ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATIONS AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
Belgium	Laboratories SMB s.a. 26-28 Rue de la Pastorale B-1080 Bruxelles Belgium	Algophene smb	30 mg/400 mg	Capsule, hard	Oral use
Cyprus	Remedica LTD PO Box 51706 3508 Lemesos Cyprus	Destirol	32.5 mg/325 mg	Tablet	Oral use
Cyprus	Interpak LTD PO Box 51166 3502 Lemesos Cyprus	Dologesic	32.5 mg/325 mg	Tablet	Oral use
Cyprus	Medochemie LTD Medochemie Building 1-10 Constantinoupoleos Str., 3011 Limassol, Cyprus	Medonol	32.5 mg/325 mg	Tablet	Oral use
Cyprus	Phadisco LTD PO Box 22173 1518 Lefkosia Cyprus	Distalgesic	32.5 mg/325 mg	Tablet	Oral use
France	Arrow Generiques 26, avenue Tony Garnier 69007 Lyon France	Dextropropoxyphene Paracetamol almus	30 mg/400 mg	Capsule, hard	Oral use
France	Arrow Generiques 26, avenue Tony Garnier 69007 Lyon France	Dextropropoxyphene Paracetamol arrow	30 mg/400 mg	Capsule, hard	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	Sanofi-aventis France 1-13 Bd Romain Rolland 75014 Paris France	Dextropropoxyphene Paracetamol Biogalenique	30 mg/400 mg	Capsule, hard	Oral use
France	Sanofi- aventis France 1-13, boulevard Romain Rolland 75014 Paris France	Di-antalvic	30 mg/400 mg	Suppository	Rectal use
France	Biogaran 15, boulevard Charles de Gaulle 92700 Colombes France	Dextropropoxyphene Paracetamol biogaran	30 mg/400 mg	Capsule, hard	Oral use
France	Bouchara Recordati 68, rue Marjolin, BP 67 92302 Levallois-Perret Cedex France	Dioalgo	30 mg/400 mg	Capsule, hard	Oral use
France	Chemical Farma 3 quai Louis Blériot 75016 PARIS France	Dextroref	30 mg/400 mg	Capsule, hard	Oral use
France	Dci Pharma 180, rue Eugène Avinée 59120 Loos France	Dextropropoxyphene Paracetamol dci Pharma	30 mg/400 mg	Capsule, hard	Oral use
France	EG Labo - Laboratoires EuroGenerics "Le Quintet" bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	Dextropropoxyphene Paracetamol eg	30 mg/400 mg	Capsule, hard	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	Expanpharm International 6, rue de la Rochefoucauld 16000 Angoulême France	Dextropropoxyphene Paracetamol Expanpharm	30 mg/400 mg	Capsule, hard	Oral use
France	Substipharm 8 Rue Bellini 75116 Paris France	Dextropropoxyphene Paracetamol hexal	30 mg/400 mg	Capsule, hard	Oral use
France	Teva Santé Le Palatin 1 1 cours du Triangle 92936 Paris La Défense Cedex France	Dextropropoxyphene Paracetamol ivax	30 mg/400 mg	Capsule, hard	Oral use
France	Labo Concept Pharm 26, boulevard Paul Vaillant Couturier 94200 Ivry Sur Seine France	Dextropropoxyphene Paracetamol isomed	30 mg/400 mg	Capsule, hard	Oral use
France	Qualimed 117 Allée des Parcs 69800 Saint Priest France	Dextropropoxyphene Paracetamol qualimed	30 mg/400 mg	Capsule, hard	Oral use
France	Ranbaxy Pharmacie Generiques 11-15 Quai de Dion Bouton 92800 Puteaux France	Dextropropoxyphene Paracetamol rpg	30 mg/400 mg	Capsule, hard	Oral use
France	Laboratoires Alter 3, avenue de la Baltique ZI de Courtaboeuf 91140 Villebon Sur Yvette France	Dextropropoxyphene Paracetamol alter	30 mg/400 mg	Capsule, hard	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	Sanofi-aventis France 1-13, boulevard Romain Rolland75014 Paris France	Di-antalvic	30 mg/400 mg	Capsule, hard	Oral use
France	Laboratoires Therabel Lucien Pharma 19 Rue Alphone de Neuville 75017 Paris Fran ce	Di dolko	30 mg/400 mg	Capsule, hard	Oral use
France	Leurquin Mediolanum 68-88, rue Louis Ampère 93330 Neuilly-sur-Marne France	Talvidol	30 mg/400 mg	Capsule, hard	Oral use
France	Mylan SAS 117 Allée des Parcs 69800 Saint Priest France	Dextropropoxyphene Paracetamol Mylan	30 mg/400 mg	Capsule, hard	Oral use
France	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm Germany	Dextropropoxyphene Paracetamol Ratiopharm	30 mg/400 mg	Capsule, hard	Oral use
France	Sandoz 49, avenue Georges Pompidou 92300 Levallois-Perret France	Dextropropoxyphene Paracetamol G Gam	30 mg/400 mg	Capsule, hard	Oral use
France	Sandoz 49, avenue Georges Pompidou 92300 Levallois-Perret France	Dextropropoxyphene Paracetamol Sandoz	30 mg/400 mg	Capsule, hard	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	Teva Santé Le Palatin 1 1, cours du Triangle 92936 Paris la Défense Cedex France	Dextropropoxyphene Paracetamol Teva	30 mg/400 mg	Capsule, hard	Oral use
France	Sodephar 176, rue de l'Arbrisseau 59000 Lille France	Dextropropoxyphene Paracetamol Sodephar	30 mg/400 mg	Capsule, hard	Oral use
France	Actavis France Centre d'Affaires la Boursidière 92357 le Plessis-Robinson France	Dextropropoxyphene Paracetamol Actavis	30 mg/400 mg	Capsule, hard	Oral use
France	Actavis France Centre d'Affaires la Boursidière 92357 le Plessis-Robinson France	Dexap	30 mg/400 mg	Capsule, hard	Oral use
France	Sanofi-aventis France 1-13 Bd Romain Rolland 75014 Paris France	Dialgirex	30 mg/400 mg	Capsule, hard	Oral use
France	Sanofi-aventis France 1-13 Bd Romain Rolland 75014 Paris France	Dextropropoxyphene/ Paracetamol Theraplix	30 mg/400 mg	Capsule, hard	Oral use
