Co-ordination group for Human Use
EMEA/H/A-31/1400
EMA/CMDh/191907/2015

Agreement of the co-ordination group for mutual Recognition and decentralised procedures for human use, pursuant to article 107k(1) and (2) of directive 2001/83/EC,

Medicinal products:

Invented names:	see Annex I
Active substance:	hydroxyzine
Pharmaceutical forms:	see Annex I
Strengths:	see Annex I
Routes of administration:	see Annex I

Basis for agreement

Pursuant to Article 31 of directive 2001/83/EC, Hungary initiated a procedure on 25 April 2014 based on concerns resulting from the evaluation of data from pharmacovigilance activities. The notification for the procedure is appended to this agreement.

The evaluation procedure started on 08 May 2014.

The Pharmacovigilance Risk Assessment Committee (PRAC) recommendation was adopted on 12 February 2015 and is appended to this agreement.

The steps taken for the assessment of the referred matter are detailed in the PRAC assessment report appended to this agreement.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use (CMDh) has considered the recommendation of PRAC in accordance with Article 107k(1) and (2) of Directive 2001/83/EC.

Agreement

1. The CMDh, having considered the PRAC recommendation, agreed by consensus that the marketing authorisations for hydroxyzine-containing medicinal products should be varied.

   The Icelandic and the Norwegian CMDh members agree with the above-mentioned agreement of the CMDh.

2. The scientific conclusions and the detailed explanation of the scientific grounds for the differences from the PRAC recommendation are set out in Annex II.

3. The amendments to be introduced to the product information of hydroxyzine-containing medicinal products are set out in Annex III.

4. The timetable for the implementation of the agreement is set out in Annex IV.

To the extent that other medicinal products containing hydroxyzine not included in Annex I are currently authorised in the EU, or are subject to future authorisation procedures by the Member States, the CMDh recommends that the Member States concerned take due consideration of the scientific conclusions set out in Annex II.

This agreement is forwarded to the Member States, to Iceland and Norway and to the marketing authorisation holders for the above mentioned medicinal products, together with its annexes and appendices.

London, 25 March 2015

On behalf of the CMDh

Dr Peter Bachmann, Chair

Annex I

List of the names, pharmaceutical forms, strengths of the medicinal products, routes of administration, and marketing authorisation holders in the Member States

