.7 Effects on ability to drive and use machines

Remeron has minor or moderate influence on the ability to drive and use machines. Remeron may impair concentration and alertness (particularly in the initial phase of treatment). Patients should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

4.9 Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Remeron.

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with Remeron in randomized placebo-controlled trials (see below) are somnolence, sedation, dry mouth, weight increased, increase in appetite, dizziness and fatigue.

All randomized placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of Remeron. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1501 patients (134 person years) receiving doses of mirtazapine up to 60 mg and 850 patients (79 person years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorized incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with Remeron than with placebo, added with adverse reactions from spontaneous reporting. The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

Table 1. Adverse reactions of Remeron

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known
Investigations	▪ Weight increased[1]				
Blood and the lymphatic system disorders					▪ Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anemia thrombocytopenia) ▪ Eosinophilia
Nervous system disorders	▪ Somnolence[1, 4] ▪ Sedation[1, 4] ▪ Headache[2]	▪ Lethargy[1] ▪ Dizziness ▪ Tremor	▪ Paraesthesia[2] ▪ Restless legs ▪ Syncope	▪Myoclonus	▪ Convulsions (insults) ▪ Serotonin syndrome ▪ Oral paraesthesia
Gastrointestinal disorders	▪ Dry mouth	▪ Nausea[3] ▪ Diarrhea[2] ▪ Vomiting[2]	▪ Oral hypoaesthesia		▪ Mouth oedema
Skin and subcutaneous tissue disorders		▪ Exanthema[2]			
Musculoskeletal and connective tissue disorders		▪ Arthralgia ▪ Myalgia ▪ Back pain[1]			
Metabolism and nutrition disorders	▪ Increase in appetite[1]				▪ Hyponatraemia
Vascular disorders		▪ Orthostatic hypotension	▪ Hypotension[2]		
General disorders and administration site conditions		▪ Oedema peripheral[1] ▪ Fatigue			
Hepatobiliary disorders				▪ Elevations in serum transaminase activities	
Psychiatric disorders		▪ Abnormal dreams ▪ Confusion ▪ Anxiety[2, 5] ▪ Insomnia[3, 5]	▪ Nightmares[2] ▪ Mania ▪ Agitation[2] ▪ Hallucinations ▪ Psychomotor restlessness (incl. akathisia, hyperkinesia)		▪ Suicidal ideation[6] ▪ Suicidal behaviour[6]
Endocrine disorders					▪ Inappropriate antidiuretic hormone secretion

[1] In clinical trials these events occurred statistically significantly more frequently during treatment with Remeron than with placebo.
[2] In clinical trials these events occurred more frequently during treatment with placebo than with Remeron, however not statistically significantly more frequently.
[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with Remeron.
[4]N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy.

[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.
[6] Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).

In laboratory evaluations in clinical trials transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with Remeron than with placebo).

4.9 Overdose

Present experience concerning overdose with Remeron alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses.
Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. Activated charcoal or gastric lavage should also be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antidepressants, ATC code: N06AX11

Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.
The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 Pharmacokinetic properties

After oral administration of Remeron, the active substance mirtazapine is rapidly and well absorbed (bioavailability ≈ 50 %), reaching peak plasma levels after approx. two hours. Binding of mirtazapine to plasma proteins is approx. 85 %. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

Mirtazapine is extensively metabolized and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.
The clearance of mirtazapine may be decreased as a result of renal or hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity or genotoxicity.
In reproductive toxicity studies in rats and rabbits no teratogenic effects were observed. At two-fold systemic exposure compared to maximum human therapeutic exposure, there was an increase in post-implantation loss, decrease in the pup birth weights, and reduction in pup survival during the first three days of lactation in rats.
Mirtazapine was not genotoxic in a series of tests for gene mutation and chromosomal and DNA damage. Thyroid gland tumours found in a rat carcinogenicity study and hepatocellular neoplasms found in a mouse carcinogenicity study are considered to be species-specific, non-genotoxic responses associated with long-term treatment with high doses of hepatic enzyme inducers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
maize starch
hyprolose
magnesium stearate
silica, colloidal anhydrous
lactose monohydrate
Tablet coating:
hypromellose
Macrogol 8000
titanium dioxide (E171)
yellow iron oxide (E172) (15 and 30 mg film-coated tablets only)
red iron oxide (E172) (30 mg film-coated tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

6.6 Nature and contents of container

Remeron 15, 30 and 45 mg film-coated tablets are packed in blisters made of opaque polyvinyl chloride film and aluminium foil containing a heat-seal coating on the side in contact with the film-coated tablets. Blisters containing 7 and 10 film-coated tablets are available.

Remeron 15, 30 and 45 mg film-coated tablets are also available in HDPE bottles with a tamper-evident LDPE cap.
Bottles contain 250 film-coated tablets.

The following pack sizes are available for the 15 mg film-coated tablets in blisters:

30 (3x10), 60 (6x10), 90 (9x10) and 100 (10x10) film-coated tablets; 14 (2x7), 28 (4x7), 56 (8x7), and 70 (10x7) film-coated tablets.

The following pack sizes are available for the 30 mg film-coated tablets in blisters:
10 (1x10), 20 (2x10), 30 (3x10), 50 (5x10), 60 (6x10), 90 (9x10), 100 (10x10), 200 (20x10) and 500 (50x10) film-coated tablets; 14 (2x7), 28 (4x7), 56 (8x7), and 70 (10x7) film-coated tablets.