France	Zydus France 25, rue des Peupliers ZAC Les Hautes Pâtures Parc d'Activités des Peupliers 92000 Nanterre France	Dextropropoxyphene Paracetamol Zydus	30 mg/400 mg	Capsule, hard	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	Alter 3, avenue de la Baltique 91140 Villebon Sur Yvette France	Dextropropoxyphene/ Paracetamol/ Cafeine Alter	27 mg/400 mg/30 mg	Tablet	Oral use
France	Arrow Generiques 26, avenue Tony Garnier 69007 Lyon France	Dextropropoxyphene/ Paracetamol/ Cafeine Almus	27 mg/400 mg/30 mg	Tablet	Oral use
France	Arrow Generiques 26, avenue Tony Garnier 69007 Lyon France	Dextropropoxyphene/ Paracetamol/Cafeine Arrow	27 mg/400 mg/30 mg	Tablet	Oral use
France	Arrow Generiques 26, avenue Tony Garnier 69007 Lyon France	Dextropropoxyphene/ Paracetamol/ Cafeine Offilink	27 mg/400 mg/30 mg	Tablet	Oral use
France	Plus Pharmacie 26, boulevard Paul Vaillant-Couturier 94200 Ivry-sur-Seine France	Dextropropoxyphene / Paracetamol / Cafeine Isomed	27 mg/400 mg/30 mg	Tablet	Oral use
France	Biogaran 15, boulevard Charles de Gaulle 92700 Colombes France	Dextropropoxyphene/ Paracetamol/ Cafeine Biogaran	27 mg/400 mg/30 mg	Tablet	Oral use
France	Eg Labo - Laboratoires EUROGENERICS "Le Quintet" - bâtiment A 92517 Boulogne Billancourt Cedex France	Dextropropoxyphene/ Paracetamol/ Cafeine Eg	27 mg/400 mg/30 mg	Tablet	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	Ranbaxy Pharmacie Generiques 1115 Quai de Dion Bouton Immeuble Avant Seine 92816 Puteaux Cédex France	Dextropropoxyphene/ Paracetamol/ Cafeine Rpg	27 mg/400 mg/30 mg	Tablet	Oral use
France	Mylan SAS 117 Allée des Parcs 69800 Saint Priest France	Dextropropoxyphene/ Paracetamol/ Cafeine Mylan	27 mg/400 mg/30 mg	Tablet	Oral use
France	Mylan SAS 117 Allée des Parcs 69800 Saint Priest France	Dextropropoxyphene/ Paracetamol/Cafeine Mylan Pharma	27 mg/400 mg/30 mg	Tablet	Oral use
France	Qualimed (Lyon) 117 Allée des Parcs 69800 Saint Priest France	Dextropropoxyphene/ Paracetamol/ Cafeine Qualimed	27 mg/400 mg/30 mg	Tablet	Oral use
France	Laboratoire Ratiopharm 19, boulevard Paul Vaillant Couturier 94200 Ivry sur Seine France	Dextropropoxyphene/ Paracetamol/ Cafeine Ratiopharm	27 mg/400 mg/30 mg	Tablet	Oral use
France	Sandoz 49, avenue Georges Pompidou 92593 Levallois-Perret France	Dextropropoxyphene/ Paracetamol/ Cafeine G Gam	27 mg/400 mg/30 mg	Tablet	Oral use
France	Sandoz 49, avenue Georges Pompidou 92300 Levallois-Perret France	Dextropropoxyphene/ Paracetamol/ Cafeine Sandoz	27 mg/400 mg/30 mg	Tablet	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
France	TEVA Santé Le Palatin 1 1, cours du Triangle 92936 Paris la Défense Cedex France	Dextropropoxyphene/ Paracetamol/ Cafeine Teva	27 mg/400 mg/30 mg	Tablet	Oral use
France	Zydus France 25, rue des Peupliers ZAC Les Hautes Pâtures Parc d'Activités des Peupliers 92000 Nanterre France	Dextropropoxyphene/ Paracetamol/ Cafeine Zydus	27 mg/400 mg/30 mg	Tablet	Oral use
France	Sanofi-aventis France 1-13 Bd Romain Rolland 75014 Paris France	Propofan	27 mg/400 mg/30 mg	Tablet	Oral use
France	Sanofi-aventis France 1-13 Bd Romain Rolland 75014 Paris France	Dextropropoxyphene/ Paracetamol/ Cafeine Winthrop	27 mg/400 mg/30 mg	Tablet	Oral use
Luxembourg	S.M.B 26-28 rue de la Pastorale B-1080 Bruxelles Belgium	Algophene	30 mg/400 mg	Capsule	Oral use
Malta	Medochemie LTD Medochemie Building 1-10 Constantinoupoleos Str., 3011 Limassol, Cyprus	Medonol	32.5 mg/325 mg	Tablet	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Invented Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
Malta	Phadisco Ltd 185 Giannou Kranidioti Avenue CY-2235 Latsia Cyprus	Distalgesic	32.5 mg/325 mg	Tablet	Oral use
Norway	Actavis group hf Dalshraun 1 220 Hafnafjordur Iceland	Aporex	70 mg/400 mg	Tablet	Oral use
Portugal	Ferraz Lynce S.A Rua Consiglieri Pedroso 123 Queluz de Baixo Apartado 1001 2731 901 Barcarena Portugal	Algifene	25 mg/300 mg	Coated tablet	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Product Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
Belgium	Pfizer s-a. Boulevard de la Plaine 111050 Bruxelles Belgium	Depronal	150 mg	Prolonged-release capsule, hard	Oral use
Denmark	Dansk Lægemiddelforsyning DLF ApS, Lodshusvej 11, DK-4230 Skælskør Denmark	Abalgin	65 mg	Capsule, hard	Oral use
Denmark	Dansk Lægemiddelforsyning DLF ApS, Lodshusvej 11, DK-4230 Skælskør Denmark	Abalgin	65 mg	Film-coated tablet	Oral use
Denmark	Dansk Lægemiddelforsyning DLF ApS, Lodshusvej 11, DK-4230 Skælskør Denmark	Abalgin retard	150 mg	Prolonged-release capsule	Oral use
Denmark	NordMedica A/S, Bredgade 41, DK-1260 Copenhagen K Denmark	Doloxene	100 mg	Capsule, hard	Oral use
Finland	Alternova A/S, Lodshusvej 11 4230 Skaelskoer Denmark	Abalgin	65 mg	Capsule, hard	Oral use
Finland	Alternova A/S, Lodshusvej 11 4230 Skaelskoer Denmark	Abalgin retard	150 mg	Prolonged-release capsule, hard	Oral use
France	Sanofi Aventis France 1-13 boulevard Romain Rolland 75014 Paris France	Antalvic adultes	65mg	Tablet	Oral use