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Austria	UCB Pharma GmbH Geiselbergstraße 17-19 1110 Wien Austria	Hydroxyzine dihydrochloride	Atarax 25 mg - Filmtabletten	25 mg	Film-coated tablet	Oral use
Belgium	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	10 mg	Film-coated tablet	Oral use
Belgium	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use
Belgium	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	100 mg	Film-coated tablet	Oral use
Bulgaria	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use
Bulgaria	Actavis EAD 29 Atanas Dukov Str. Sofia 1407 Bulgaria	Hydroxyzine hydrochloride	Neurolax	25 mg	Film-coated tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Cyprus	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use
Cyprus	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	2 mg/ml	Syrup	Oral use
Czech Republic	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine dihydrochloride	Atarax	25 mg	Film-coated tablet	Oral use
Denmark	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	2 mg/ml	Oral solution	Oral use
Denmark	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	10 mg	Film-coated tablet	Oral use
Denmark	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Finland	UCB Pharma Oy Finland Itsehallintokuja 6 02600 ESPOO Finland	Hydroxyzine hydrochloride	ATARAX	2 mg/ml	Syrup	Oral use
Finland	UCB Pharma Oy Finland Itsehallintokuja 6 02600 ESPOO Finland	Hydroxyzine hydrochloride	ATARAX	25 mg	Film-coated tablet	Oral use
France	UCB Pharma S.A. 420 Avenue Estienne d'Orves Défense Ouest 92700 Colombes France	Hydroxyzine hydrochloride	ATARAX 100 mg, comprimé pelliculé sécable	100 mg	Film-coated tablet	Oral Use
France	UCB Pharma S.A. 420 Avenue Estienne d'Orves Défense Ouest 92700 Colombes France	Hydroxyzine hydrochloride	ATARAX 100 mg/2 ml, solution injectable	100 mg/2 ml	Solution for injection	Intravenous use
France	UCB Pharma S.A. 420 Avenue Estienne d'Orves Défense Ouest 92700 Colombes France	Hydroxyzine hydrochloride	ATARAX 25 mg, comprimé pelliculé sécable	25 mg	Film-coated tablet	Oral Use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
France	UCB Pharma S.A. 420 Avenue Estienne d'Orves Défense Ouest 92700 Colombes France	Hydroxyzine hydrochloride	ATARAX sirop	2 mg/ml	Syrup	Oral Use
France	Laboratoire Renaudin Z A. Errobi Itxassou 64250 Cambo les Bains France	Hydroxyzine hydrochloride	HYDROXYZINE RENAUDIN 100 mg /2 ml, solution injectable	100 mg/2 ml	Solution for injection	Intravenous use
France	Inopharm limited 7 Florinis Street Greg Tower, 6th Floor PO Box 24854 1304 Nicosia Cyprus	Hydroxyzine hydrochloride	HYDROLAX 25 mg, comprimé pelliculé sécable	25 mg	Film-coated tablet	Oral Use
France	Inopharm limited 7 Florinis Street Greg Tower, 6th Floor PO Box 24854 1304 Nicosia Cyprus	Hydroxyzine hydrochloride	HYDROXYZINE INOPHARM 25 mg, comprimé pelliculé sécable	25 mg	Film-coated tablet	Oral Use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
France	Inopharm limited 7 Florinis Street Greg Tower, 6th Floor PO Box 24854 1304 Nicosia Cyprus	Hydroxyzine hydrochloride	RAXTA 25 mg, comprimé pelliculé sécable	25 mg	Film-coated tablet	Oral Use
France	Inopharm limited 7 Florinis Street Greg Tower, 6th Floor PO Box 24854 1304 Nicosia Cyprus	Hydroxyzine hydrochloride	TADRO 25 mg, comprimé pelliculé sécable	25 mg	Film-coated tablet	Oral Use
France	Arrow Generiques 26 Avenue Tony Garnier 69007 Lyon France	Hydroxyzine hydrochloride	HYDROXYZINE ARROW 25 mg, comprimé pelliculé sécable	25 mg	Film-coated tablet	Oral Use
Germany	UCB Pharma GmbH Alfred-Nobel-Str. 10 40789 Monheim Germany	Hydroxyzine hydrochloride	AH 3 N Tabletten	25 mg	Film-coated tablet	Oral use