The following pack sizes are available for the 45 mg film-coated tablets in blisters:
10 (1x10), 20 (2x10), 30 (3x10), 50 (5x10), 100 (10x10), 200 (20x10) and 500 (50x10) film-coated tablets; 14 (2x7), 28 (4x7), 56 (8x7), and 70 (10x7) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton, 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 15 mg mirtazapine

3. LIST OF EXCIPIENTS

Lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
70 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 15

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle, 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 15 mg mirtazapine

3. LIST OF EXCIPIENTS

Lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

250 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 15

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister, 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton, 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 30 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 30 mg mirtazapine

3. LIST OF EXCIPIENTS

Lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets
200 film-coated tablets
500 film-coated tablets

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
70 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 30

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle, 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 30 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 30 mg mirtazapine

3. LIST OF EXCIPIENTS

Lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

250 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 30

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister, 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 30 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton, 45 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 45 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 45 mg mirtazapine

3. LIST OF EXCIPIENTS

Lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets
200 film-coated tablets
500 film-coated tablets

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
70 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle, 45 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 45 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 45 mg mirtazapine

3. LIST OF EXCIPIENTS

Lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

250 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron 45

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister, 45 mg

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 45 mg film-coated tablets
[See Annex I - To be completed nationally]

Mirtazapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Remeron and associated names (see Annex I) 15 mg film-coated tablets
Remeron and associated names (see Annex I) 30 mg film-coated tablets
Remeron and associated names (see Annex I) 45 mg film-coated tablets

[See Annex I - To be completed nationally]

Mirtazapine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

2. WHAT REMERON IS AND WHAT IT IS USED FOR

Remeron is one of a group of medicines called **antidepressants**.
Remeron is used to treat depressive illness.

4. BEFORE YOU TAKE REMERON

Do not take Remeron
- if you are **allergic** (hypersensitive) to mirtazapine or any of the other ingredients of Remeron. If so, you must talk to your doctor as soon as you can before taking Remeron.
- if you are taking or have recently taken (within the last two weeks) medicines called monoamine oxidase inhibitors (MAO-Is).

Take special care with Remeron
Use in children and adolescents under 18 years of age
Remeron should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Remeron for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Remeron for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Remeron. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Remeron in this age group have not yet been demonstrated.

Thoughts of suicide and worsening of your depression
If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:

- if you have previously had thoughts about killing or harming yourself.
- if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

→ If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Also take special care with Remeron

- if you have, or have ever had one of the following conditions.
  → Tell your doctor about these conditions before taking Remeron, if not done previously
  -**seizures** (epilepsy). If you develop seizures or your seizures become more frequent, stop taking Remeron and contact your doctor immediately;
  -**liver disease**, including jaundice. If jaundice occurs, stop taking Remeron and contact your doctor immediately;
  -**kidney disease**;
  -**heart disease**, or **low blood pressure**;
  -**schizophrenia**. If psychotic symptoms, such as paranoid thoughts become more frequent or severe, contact your doctor straight away;
  -**manic depression** (alternating periods of feeling elated/overactivity and depressed mood). If you start feeling elated or over-excited, stop taking Remeron and contact your doctor immediately;
  -**diabetes** (you may need to adjust your dose of insulin or other antidiabetic medicines);
  -**eye disease**, such as increased pressure in the eye (glaucoma);
  -**difficulty in passing water** (urinating), which might be caused by an enlarged prostate.
- if you develop signs of infection such as inexplicable high fever, sore throat and mouth ulcers.
  → Stop taking Remeron and consult your doctor immediately for a blood test.
  In rare cases these symptoms can be signs of disturbances in blood cell production in the bone marrow. While rare, these symptoms most commonly appear after 4-6 weeks of treatment.
- if you are an elderly person. You could be more sensitive to the side-effects of antidepressants.

Taking other medicines
Tell your doctor or pharmacist if you are taking (or plan to take) any of the medicines in the following list.
Please also tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not take Remeron in combination with:

- **monoamine oxidase inhibitors** (MAO inhibitors). Also, do not take Remeron during the two weeks after you have stopped taking MAO inhibitors. If you stop taking Remeron, do not take MAO inhibitors during the next two weeks either.
  Examples of MAO inhibitors are moclobemide, tranylcypromine (both are antidepressants) and selegiline (used for Parkinson's disease).

Take care when taking Remeron in combination with:

- **antidepressants such as SSRIs, venlafaxine and L-tryptophan or triptans** (used to treat migraine)**, tramadol** (a pain-killer)**, linezolid** (an antibiotic)**, lithium** (used to treat some

psychiatric conditions) **and St. Johns Wort – Hypericum perforatum preparations** (a herbal remedy for depression**)**. In very rare cases Remeron alone or the combination of Remeron with these medicines, can lead to a so-called serotonin syndrome. Some of the symptoms of this syndrome are: inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness. If you get a combination of these symptoms, talk to your doctor immediately.

- **the antidepressant nefazodone**. It can increase the amount of Remeron in your blood. Inform your doctor if you are using this medicine. It might be needed to lower the dose of Remeron, or when use of nefazodone is stopped, to increase the dose of Remeron again.
- **medicines for anxiety or insomnia** such as benzodiazepines;
  medicines for schizophrenia such as olanzapine;
  medicines for allergies such as cetirizine;
  medicines for severe pain such as morphine.
  In combination with these medicines Remeron can increase the drowsiness caused by these medicines.
- **medicines for infections**; medicines for bacterial infections (such as erythromycin, medicines for fungal infections (such as ketoconazole) and medicines for HIV/AIDS (such as HIV-protease inhibitors).
  In combination with Remeron these medicines can increase the amount of Remeron in your blood. Inform your doctor if you are using these medicines. It might be needed to lower the dose of Remeron, or when these medicines are stopped, to increase the dose of Remeron again.
- **medicines for epilepsy** such as carbamazepine and phenytoin;
  medicines for tuberculosis such as rifampicin.
  In combination with Remeron these medicines can reduce the amount of Remeron in your blood. Inform your doctor if you are using these medicines. It might be needed to increase the dose of Remeron, or when these medicines are stopped to lower the dose of Remeron again.
- **medicines to prevent blood clotting** such as warfarin.
  Remeron can increase the effects of warfarin on the blood. Inform your doctor if you are using this medicine. In case of combination it is advised that a doctor monitors your blood carefully.