Dextropropoxyphene containing medicinal products with Marketing Authorisation in the European Union

Member State	**Marketing Authorisation Holder**	**Product Name**	**Strength/ dextropropoxyphene/ paracetamol/ caffeine**	**Pharmaceutical Form**	**Route of Administration**
Greece	Stargen Ltd Favierou 48 Athens 10439 Greece	Romidon	65 mg	Capsule, hard	Oral use
Luxembourg	PFIZER s-a. Boulevard de la Plaine 11 1050 Bruxelles Belgium	Depronal	150 mg	Prolonged-release capsule	Oral use
Netherlands	Pfizer B.V. Rivium Westlaan 142 2909 LD Capelle a/d Ijssel Nederlands	Depronal	150 mg	Modified release capsule	Oral use
Spain	Parke Davis, S.L. Avda. de Europa, 20 B. Parque Empresarial La Moraleja; Alcobendas; 28108 Madrid España	Deprancol a.s.	150 mg	Prolonged-release capsule, hard	Oral use
Sweden	Meda AB, Box 906 170 09 Solna Sweden	Doloxene	50 mg	Capsule, hard	Oral use
Sweden	Meda AB, Box 906 170 09 Solna Sweden	Doloxene	100 mg	Capsule, hard	Oral use
Sweden	BioPhausia AB, Blasieholmsgatan 2 111 48 Stockholm Sweden	Dexofen	50 mg	Tablet	Oral use
Sweden	BioPhausia AB, Blasieholmsgatan 2 111 48 Stockholm Sweden	Dexofen	100 mg	Tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR WITHDRAWAL OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EUROPEAN MEDICINES AGENCY