Germany	UCB Pharma GmbH Alfred-Nobel-Str. 10 40789 Monheim Germany	Hydroxyzine hydrochloride	Atarax Tabletten	25 mg	Film-coated tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Greece	Olvos Science AE Eleftherias 4 145 64, Kifisia Greece	Hydroxyzine	EFIDAC	5%	Gel	Cutaneous use
Greece	UCB A.E. Ag. Dimitriou 63 17456, Alimos, Athens Greece	Hydroxyzine	ATARAX	25 mg	Film-coated tablet	Oral use
Greece	UCB A.E. Ag. Dimitriou 63 17456, Alimos, Athens Greece	Hydroxyzine	ATARAX	100 mg/2 ml	Solution for injection	Intramuscular use
Greece	UCB A.E. Ag. Dimitriou 63 17456, Alimos, Athens Greece	Hydroxyzine	ATARAX	10 mg/5 ml	Oral solution	Oral use
Greece	UCB A.E. Ag. Dimitriou 63 17456, Alimos, Athens Greece	Hydroxyzine	ATARAX	100 mg	Film-coated tablet	Oral use
Greece	Uni-Pharma Kleon Tsetis Farmakeftika Ergastria ABEE 14 Km. Nat. Road Athens-Lamia 14564, K. Kifisia Greece	Hydroxyzine	IREMOFAR	25 mg	Film-coated tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Greece	Uni-Pharma Kleon Tsetis Farmakeftika Ergastria ABEE 14 Km. Nat. Road Athens-Lamia 14564, K. Kifisia Greece	Hydroxyzine	IREMOFAR	10 mg/5 ml	Oral solution	Oral use
Greece	Uni-Pharma Kleon Tsetis Farmakeftika Ergastria ABEE 14 Km. Nat. Road Athens-Lamia 14564, K. Kifisia Greece	Hydroxyzine	IREMOFAR	5%	Gel	Cutaneous use
Hungary	UCB Magyarország Kft. Árpád fejedelem útja 26-28 1023 Budapest Hungary	Hydroxyzine hydrochloride	Atarax 25 mg filmtabletta	25 mg	Film-coated tablet	Oral use
Iceland	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	2 mg/ml	Oral solution	Oral use
Iceland	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Ireland	UCB Pharma Ireland Ltd United Drug House Magna Drive, Magna Business Park Citywest Road Dublin 24 Ireland	Hydroxyzine hydrochloride	Ucerax 10mg/5ml Syrup	2 mg/ml	Syrup	Oral use
Ireland	UCB Pharma Ireland Ltd United Drug House Magna Drive, Magna Business Park Citywest Road Dublin 24 Ireland	Hydroxyzine hydrochloride	Ucerax 25mg Film-coated Tablets	25 mg	Film-coated tablet	Oral use
Italy	UCB Pharma S.p.a. Via Gadames 57 20151 Milano Italy	Hydroxyzine hydrochloride	ATARAX	2 mg/ml	Syrup	Oral use
Italy	UCB Pharma S.p.a. Via Gadames 57 20151 Milano Italy	Hydroxyzine hydrochloride	ATARAX	25 mg	Film-coated tablet	Oral use
Italy	UCB Pharma S.p.a. Via Gadames 57 20151 Milano Italy	Hydroxyzine hydrochloride	ATARAX	100 mg/2 ml	Solution for injection	Intramuscular use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Luxembourg	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine dihydrochloride	Atarax	10 mg	Coated tablet	Oral use
Luxembourg	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine dihydrochloride	Atarax	25 mg	Coated tablet	Oral use
Luxembourg	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine dihydrochloride	Atarax	100 mg	Coated tablet	Oral use
Malta	Alliance Pharmaceuticals Limited Avonbridge House Bath Road, Chippenham Wiltshire SN15 2BB United Kingdom	Hydroxyzine dihydrochloride	Atarax 10mg tablets	10 mg	Tablet	Oral use
Malta	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine dihydrochloride	Atarax 25mg tablets	25 mg	Tablet	Oral use
Malta	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine dihydrochloride	Atarax Syrup 0.2%	2 mg/ml	Syrup	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Norway	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine	Atarax	10 mg	Film-coated tablet	Oral use
Norway	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine	Atarax	25 mg	Film-coated tablet	Oral use
Poland	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	2 mg/ml	Syrup	Oral use
Poland	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	10 mg	Film-coated tablet	Oral use