Taking Remeron with food and drink
You may get drowsy if you drink alcohol while you are taking Remeron.
You are advised not to drink any alcohol.
You can take Remeron with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Limited experience with Remeron administration to pregnant women does not indicate an increased risk. However, caution should be exercised when used during pregnancy.
If you are taking Remeron and you become pregnant or you plan to get pregnant, ask your doctor whether you may continue taking Remeron. If you use Remeron until, or shortly before birth, your baby should be supervised for possible adverse effects.
Ask your doctor whether you can breast-feed, while taking Remeron.

Driving and using machines
Remeron can affect your concentration or alertness. Make sure these abilities are not affected before you drive or operate machinery.

Important information about some of the ingredients of Remeron
Remeron tablets contain lactose. If you have been told by your doctor that you have an intolerance for some sugars, contact your doctor before taking this medicinal product.

5. HOW TO TAKE REMERON

Always take Remeron exactly as your doctor or pharmacist tells you to. You should check with your doctor or pharmacist if you are not sure.

How much to take
The usual starting dose is 15 or 30 mg every day. Your doctor may advise you to increase your dose after a few days to the amount that is best for you (between 15 and 45 mg per day). The dose is usually the same for all ages. However, if you are an elderly person or if you have renal or liver disease, your doctor may adapt the dose.

When to take Remeron
→ Take Remeron at the same time each day.It is best to take Remeron as a single dose before you go to bed. However your doctor may suggest you to split your dose of Remeron – once in the morning and once at night-time before you go to bed. The higher dose should be taken before you go to bed. Take your tablets orally. Swallow your prescribed dose of Remeron without chewing, with some water or juice.

When can you expect to start feeling better
Usually Remeron will start working after 1 to 2 weeks and after 2 to 4 weeks you may start to feel better.
It is important that, during the first few weeks of the treatment, you talk with your doctor about the effects of Remeron:
→ 2 to 4 weeks after you have started taking Remeron, talk to your doctor about how this medicine has affected you.
If you still don't feel better, your doctor may prescribe a higher dose. In that case, talk to your doctor again after another 2 to 4 weeks.
Usually you will need to take Remeron until your symptoms of depression have disappeared for 4 to 6 months.

If you take more Remeron than you should
→ If you or someone else have taken too much Remeron, call a doctor straight away**.**
The most likely signs of an overdose of Remeron (without other medicines or alcohol) are **drowsiness, disorientation and increased heart rate**.

If you forget to take Remeron
If you are supposed to take your dose **once a day**
- If you have forgotten to take your dose of Remeron, do not take the missed dose. Just skip it. Take your next dose at the normal time.

If you are supposed to take your dose **twice a day**
- if you have forgotten to take your morning dose, simply take it together with your evening dose.
- if you have forgotten to take your evening dose, do not take it with the next morning dose; just skip it and continue with your normal morning and evening doses.
- if you have forgotten to take both doses, do not attempt to make up for the missed doses. Skip both doses and continue the next day with your normal morning and evening doses.

If you stop taking Remeron
→ Only stop taking Remeron in consultation with your doctor.
If you stop too early, your depression might come back. Once you are feeling better, talk to your doctor. Your doctor will decide when treatment can be stopped.
Do not suddenly stop taking Remeron, even when your depression has lifted. If you suddenly stop taking Remeron you may feel sick, dizzy, agitated or anxious, and have headaches. These symptoms can be avoided by stopping gradually. Your doctor will tell you how to decrease the dose gradually.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Remeron can cause side effects, although not everybody gets these side effects. Some side effects are more likely to occur than others. The possible side effects of Remeron are listed below and can be divided as:

- **Very common**: affects more than 1 user in 10
- **Common**: affects 1 to 10 users in 100
- **Uncommon**: affects 1 to 10 users in 1,000
- **Rare**: affects 1 to 10 users in 10,000
- **Very rare**: affects less than 1 user in 10,000
- **Not known**: cannot be estimated from the available data

Very common:

- increase in appetite and weight gain
- drowsiness or sleepiness
- headache
- dry mouth

Common:

- lethargy
- dizziness
- shakiness or tremor
- nausea
- diarrhoea
- vomiting
- rash or skin eruptions (exanthema)
- pain in your joints (arthralgia) or muscles (myalgia)
- back pain
- feeling dizzy or faint when you stand up suddenly (orthostatic hypotension)
- swelling (typically in ankles or feet) caused by fluid retention (oedema)
- tiredness
- vivid dreams
- confusion
- feeling anxious
- sleeping problems

Uncommon*:*

- feeling elated or emotionally 'high' (mania)
  → Stop taking Remeron and tell your doctor straight away.
- abnormal sensation in the skin e.g. burning, stinging, tickling or tingling (paraesthesia)
- restless legs
- fainting (syncope)
- sensations of numbness in the mouth (oral hypoaesthesia)
- low blood pressure
- nightmares
- feeling agitated
- hallucinations
- urge to move

Rare:

- yellow colouring of eyes or skin; this may suggest disturbance in liver function (jaundice)
  → Stop taking Remeron and tell your doctor straight away.
- muscle twitching or contractions (myoclonus)

Not known:

- signs of infection such as sudden unexplainable high fever, sore throat and mouth ulcers (agranulocytosis)
  → Stop taking Remeron and contact your doctor straight away for a blood test**.**
  In rare cases Remeron can cause disturbances in the production of blood cells (bone marrow depression). Some people become less resistant to infection because Remeron can cause a temporary shortage of white blood cells (granulocytopenia). In rare cases Remeron can also cause a shortage of red and white blood cells, as well as blood platelets (aplastic anemia), a shortage of blood platelets (thrombocytopenia) or an increase in the number of white blood cells (eosinophilia).
- epileptic attack (convulsions)
  → Stop taking Remeron and tell your doctor straight away.
- a combination of symptoms such as inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness. In very rare cases these can be signs of serotonin syndrome.
  → Stop taking Remeron and tell your doctor straight away.
- thoughts of harming or killing yourself
  → Contact your doctor or go to a hospital straight away.
- abnormal sensations in the mouth (oral paraesthesia)
- swelling in the mouth (mouth oedema)
- hyponatraemia
- inappropriate anti-diuretic hormone secretion

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE REMERON

Keep out of the reach and sight of children.