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF DEXTROPROPOXYPHENE CONTAINING MEDICINAL PRODUCTS (see Annex I)

Dextropropoxyphene containing medicinal products (as single component or combination with paracetamol or paracetamol/caffeine) are used in the symptomatic treatment of pain and are currently authorised in several Member States. Across Member States, the authorised indications considerably vary from “moderate to severe pain”, “mild to moderate pain”, and “acute and chronic pains of different origins”.

On the basis of evidence of harm from reports of fatal overdose, of divergent safety reviews and previous regulatory action taken in several Member States, the European Commission initiated a referral under Article 31(2) of Directive 2001/83/EC, as amended, to address this public health issue for medicinal products containing dextropropoxyphene and paracetamol, and therefore referred the matter to the CHMP on 30 November 2007.

After considering the CHMP’s major concerns over the toxicity of dextropropoxyphene, given its narrow therapeutic index and its adverse effects on the cardio - respiratory system as well as the lack of information in relation to the use of single component dextropropoxyphene medicinal products, the European Commission agreed on 31 March 2009 to the extension of the scope of the referral to also include authorised medicinal products containing only dextropropoxyphene.

The CHMP reviewed the data submitted by the MAHs to address the above-mentioned concerns as well as the available data from Member States in relation to drug poisoning that involves dextropropoxyphene and the investigation of suspicious deaths in their countries.

Efficacy

Available efficacy data are limited due to methodological shortcomings such as the absence of a sample size calculation in the majority of the double-blind studies in acute pain and the lack of long term efficacy data to support the use of the fixed combination of dextropropoxyphene and paracetamol as a prolonged treatment.