Poland	UCB Pharma S.A. Allée de la Recherche, 60 1070 Bruxelles Belgium	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use
Poland	Aflofarm Farmacja Polska Sp. z o.o. ul. Partyzancka 133/151 95-200 Pabianice Poland	Hydroxyzine hydrochloride	Hydroxyzinum Aflofarm	2 mg/ml	Syrup	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Poland	Biogened S.A ul. Pojezierska 99 91-342 Łódź Poland	Hydroxyzine hydrochloride	Hydroxyzinum Biogened	1,6 mg/g	Syrup	Oral use
Poland	Chemiczno-Farmaceutyczna Spółdzielnia Pracy ESPEFA ul. J. Lea 208 30-133 Kraków Poland	Hydroxyzine hydrochloride	Hydroxyzinum Espefa	2 mg/ml	Syrup	Oral use
Poland	Chemiczno-Farmaceutyczna Spółdzielnia Pracy ESPEFA ul. J. Lea 208 30-133 Kraków Poland	Hydroxyzine hydrochloride	Hydroxyzinum Espefa	25 mg	Film-coated tablet	Oral use
Poland	Chemiczno-Farmaceutyczna Spółdzielnia Pracy ESPEFA ul. J. Lea 208 30-133 Kraków Poland	Hydroxyzine hydrochloride	Hydroxyzinum Espefa	10 mg	Film-coated tablet	Oral use
Poland	Teva Pharmaceuticals Polska Sp. z o.o. ul. Emilii Plater 53 00-113 Warszawa Poland	Hydroxyzine hydrochloride	Hydroxyzinum Teva	50 mg/ml	Solution for infusion	Intramuscular use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Poland	PharmaSwiss Ceska Republika s.r.o. Jankovcova 1569/2c 17000 Praha 7 PSC 170 00 Holesovice Czech Republic	Hydroxyzine hydrochloride	Hydroxyzinum VP	2 mg/ml	Syrup	Oral use
Poland	PharmaSwiss Ceska Republika s.r.o. Jankovcova 1569/2c 17000 Praha 7 PSC 170 00 Holesovice Czech Republic	Hydroxyzine hydrochloride	Hydroxyzinum VP	10 mg	Film-coated tablet	Oral use
Poland	PharmaSwiss Ceska Republika s.r.o. Jankovcova 1569/2c 17000 Praha 7 PSC 170 00 Holesovice Czech Republic	Hydroxyzine hydrochloride	Hydroxyzinum VP	25 mg	Film-coated tablet	Oral use
Portugal	UCB Pharma (Produtos Farmacêuticos), Lda. Rua Victor Câmara, Edifício Q 60, D. Maria I, Piso 1 Fracção D, Quinta da Fonte 2770-229 Paço de Arcos Porgutal	Hydroxyzine	Atarax	25 mg	Film-coated tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Portugal	UCB Pharma (Produtos Farmacêuticos), Lda. Rua Victor Câmara, Edifício Q 60, D. Maria I, Piso 1 Fracção D, Quinta da Fonte 2770-229 Paço de Arcos Portugal	Hydroxyzine	Atarax	2 mg/ml	Syrup	Oral use
Slovak Republic	UCB s.r.o Thámova 13 180 00 Praha 8 Czech Republic	Hydroxyzine	ATARAX	25 mg	Film-coated tablet	Oral use
Spain	UCB Pharma, S.A. Paseo de la Castellana 141 planta 15 Madrid 28046 Spain	Hydroxyzine dihydrochloride	ATARAX 25 mg COMPRIMIDOS	25 mg	Film-coated tablet	Oral use
Spain	UCB Pharma, S.A. Paseo de la Castellana 141 planta 15 Madrid 28046 Spain	Hydroxyzine dihydrochloride	ATARAX 2mg/ml JARABE	2 mg/ml	Syrup	Oral use
Spain	DERMOGEN PHARMA, S.A. Aragoneses, 15 28108 Alcobendas (Madrid) Spain	Hydroxyzine dihydrochloride Propyphenazone Codeine phosphate	DOLODENS GRAGEAS	15 mg 100 mg 10 mg	Tablet	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
Sweden	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	10 mg	Film-coated tablet	Oral use
Sweden	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	25 mg	Film-coated tablet	Oral use
Sweden	UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Copenhagen S Denmark	Hydroxyzine hydrochloride	Atarax	2 mg/ml	Oral solution	Oral use
The Netherlands	UCB Pharma B.V. Lage Mosten 33 4822 NK BREDA The Netherlands	Hydroxyzine dihydrochloride	Hydroxyzine-2 HCl 10	10 mg	Film-coated tablet	Oral use
The Netherlands	UCB Pharma B.V. Lage Mosten 33 4822 NK BREDA The Netherlands	Hydroxyzine dihydrochloride	Hydroxyzine-2 HCl 25	25 mg	Film-coated tablet	Oral use
United Kingdom	UCB Pharma Limited 208 Bath Road, Slough Berkshire SL1 3WE United Kingdom	Hydroxyzine hydrochloride	Ucerax 10mg/5ml Syrup	2 mg/ml	Oral solution	Oral use