Do not use Remeron after the expiry date which is stated on the carton and the blister or bottle. The expiry date refers to the last day of that month.

Do not store above 30 °C
Store in the original package in order to protect from light and moisture

Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Remeron contains

- The active substance is mirtazapine.
  Remeron 15 mg film-coated tablets contain 15 mg mirtazapine per film-coated tablet.
  Remeron 30 mg film-coated tablets contain 30 mg mirtazapine per film-coated tablet.
  Remeron 45 mg film-coated tablets contain 45 mg mirtazapine per film-coated tablet.
- The other ingredients are:
  Tablet core: maize starch, hyprolose, magnesium stearate, silica, colloidal anhydrous, lactose

monohydrate
Tablet coating: hypromellose, Macrogol 8000, titanium dioxide (E171)
The tablet core of Remeron 15 mg film-coated tablets also contains yellow iron oxide (E172)
The tablet coating of Remeron 30 mg film-coated tablets also contain yellow iron oxide (E172) and red iron oxide (E 172).

What Remeron looks like and contents of the pack

Remeron are film-coated tablets.
Remeron 15 mg film-coated tablets are oval, biconvex, yellow, scored and coded with 'Organon' on one side and with ‘TZ/3’ on the other side.
The tablet can be divided into equal halves.
Remeron 30 mg film-coated tablets are oval, biconvex, red-brown, scored and coded with ‘Organon’ on one side and with ‘TZ/5’ on the other side.
The tablet can be divided into equal halves.
Remeron 45 mg film-coated tablets are oval, biconvex, white and coded with ‘Organon’ on one side and with ‘TZ/7’ on the other side.

Remeron 15, 30 and 45 mg film-coated tablets are packed in blisters or bottles.

For Remeron 15 mg film-coated tablets in blisters the following pack sizes are available: 30, 60, 90 and 100 tablets; 14, 28, 56 and 70 tablets; for Remeron 15 mg film-coated tablets in bottles a pack size of 250 tablets is available (not all pack sizes may be marketed).

For Remeron 30 mg film-coated tablets in blisters the following pack sizes are available: 10, 20, 30, 50, 60, 90, 100, 200 and 500 tablets; 14, 28, 56 and 70 tablets; for Remeron 30 mg film-coated tablets in bottles a pack size of 250 tablets is available (not all pack sizes may be marketed).

For Remeron 45 mg film-coated tablets in blisters the following pack sizes are available: 10, 20, 30, 50, 100, 200 and 500 tablets; 14, 28, 56 and 70 tablets; for Remeron 45 mg film-coated tablets in bottles a pack size of 250 tablets is available (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:
[not applicable for art 30 referral]

This leaflet was last revised/approved in .

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg/ml oral solution

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of Remeron oral solution contains 15 mg of mirtazapine.

Excipients:
1 ml of Remeron oral solution contains 700 mg maltitol liquid.
Remeron oral solution contains 0.3 % v/v ethanol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear, colourless-to-straw aqueous solution with a characteristic citrus-orange odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of episodes of major depression.

4.2 Posology and method of administration

Adults
The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg. Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Elderly
The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children and adolescents under the age of 18 years
Remeron should not be used in children and adolescents under the age of 18 years (see section 4.4).

Renal impairment
The clearance of mirtazapine may be decreased in patients with moderate to severe renal impairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing Remeron to this category of patients (see section 4.4).

Hepatic impairment
The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into account when prescribing Remeron to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

Mirtazapine has an elimination half-life of 20-40 hours and therefore Remeron is suitable for once daily administration. It should be taken preferably as a single night-time dose before going to bed. Remeron may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).

The solution should be taken orally, in a glass containing some water.

Preparation of the bottle
Removing the screw cap from the bottle
The cap should be pressed downwards while at the same time rotating it anti-clockwise. The seal attached to the cap will break first; further pressing and turning will unscrew the cap. This procedure is given in symbolic instructions on the top of the screw cap.

Applying the metering pump to the bottle
After taking the pump out of the plastic bag it should be fitted onto the bottle by carefully inserting the plastic tube into the bottle opening. The pump should be pressed onto the top of the bottle and screwed until it locks tightly on the bottle. After a click, there should be one final tightening to ensure that the pump is securely screwed in place.

Using the metering pump to dispense the oral solution
The nozzle has two positions and can be turned gently – anti-clockwise (unlocked position) and clockwise (locked position). In the locked position, the nozzle cannot be pressed down and no oral solution can be discharged. The unlocked position is the normal position for discharging the oral solution. The nozzle should be turned gently anti-clockwise until it cannot be turned any further (about one-quarter turn); the pump is then ready for use.

Dosing the oral solution
Preparing the metering pump for dosing
When the pump is pressed for the first time it will not discharge the correct quantity of oral solution. Therefore, the pump must be prepared (primed) by fully pressing down the nozzle 3 times; the oral solution which comes out of the nozzle should be disposed of. Thereafter, each pump will give the correct dose (1 ml containing 15 mg of the active substance mirtazapine).

Using the metering pump for normal dosing
The bottle should be placed on a flat level surface, such as a table top. The nozzle should be pressed in a firm, smooth, continuous action (not too slowly) all the way down until it stops, holding a glass containing some water under the opening of the nozzle. The nozzle can then be released and the pump is ready for the following dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with mirtazapine gradually to avoid withdrawal symptoms (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age
Remeron should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly

aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany therapy with antidepressants especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
With regard to the chance of suicide, in particular at the beginning of treatment, only a limited quantity of Remeron oral solution should be given to the patient.

Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with Remeron. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with Remeron. In the postmarketing period with Remeron very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases mostly concerned patients with an age above 65. The physician should be alert for symptoms like fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken.

Jaundice
Treatment should be discontinued if jaundice occurs.

Conditions which need supervision
Careful dosing as well as regular and close monitoring is necessary in patients with:
- epilepsy and organic brain syndrome: Although clinical experience indicates that epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Remeron should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency.
- hepatic impairment: Following a single 15 mg oral dose of mirtazapine, the clearance of mirtazapine was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine was about 55 % increased.
- renal impairment: Following a single 15 mg oral dose of mirtazapine, in patients with moderate (creatinine clearance < 40 ml/min) and severe (creatinine clearance ≤ 10 ml/min) renal impairment the clearance of mirtazapine was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 %increased respectively. No significant differences were found in patients with mild renal impairment (creatinine clearance < 80 ml/min) as compared to the control group.

– cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered.
– low blood pressure.
– diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Like with other antidepressants, the following should be taken into account:
– Worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.
– When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
– Although Remeron is not addictive, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to the underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.
– Care should be taken in patients with micturition disturbances like prostate hypertrophy and in patients with acute narrow-angle glaucoma and increased intra-ocular pressure (although there is little chance of problems with Remeron because of its very weak anticholinergic activity).
– Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported very rarely with the use of mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatraemia.

Serotonin syndrome
Interaction with serotonergic active substances: serotonin syndrome may occur when selective serotonin reuptake inhibitors (SSRIs) are used concomitantly with other serotonergic active substances (see section 4.5). Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with Remeron alone (see section 4.8).

Elderly patients
Elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with Remeron, undesirable effects have not been reported more often in elderly patients than in other age groups.

Maltitol liquid
This medicinal product contains maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Ethanol
This medicinal product contains small amounts of ethanol, less than 100 mg per daily dose.

Switching from tablets to oral solution

There are slight pharmacokinetic differences between oral solution and tablets; although these differences are likely to be of no clinical relevance, care should be taken when switching from tablets to oral solution.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors (see section 4.3).
  In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects (serotonin syndrome: see section 4.4). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine.
- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine.
- Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages while taking mirtazapine.
- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalized ratio (INR) in subjects treated with warfarin. As at a higher dose of mirtazapine a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40 % and 50 % respectively.
- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapine may increase more than 50 %. Caution should be exercised and the dose may have to be decreased when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptyline, risperidone or lithium.

4.8 Pregnancy and lactation

Limited data of the use of mirtazapine in pregnant women do not indicate an increased risk for congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance, however developmental toxicity has been observed (see section 5.3). Caution should be exercised when prescribing to pregnant women. If Remeron is used until, or shortly before birth, postnatal monitoring of the newborn is recommended to account for possible discontinuation effects. Animal studies and limited human data have shown excretion of mirtazapine in breast milk only in very small amounts. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Remeron should be made taking into account the benefit of breast-feeding to the child and the benefit of Remeron therapy to the woman.

4.7 Effects on ability to drive and use machines

Remeron has minor or moderate influence on the ability to drive and use machines. Remeron may impair concentration and alertness (particularly in the initial phase of treatment). Patients should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

4.10 Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Remeron.

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with Remeron in randomized placebo-controlled trials (see below) are somnolence, sedation, dry mouth, weight increased, increase in appetite, dizziness and fatigue.

All randomized placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of Remeron. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1501 patients (134 person years) receiving doses of mirtazapine up to 60 mg and 850 patients (79 person years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorized incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with Remeron than with placebo, added with adverse reactions from spontaneous reporting. The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

Table 1. Adverse reactions of Remeron

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known
Investigations	▪ Weight increased[1]				
Blood and the lymphatic system disorders					▪ Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anemia thrombocytopenia) ▪ Eosinophilia
Nervous system disorders	▪ Somnolence[1, 4] ▪ Sedation[1, 4] ▪ Headache[2]	▪ Lethargy[1] ▪ Dizziness ▪ Tremor	▪ Paraesthesia[2] ▪ Restless legs ▪ Syncope	▪Myoclonus	▪ Convulsions (insults) ▪ Serotonin syndrome ▪ Oral paraesthesia
Gastrointestinal disorders	▪ Dry mouth	▪ Nausea[3] ▪ Diarrhea[2] ▪ Vomiting[2]	▪ Oral hypoaesthesia		▪ Mouth oedema
Skin and subcutaneous tissue disorders		▪ Exanthema[2]			
Musculoskeletal and connective tissue disorders		▪ Arthralgia ▪ Myalgia ▪ Back pain[1]			
Metabolism and nutrition disorders	▪ Increase in appetite[1]				▪ Hyponatraemia
Vascular disorders		▪ Orthostatic hypotension	▪ Hypotension[2]		
General disorders		▪ Oedema			

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known
and administration site conditions		peripheral[1] ▪ Fatigue			
Hepatobiliary disorders				▪ Elevations in serum transaminase activities	
Psychiatric disorders		▪ Abnormal dreams ▪ Confusion ▪ Anxiety[2, 5] ▪ Insomnia[3, 5]	▪ Nightmares[2] ▪ Mania ▪ Agitation[2] ▪ Hallucinations ▪ Psychomotor restlessness (incl. akathisia, hyperkinesia)		▪ Suicidal ideation[6] ▪ Suicidal behaviour[6]
Endocrine disorders					▪ Inappropriate antidiuretic hormone secretion

[1] In clinical trials these events occurred statistically significantly more frequently during treatment with Remeron than with placebo.
[2] In clinical trials these events occurred more frequently during treatment with placebo than with Remeron, however not statistically significantly more frequently.
[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with Remeron.
[4] N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy
[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.
[6] Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).