Although available meta-analyses mostly included single dose studies, these data also provided further insights in the efficacy of the dextropropoxyphene containing medicinal products. For a single dose of dextropropoxyphene 65 mg in postoperative pain the number needed to treat to benefit for at least 50% pain relief was 7.7 (95% confidence interval 4.6 to 22) when compared with placebo over 4-6 hours. This means that one in every eight subjects with pain of moderate to severe intensity would experience at least 50% pain relief with dextropropoxyphene 65 mg who would not have done so with placebo. For the equivalent dose of dextropropoxyphene combined with paracetamol 650 mg the NNT was 4.4 (3.5 to 5.6) when compared with placebo, indicating higher efficacy.

In acute pain, the fixed combination of dextropropoxyphene and paracetamol appeared to be an effective analgesic; this is to be expected, as paracetamol alone is an effective analgesic. However, there is no clear evidence from clinical trials of superiority of efficacy of the combination of dextropropoxyphene and paracetamol compared with normal therapeutic doses of paracetamol alone, the trials which have suggested superiority to paracetamol alone have used sub-therapeutic doses of paracetamol. Ibuprofen has also shown to be more effective, as a single dose, in the management of severe postoperative pain; tramadol being equally effective in this setting.

In chronic pain, other combinations of paracetamol and an opioid (such as a fixed-dose combination of paracetamol and codeine phosphate), or a combination of a non-steroidal anti-inflammatory drug (NSAID) and an opioid other than dextropropoxyphene have been shown to be at least as effective as the fixed combination of dextropropoxyphene and paracetamol.

Safety

The overall safety profile of the dextropropoxyphene containing medicinal products is based on an extensive post-marketing experience (over 40 years).

The most frequently reported adverse reactions with fatal outcome involved hepatobiliary disorders, skin disorders, general disorders, blood and lymphatic disorders, nervous system disorders, gastrointestinal disorders and cardiac disorders.

However, the key safety concern with dextropropoxyphene is that it has a very narrow therapeutic index under normal conditions of use: following overdose, cardiac arrhythmias (which cannot be reversed using naloxone) and opioid side effects (such as respiratory depression) are rapid in onset and often fatal – there is evidence that the case fatality rate is higher than, for example, for tricyclic antidepressants.

The narrow therapeutic index means that accidental overdose is a real possibility under normal conditions of use, particularly for patients on certain concomitant medications or when combined with even a small amount of alcohol.

Since the benefit/risk reviews of dextropropoxyphene containing products were carried out in the UK, Sweden, France, and Ireland in 2005 – following which the fixed dose combination product (paracetamol + dextropropoxyphene) was withdrawn from the market in the UK, Sweden, and Ireland – a substantial body of important new safety information has become available.

In particular, more comprehensive mortality data at a national level from France, notably forensic toxicology results, provided evidence of a significantly greater number of deaths associated with the use of dextropropoxyphene-containing products than had previously been estimated.

Similarly in Ireland, analysis in 2009 of further data from the Alcohol and Drug Research Unit of the Health Research Board revealed significant under-reporting of deaths associated with dextropropoxyphene-containing products – indicating fatality rates fifteen-fold higher than previously reported.

Also, research in the UK demonstrated the benefits of the withdrawal of dextropropoxyphene from the market – with clear evidence of a fall in number of deaths associated with dextropropoxyphene, but without any rise in mortality from poisoning with other common analgesics.

After reviewing all the available data, the CHMP considered that the different figures provided by the data sources (spontaneous reports, forensic and poison centres, national mortality statistics) showed overall a significant number of deaths in which dextropropoxyphene is present at toxic levels.

On the basis of the available data sources, the CHMP was of the opinion that spontaneous reporting was significantly underestimating the number of reported deaths associated with dextropropoxyphene. The CHMP also considered that data collected from national poison centres have limitations in this situation as dextropropoxyphene can cause death extremely rapidly (in under an hour); if a patient dies before reaching medical attention, the poisons centre is unlikely to be contacted. Because of this, the most

reliable data come from forensic analysis and national mortality statistics, and complete review of the fatal overdoses associated with dextropropoxyphene (alone and in combination with paracetamol/caffeine) supported the major concern over the fatal toxicity of dextropropoxyphene containing products under normal conditions of use due to their narrow therapeutic index.