Member State (in EEA)	Marketing authorisation holder	INN	Invented name	Strength	Pharmaceutical form	Route of administration
United Kingdom	UCB Pharma Limited 208 Bath Road, Slough Berkshire SL1 3WE United Kingdom	Hydroxyzine hydrochloride	Ucerax 25 mg film-coated tablets	25 mg	Coated tablet	Oral use
United Kingdom	Alliance Pharmaceuticals Limited Avonbridge House Bath Road, Chippenham Wiltshire SN15 2BB United Kingdom	Hydroxyzine hydrochloride	Atarax 10mg film-coated tablets	10 mg	Tablet	Oral use
United Kingdom	Alliance Pharmaceuticals Limited Avonbridge House Bath Road, Chippenham Wiltshire SN15 2BB United Kingdom	Hydroxyzine hydrochloride	Atarax 25mg film-coated tablets	25 mg	Coated tablet	Oral use

Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Scientific conclusions and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Hydroxyzine hydrochloride is a first generation antihistamine first authorised in the 1950s and available in 24 EEA member states. The products are nationally authorised as prescription-only medicines, for use in a number of indications including the treatment of anxiety disorders, skin conditions (such as pruritus, dermatitis or urticaria) for preoperative sedation and for the treatment of sleep disorders.

On 7th March 2014, the Hungarian competent authority was informed of new data on the potential risk for developing QT interval prolongation and/or Torsades de Pointes after exposure to hydroxyzine. The Hungarian competent authority considered it to be in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) under Article 31 of Directive 2001/83/EC. The PRAC was requested to review the benefit-risk balance of hydroxyzine-containing products, in particular giving consideration to their pro-arrhythmogenic potential in all authorised indications and target populations and to give its recommendation on whether any regulatory measures should be taken on the marketing authorisations. In the context of the review, the PRAC consulted the EMA Paediatric Committee (PDCO) and the Geriatric Expert Group (GEG).

The PRAC reviewed all available data, including pre-clinical data, clinical efficacy and safety data and post-marketing safety data, as well as input from the PDCO and the GEG, in the context of its review of the potential risk for developing QT interval prolongation and Torsades de Pointes after exposure to hydroxyzine. The PRAC considered that the efficacy data did not raise any new concerns. Based on the available non-clinical data, the PRAC concluded that hydroxyzine has the potential to block hERG channels and other types of cardiac channels, resulting in a potential risk of QT interval prolongation and cardiac arrhythmia events. This potential risk was confirmed by clinical and post-marketing data, which also identified the at-risk population as consisting of patients with risk factors for QT interval prolongation, such as cardiac medical history, concomitant medications associated with QT interval prolongation and electrolyte imbalance. This is in line with the concept of the repolarisation reserve, which proposes that the concomitant action of multiple factors is required for the exhaustion of the repolarisation reserve, opening the way to the occurrence of cardiac electrophysiological disturbances.

The risk did not differ between indications and no dose effect could be observed based on post-marketing data, despite pre-clinical data suggesting that hydroxyzine has a dose-dependent hERG inhibitory effect. The PRAC considered that the potential risk of QT interval prolongation and Torsades de Pointes can be adequately minimised through appropriate risk minimisation measures targeting the identified risk factors and restricting the use of hydroxyzine, in particular in the at-risk populations. A maximum daily dose of 100 mg was found to be efficacious and well-tolerated and the PRAC therefore recommended restricting the maximum daily dose to 100 mg per day in adults, with corresponding changes in the paediatric and elderly populations, based on pharmacokinetic data. The PRAC also recommended that the treatment duration should be as short as possible. The PRAC recommended that hydroxyzine should be contra-indicated in patients with a known acquired or congenital QT interval prolongation as well as in patients with a known risk factor to QT interval prolongation including a known cardiovascular disease, significant electrolytes imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, concomitant use with other drugs known to prolong the QT interval and/or induce Torsades de Pointes. In addition, further changes to the product information were implemented, including a revision of the posology and a warning that use in the elderly is not recommended due to the anticholinergic effects. The PRAC also

requested the MAHs to circulate a 'Direct healthcare professional' communication (DHPC), assess the effectiveness of the risk minimisation measures and continue to monitor the risks of QT interval prolongation, Torsades de Pointes, ventricular arrhythmia, sudden death and cardiac arrest.

The PRAC concluded that the benefit-risk of the hydroxyzine-containing products remains positive, provided that the agreed changes to the product information and the additional risk minimisation measures are implemented.

Overall conclusion and grounds for the variation to the Marketing Authorisations

Whereas

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC;
- The PRAC reviewed the totality of the available data in relation to the potential risk for developing QT interval prolongation and/or Torsades de Pointes after exposure to hydroxyzine, including pre-clinical data, clinical efficacy and safety data and post-marketing safety data, the MAHs' submissions as well as reports from the Paediatric Committee and the Geriatric Expert Group;
- The PRAC considered that the available efficacy data did not raise any new concerns;
- The PRAC considered that the available safety data confirms the potential risk of QT interval prolongation associated with the use of hydroxyzine;
- The PRAC considered the known risk factors for QT interval prolongation and was of the opinion that the potential risk for QT interval prolongation can be adequately minimised by restricting the use of hydroxyzine, particularly in at-risk patient populations;
- The PRAC agreed on measures including a revision of the posology, contraindications in patients with a known acquired or congenital QT interval prolongation and patients with a known risk factor to QT interval prolongation, a warning that use in the elderly is not recommended due to the anticholinergic effect and a request to the MAHs to assess the effectiveness of the risk minimisation measures.