In laboratory evaluations in clinical trials transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with Remeron than with placebo).

4.9 Overdose

Present experience concerning overdose with Remeron alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses.
Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. Activated charcoal or gastric lavage should also be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antidepressants, ATC code: N06AX11

Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.

The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 Pharmacokinetic properties

After oral administration of Remeron, the active substance mirtazapine is rapidly and well absorbed (bioavailability ≈ 50 %), reaching peak plasma levels after approx. one hour. Binding of mirtazapine to plasma proteins is approx. 85 %. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

Mirtazapine is extensively metabolized and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.
The clearance of mirtazapine may be decreased as a result of renal or hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity or genotoxicity. In reproductive toxicity studies in rats and rabbits no teratogenic effects were observed. At two-fold systemic exposure compared to maximum human therapeutic exposure, there was an increase in post-implantation loss, decrease in the pup birth weights, and reduction in pup survival during the first three days of lactation in rats. Mirtazapine was not genotoxic in a series of tests for gene mutation and chromosomal and DNA damage. Thyroid gland tumours found in a rat carcinogenicity study and hepatocellular neoplasms found in a mouse carcinogenicity study are considered to be species-specific, non-genotoxic responses associated with long-term treatment with high doses of hepatic enzyme inducers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-methionine
sodium benzoate (E211)
saccharin sodium (E954)
citric acid monohydrate (E330)
glycerol (E422)
maltitol liquid (E965)
orange tangerine flavour No. PHL-132597 (contains ethanol)
purified water

6.2 Incompatibilities

The oral solution should not be mixed with fluids other than water.

6.3 Shelf life

2 years
Shelf life after *first* opening of the bottle: 6 weeks

6.4 Special precautions for storage

Do not store above 25 °C

6.7 Nature and contents of container

The carton contains one brown (type III) glass bottle containing 66 ml of Remeron oral solution and one metering pump.
The supplied bottle with Remeron oral solution is closed with a sealed, polypropylene screw cap which has child-resistant features. The supplied metering pump is packed in a sealed polyethylene bag.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton and label, 15 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Remeron and associated names (see Annex I) 15 mg/ml oral solution
[See Annex I - To be completed nationally]

Mirtazapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of oral solution contains 15 mg mirtazapine

3. LIST OF EXCIPIENTS

Maltitol liquid

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
1 bottle containing 66 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Do not use the bottle more than 6 weeks after opening.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Remeron

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Remeron and associated names (see Annex I) 15 mg/ml oral solution

[See Annex I - To be completed nationally]

Mirtazapine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

3. WHAT REMERON IS AND WHAT IT IS USED FOR

Remeron is one of a group of medicines called **antidepressants**.
Remeron is used to treat depressive illness.

6. BEFORE YOU TAKE REMERON

Do not take Remeron
- if you are **allergic** (hypersensitive) to mirtazapine or any of the other ingredients of Remeron. If so, you must talk to your doctor as soon as you can before taking Remeron.
- if you are taking or have recently taken (within the last two weeks) medicines called monoamine oxidase inhibitors (MAO-Is).

Take special care with Remeron

Use in children and adolescents under 18 years of age
Remeron should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Remeron for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Remeron for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Remeron. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Remeron in this age group have not yet been demonstrated.

Thoughts of suicide and worsening of your depression
If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:

- if you have previously had thoughts about killing or harming yourself.
- if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

→ If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Also take special care with Remeron

- if you have, or have ever had one of the following conditions.
  → Tell your doctor about these conditions before taking Remeron, if not done previously
  -**seizures** (epilepsy). If you develop seizures or your seizures become more frequent, stop taking Remeron and contact your doctor immediately;
  -**liver disease**, including jaundice. If jaundice occurs, stop taking Remeron and contact your doctor immediately;
  -**kidney disease**;
  -**heart disease**, or **low blood pressure**;
  -**schizophrenia**. If psychotic symptoms, such as paranoid thoughts become more frequent or severe, contact your doctor straight away;
  -**manic depression** (alternating periods of feeling elated/overactivity and depressed mood). If you start feeling elated or over-excited, stop taking Remeron and contact your doctor immediately;
  -**diabetes** (you may need to adjust your dose of insulin or other antidiabetic medicines);
  -**eye disease**, such as increased pressure in the eye (glaucoma);
  -**difficulty in passing water** (urinating), which might be caused by an enlarged prostate.
- if you develop signs of infection such as inexplicable high fever, sore throat and mouth ulcers.
  → Stop taking Remeron and consult your doctor immediately for a blood test. In rare cases these symptoms can be signs of disturbances in blood cell production in the bone marrow. While rare, these symptoms most commonly appear after 4-6 weeks of treatment.
- if you are an elderly person. You could be more sensitive to the side-effects of antidepressants.

Taking other medicines
Tell your doctor or pharmacist if you are taking (or plan to take) any of the medicines in the following list.
Please also tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not take Remeron in combination with:

- **monoamine oxidase inhibitors** (MAO inhibitors). Also, do not take Remeron during the two weeks after you have stopped taking MAO inhibitors. If you stop taking Remeron, do not take MAO inhibitors during the next two weeks either.
  Examples of MAO inhibitors are moclobemide, tranylcypromine (both are antidepressants) and selegiline (used for Parkinson's disease).

Take care when taking Remeron in combination with:

- **antidepressants such as SSRIs,venlafaxine and L-tryptophan, or triptans** (used to treat migraine)**, tramadol** (a pain-killer), **linezolid** (an antibiotic)**, lithium** (used to treat some psychiatric conditions) **and St. John's Wort – Hypericum perforatum preparations** (a

herbal remedy for depression). In very rare cases Remeron alone or the combination of Remeron with these medicines, can lead to a so-called serotonin syndrome. Some of the symptoms of this syndrome are: inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes, and unconsciousness. If you get a combination of these symptoms, talk to your doctor immediately.