The PRAC, as a consequence, concluded that the benefit-risk balance of the hydroxyzine-containing products identified in Annex I remains favourable, subject to the agreed amendments to the product information and additional pharmacovigilance activities and additional risk minimisation measures.

The PRAC therefore recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I and for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation.

2 – Detailed explanation of the scientific grounds for differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, the CMDh considered that additional changes were necessary to the wording proposed for the Summary of Product Characteristics (SmPC) and the Package Leaflet, to provide appropriate guidance on the recommendation regarding the maximum daily dose in children and adolescents over 40 kg of body weight but below 18 years of age. The CMDh

noted that the pharmacokinetic data reviewed during the procedure indicates that the half-life of hydroxyzine appears to display a linear increase with age (the half-life in children 12 months of age is 4 hours, compared to 11 hours for children aged 14 years, 14 hours in adults and 29 hours in the elderly). As the recommendation in children below 40 kg in weight is 2 mg/kg/day, the maximum daily dose in this population is 80 mg per day. Because 40 kg in weight is generally considered to be the weight of a child aged 12 years, the CMDh considered that based on the available pharmacokinetic data, the adult maximum daily dose of 100 mg per day would be considered appropriate also for children over 40 kg in weight. The CMDh amended the product information accordingly, revising the wording of Section 4.2 of the SmPC as follows: "*In adults and children over 40 kg in weight, the maximum daily dose is 100 mg per day*" and clarifying the wording of the recommendation in children up to 40 kg in weight. The wording of Section 3 of the Package Leaflet was amended accordingly.

In addition, the CMDh agreed that when implementing the agreed changes to the product information, the MAHs should also revise the posology section as appropriate to introduce any changes consequential to the revised maximum daily dose recommendations. These amendments should be submitted within a Type IB variation.

For products with a paediatric formulation (syrup or oral solution), consideration should be given to making available an appropriate measuring device.

CMDh agreement

The CMDh, having considered the PRAC recommendation, agrees with the overall scientific conclusions by the PRAC and agrees that the marketing authorisations for hydroxyzine-containing medicinal products should be varied.

Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflets

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

I. Summary of Product Characteristics

Section 4.2 - Posology and method of administration

This section should be amended to reflect the following wording:

[Product name] should be used at the lowest effective dose and for the shortest possible duration.

In adults and children over 40 kg in weight, the maximum daily dose is 100 mg per day.

In the elderly, the maximum daily dose is 50 mg per day (see section 4.4).

In children up to 40 kg in weight, the maximum daily dose is 2 mg/kg/day.

Section 4.3 Contraindications

The following wording should be added to this section:

Patients with a known acquired or congenital QT interval prolongation.

Patients with a known risk factor to QT interval prolongation including a known cardiovascular disease, significant electrolytes imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, concomitant use with drugs known to prolong the QT interval and/or induce Torsade de Pointes (see sections 4.4 and 4.5).

Section 4.4 Special warnings and precautions for use

The following wording should be added to this section:

Cardiovascular effects

Hydroxyzine has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been cases of QT interval prolongation and torsade de pointes in patients taking hydroxyzine. Most of these patients had other risk factors, electrolyte abnormalities and concomitant treatment that may have been contributory (see section 4.8).

Hydroxyzine should be used at the lowest effective dose and for the shortest possible duration.

Treatment with hydroxyzine should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should seek immediate medical attention.

Patients should be advised to promptly report any cardiac symptoms.

Elderly patients

Hydroxyzine is not recommended in elderly patients because of a decrease of hydroxyzine elimination in this population as compared to adults and the greater risk of adverse reactions (e.g. anticholinergic effects) (see sections 4.2 and 4.8).