- **the antidepressant nefazodone**. It can increase the amount of Remeron in your blood. Inform your doctor if you are using this medicine. It might be needed to lower the dose of Remeron, or when use of nefazodone is stopped, to increase the dose of Remeron again.
- **medicines for anxiety or insomnia** such as benzodiazepines;
  medicines for schizophrenia such as olanzapine;
  medicines for allergies such as cetirizine;
  medicines for severe pain such as morphine.
  In combination with these medicines Remeron can increase the drowsiness caused by these medicines.
- **medicines for infections:** medicines for bacterial infections (such as erythromycin), medicines for fungal infections (such as ketoconazole) and medicines for HIV/AIDS (such as HIV-protease inhibitors).
  In combination with Remeron these medicines can increase the amount of Remeron in your blood. Inform your doctor if you are using these medicines. It might be needed to lower the dose of Remeron, or when these medicines are stopped, to increase the dose of Remeron again.
- **medicines for epilepsy** such as carbamazepine and phenytoin;
  medicines for tuberculosis such as rifampicin.
  In combination with Remeron these medicines can reduce the amount of Remeron in your blood. Inform your doctor if you are using these medicines. It might be needed to increase the dose of Remeron, or when these medicines are stopped to lower the dose of Remeron again.
- **medicines to prevent blood clotting** such as warfarin.
  Remeron can increase the effects of warfarin on the blood. Inform your doctor if you are using this medicine. In case of combination it is advised that a doctor monitors your blood carefully.

Taking Remeron with food and drink
You may get drowsy if you drink alcohol while you are taking Remeron.
You are advised not to drink any alcohol.
You can take Remeron with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Limited experience with Remeron administration to pregnant women does not indicate an increased risk. However, caution should be exercised when used during pregnancy.
If you are taking Remeron and you become pregnant or you plan to get pregnant, ask your doctor whether you may continue taking Remeron. If you use Remeron until, or shortly before birth, your baby should be supervised for possible adverse effects.
Ask your doctor whether you can breast-feed, while taking Remeron.

Driving and using machines
Remeron can affect your concentration or alertness. Make sure these abilities are not affected before you drive or operate machinery.

Important information about some of the ingredients of Remeron
Remeron oral solution contains maltitol liquid. If you have been told by your doctor that you have an intolerance for some sugars, contact your doctor before taking this medicinal product.
Remeron oral solution contains small amounts of ethanol (alcohol), less than 100 mg per daily dose.

7. HOW TO TAKE REMERON

Always take Remeron exactly as your doctor or pharmacist tells you to. You should check with your doctor or pharmacist if you are not sure.

How much to take
The usual starting dose is 15 or 30 mg every day. Your doctor may advise you to increase your dose after a few days to the amount that is best for you (between 15 and 45 mg per day). The dose is usually the same for all ages. However, if you are an elderly person or if you have renal or liver disease, your doctor may adapt the dose.

When to take Remeron
→ Take Remeron at the same time each day.
It is best to take Remeron as a single dose before you go to bed. However your doctor may suggest to split your dose of Remeron – once in the morning and once at night-time before you go to bed. The higher dose should be taken before you go to bed.

Take the oral solution as follows
Take the oral solution orally. Drink your prescribed dose of Remeron oral solution in a glass or cup mixed with some water. Remeron oral solution comes with a metering pump to help you measure your dose.

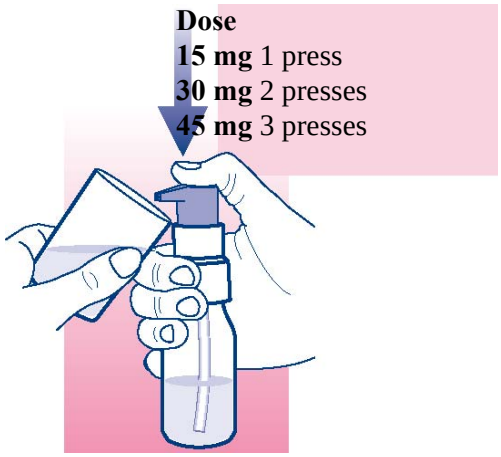
Preparing the Remeron metering pump for use
Before you take Remeron, you need to fit the pump onto the bottle.

1. **Take the screw cap off the bottle**
   Press the cap downwards and turn it anticlockwise to break the seal. Keep pressing and turning to unscrew the cap. This procedure is given in symbolic instructions on the top of the screw cap.
2. **Fit the metering pump onto the bottle**
   Take the pump out of its bag. Fit it onto the bottle, putting the plastic tube inside the bottle. Press the pump onto the top of the bottle, and turn it clockwise until it clicks tightly into place. Tighten the pump a little more to make sure it is firmly in place.
3. **Turn the nozzle to the open position**
   The nozzle has two positions – locked and open. When it is locked, no liquid will come out. To open the nozzle, turn it anticlockwise as far as it will go (about one-quarter turn).
4. **'Prime' the metering pump before you take Remeron**
   The very first time you press the pump, it will not measure out the right amount of Remeron solution. You need to prime it before your first dose.
   - Place the bottle on a flat surface.
   - Hold a glass or cup under the nozzle *(see picture).*
   - Press the nozzle down as far as it will go, three times.
   - Rinse away the liquid that comes out.

The pump is now ready for use.

Taking your dose of Remeron
The pump is used to measure your dose.

1. Place the bottle on a flat surface.
2. Pour a little water into a glass or cup, and hold it under the nozzle.
3. Each time you press the nozzle, the pump dispenses 15 mg of Remeron. Press the nozzle down as far as it will go. Use a firm, smooth action - not too slow.
4. You may need to press the nozzle more than once to get the dose your doctor has prescribed *(see picture*).
5. Drink the mixture all at once.