Section 4.5 Interaction with other medicinal products and other forms of interaction

The following wording should be added to this section:

Associations contraindicated

Co-administration of hydroxyzine with drugs known to prolong the QT interval and/or induce Torsade de Pointes e.g. class IA (e.g. quinidine, disopyramide) and III antiarrhythmics (e.g. amiodarone, sotalol), some antihistamines, some antipsychotics (e.g. haloperidol), some antidepressants (e.g. citalopram, escitalopram), some antimalarial drugs (e.g. mefloquine), some antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin), some antifungal agents (e.g. pentamidine), some gastro-intestinal medicines (e.g. prucalopride), some medicines used in cancer (e.g., toremifene, vandetanib), methadone, increase the risk of cardiac arrhythmia. Therefore, the combination is contra-indicated (see section 4.3).

Associations requiring precaution of use

Caution with bradycardia and hypokalaemia-inducing drugs.

The following wording should be present in this section:

Associations requiring precaution of use

Hydroxyzine is metabolized by alcohol dehydrogenase and CYP3A4/5 and an increase in hydroxyzine blood concentrations may be expected when hydroxyzine is co-administered with drugs known to be potent inhibitors of these enzymes.

Section 4.8 Undesirable effects

The following wording should be added to this section:

Not known: ventricular arrhythmias (e.g. Torsade de Pointes), QT interval prolongation (see section 4.4).

II. Package leaflet

The following wording should be included in the specified sections:

Section 2 "What you need to know before you <take> <use> X"

Do not <take> <use> X

- if your ECG (electrocardiogram) shows a heart rhythm problem called "QT interval prolongation"
- if you have or had a cardiovascular disease or if your heart rate is very low
- if you have low salt levels in your body (e.g. low level of potassium or of magnesium)
- if you are taking certain medicines for heart rhythm problems or medicines that may affect the heart rhythm (see "Other medicines and X")
- if anyone in your close family has died suddenly of heart problems

Warnings and precautions

X may be associated with an increased risk of heart rhythm disorder which may be life threatening. Therefore, tell your doctor if you have any heart problems or are taking any other medicines, including medicines obtained without prescription.

While taking X, seek immediate medical attention if you experience heart problems such as palpitations, trouble breathing, loss of consciousness. Treatment with hydroxyzine should be stopped.

Other medicines and X

<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.> This includes any medicines obtained without prescription. X can affect or be affected by other medicinal products.

Do not take X if you are taking medicine to treat:
- bacterial infections (e.g. the antibiotics erythromycin, moxifloxacin, levofloxacin)
- fungal infections (e.g. pentamidine)
- heart problems or high blood pressure (e.g., amiodarone, quinidine, disopyramide, sotalol)
- psychoses (e.g. haloperidol)
- depression (e.g. citalopram, escitalopram)
- gastro-intestinal disorders (e.g. prucalopride)
- allergy
- malaria (e.g. mefloquine)
- cancer (e.g. toremifene, vandetanib)
- drug abuse or severe pain (methadone)

Section 3 "How to <take> <use> X"

<Always <take> <use> this medicine exactly as your doctor <or pharmacist> has told you. Check with your <doctor> <or> <pharmacist> if you are not sure.>

X should be used at the lowest effective dose and the treatment period should be as short as possible.

In adults and children over 40 kg in weight, the maximum daily dose is 100 mg per day in all indications.

In the elderly, the maximum daily dose is 50 mg per day.

In children up to 40 kg, the maximum daily dose is 2 mg/kg/day.

If you <take> <use> more X than you should

If you have used or taken too much X, immediately contact [to be completed nationaly], in particular if a child has taken too much. In the event of overdose, symptomatic treatment could be implemented. An ECG monitoring could be undertaken, because of the possibility of a heart rhythm problem such as QT interval prolongation or Torsade de Pointes.

Section 4 "Possible side effects"

Not known (frequency cannot be estimated from the available data)

Stop taking the medicine and seek immediate medical attention if you experience any problems with the heart rhythm such as palpitations, trouble breathing or loss of consciousness.

Annex IV

Timetable for the implementation of the agreement

Timetable for the implementation of the agreement

Adoption of CMDh agreement:	March 2015 CMDh
Transmission to National Competent Authorities of the translations of the annexes to the agreement:	17 April 2015
Implementation of the agreement by the Member States (submission of the Type IB variation by the Marketing Authorisation Holder):	19 June 2015

Appendix 1

Grounds for the procedure

(notification)

Appendix 2

PRAC Recommendation