When can you expect to start feeling better
Usually Remeron will start working after 1 to 2 weeks and after 2 to 4 weeks you may start to feel better.
It is important that, during the first few weeks of the treatment, you talk with your doctor about the effects of Remeron:

→ 2 to 4 weeks after you have started taking Remeron, talk to your doctor about how this medicine has affected you.

If you still don't feel better, your doctor may prescribe a higher dose. In that case, talk to your doctor again after another 2 to 4 weeks.
Usually you will need to take Remeron until your symptoms of depression have disappeared for 4 to 6 months.

If you take more Remeron than you should
→ If you or someone else have taken too much Remeron, call a doctor straight away.
The most likely signs of an overdose of Remeron (without other medicines or alcohol) are **drowsiness, disorientation and increased heart rate**.

If you forget to take Remeron
If you are supposed to take your dose **once a day**

- If you have forgotten to take your dose of Remeron, do not take the missed dose. Just skip it. Take your next dose at the normal time.

If you are supposed to take your dose **twice a day**

- if you have forgotten to take your morning dose, simply take it together with your evening dose.
- if you have forgotten to take your evening dose, do not take it with the next morning dose; just skip it and continue with your normal morning and evening doses.
- if you have forgotten to take both doses, do not attempt to make up for the missed doses. Skip both doses and continue the next day with your normal morning and evening doses.

If you stop taking Remeron
→ Only stop taking Remeron in consultation with your doctor.
If you stop too early, your depression might come back. Once you are feeling better, talk to your doctor. Your doctor will decide when treatment can be stopped.
Do not suddenly stop taking Remeron, even when your depression has lifted. If you suddenly stop taking Remeron you may feel sick, dizzy, agitated or anxious, and have headaches. These symptoms can be avoided by stopping gradually. Your doctor will tell you how to decrease the dose gradually.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Remeron can cause side effects, although not everybody gets these side effects. Some side effects are more likely to occur than others. The possible side effects of Remeron are listed below and can be divided as:

- **Very common:** affects more than 1 user in 10
- **Common:** affects 1 to 10 users in 100
- **Uncommon**: affects 1 to 10 users in 1,000
- **Rare**: affects 1 to 10 users in 10,000
- **Very rare**: affects less than 1 user in 10,000
- **Not known**: cannot be estimated from the available data

Very common:

- increase in appetite and weight gain
- drowsiness or sleepiness
- headache
- dry mouth

Common:

- lethargy
- dizziness
- shakiness or tremor
- nausea
- diarrhoea
- vomiting
- rash or skin eruptions (exanthema)
- pain in your joints (arthralgia) or muscles (myalgia)
- back pain
- feeling dizzy or faint when you stand up suddenly (orthostatic hypotension)
- swelling (typically in ankles or feet) caused by fluid retention (oedema)
- tiredness
- vivid dreams
- confusion
- feeling anxious
- sleeping problems

Uncommon:

- feeling elated or emotionally 'high' (mania)
  → Stop taking Remeron and tell your doctor straight away.
- abnormal sensation in the skin e.g. burning, stinging, tickling or tingling (paraesthesia)
- restless legs
- fainting (syncope)
- sensations of numbness in the mouth (oral hypoaesthesia)
- low blood pressure
- nightmares
- feeling agitated
- hallucinations
- urge to move

Rare:

- yellow colouring of eyes or skin; this may suggest disturbance in liver function (jaundice)
  → Stop taking Remeron and tell your doctor straight away.
- muscle twitching or contractions (myoclonus)

Not known:

- signs of infection such as sudden inexplicable high fever, sore throat and mouth ulcers (agranulocytosis)
  → Stop taking Remeron and contact your doctor straight away for a blood test**.**
  In rare cases Remeron can cause disturbances in the production of blood cells (bone marrow depression). Some people become less resistant to infection because Remeron can cause a temporary shortage of white blood cells (granulocytopenia). In rare cases Remeron can also cause a shortage of red and white blood cells, as well as blood platelets (aplastic anemia), a shortage of blood platelets (thrombocytopenia) or an increase in the number of white blood cells (eosinophilia).
- epileptic attack (convulsions)
  → Stop taking Remeron and tell your doctor straight away.
- a combination of symptoms such as inexplicable fever, sweating, increased heart rate, diarrhoea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness. In very rare cases these can be signs of serotonin syndrome.
  → Stop taking Remeron and tell your doctor straight away.
- thoughts of harming or killing yourself
  → Contact your doctor or go to a hospital straight away.
- abnormal sensations in the mouth (oral paraesthesia)
- swelling in the mouth (mouth oedema)
- hyponatraemia
- inappropriate anti-diuretic hormone secretion

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE REMERON

Keep out of the reach and sight of children.

Do not use Remeron after the expiry date which is stated on the carton and the bottle. The expiry date refers to the last day of that month.

Do not store above 25 °C
Do not use the bottle more than 6 weeks after opening.
Make a note of the date of opening of the bottle.

Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Remeron contains

- The active substance is mirtazapine.
  Remeron 15 mg/ml oral solution contains 15 mg mirtazapine per ml solution.
- The other ingredients are L-methionine, sodium benzoate (E211), saccharin sodium (E954), citric acid monohydrate (E330), glycerol (E422), maltitol liquid (E965), orange tangerine flavour No.: PHL-132597 (contains ethanol) and purified water.

What Remeron looks like and contents of the pack

Remeron oral solution is a clear, colourless - to pale yellow solution with a citrus-orange odour. The carton contains one brown glass bottle with 66 ml of Remeron oral solution and one metering pump. The bottle containing the oral solution is closed with a child-resistant screw cap and a seal which is broken when the cap is unscrewed. The metering pump is packed in a sealed plastic bag.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:
[not applicable for art 30 referral]

This leaflet was last revised/approved in.