Risk Minimisation Measures

Risk Minimisation measures proposed by the MAHs included restriction of the use of the product (i.e. changes in SPC to restrict the population; pack size reduction), modification of the posology (e.g. reduction of posology in elderly population) and addition of further safety warnings (e.g. on concomitant use with alcohol, dependence and tolerance, combination with other central acting analgesics and overdose in children).

However no consideration was given to the need for national mortality data, and in particular forensic pathology data, to ensure that any risk minimisation measures are working: it is not possible to use routinely-collected (spontaneous) data to assess the effectiveness of the risk minimisation measures, because of the significant under-reporting of even serious adverse events, including death. In addition, in some member states it had been both difficult and time-consuming to collate the relevant data for the purposes of the Article 31 referral, and it would be impractical and, in the medium term, unfeasible to monitor the effectiveness of risk minimization activities in these countries.

Apart from the strengthened warnings, and more extensive contra-indications, proposed by several MAHs, the other proposals for changes in the SPCs and PLs – for example, in relation to indication – reflected the existing variations across Europe and were often not internally consistent: for example, the proposal that chronic pain should be explicitly contra-indicated, in the context of a SPC also having instructions in relation to repeat prescriptions “which should not exceed three months”.

One possible risk minimisation measure, a reduced pack size (e.g. to only 10 tablets), is unlikely to be of any significant benefit in risk minimisation as the lethal dose (particularly when taken with alcohol) is under 10 tablets. In addition, a smaller pack size is unlikely to result in smaller stocks of medication at home, since a patient being treated for chronic pain might well be given a month’s supply in one go.

Similarly, proposals to limit supplies for each prescription to at most 15 days, or one month, before review is needed by the prescriber, are unlikely to be of any significant benefit in risk minimisation: the patient will still have access to significant large quantity in excess of the lethal dose.

Benefit-Risk

Available data showed only limited efficacy of the dextropropoxyphene medicinal products in the symptomatic treatment of pain. While some patients find these products helpful in managing pain, results from clinical trials do not provide evidence for the superior efficacy of dextropropoxyphene alone or in combination with paracetamol, when compared with normal therapeutic doses of simple analgesics. Furthermore, the lack of long term efficacy data did not allow any definite conclusions to be drawn on the efficacy of the dextropropoxyphene medicinal products as a long-term treatment.

Although spontaneous reporting suggested that the safety signal concerning the overdose was not significant, other more complete data, particularly from forensic centres and national mortality statistics confirmed that the risk of accidental fatal overdose under normal conditions of use associated with dextropropoxyphene containing products is of major concern, mainly due to their narrow therapeutic index and high case fatality. The different figures provided by the available data sources (spontaneous reports, forensic and poison centres, national mortality statistics) showed overall a significant number of

deaths in which dextropropoxyphene is present at toxic levels. A substantial proportion of the fatal overdoses are accidental - occurring under normal conditions of use, for the licensed indication of pain - and there is a significant public health impact in relation to these cases alone.
In view of the complex context in which cases of fatal overdose occurred under normal conditions of use and in view of the narrow therapeutic index and the potential for rapid death, the CHMP was of the opinion that the above proposed risk minimisation activities of narrowing the indication, reducing the pack sizes and/or introducing further safety warnings and contraindications (including those beyond the Product Information) would not be able to reduce the risks to an acceptable level.

Based on the limited efficacy and the significant risk of fatal overdose (in particular accidental overdose), the CHMP was of the opinion that the benefit/risk balance of dextropropoxyphene containing medicinal products was negative. Therefore the CHMP recommended the withdrawal of all Marketing Authorisations for medicinal products containing dextropropoxyphene.

A group of MAHs disagreed with the opinion recommending the withdrawal of the Marketing Authorisations and requested a re-examination of the opinion.

Having considered the detailed grounds for re-examination provided by the group of MAHs in writing and in an oral explanation, the CHMP considered that the design of the proposed clinical study to demonstrate the superior efficacy for combination of dextropropoxyphene and paracetamol versus paracetamol alone was flawed, and even a well-designed study would not change the benefit-risk balance of the dextropropoxyphene medicinal products in view of the narrow therapeutic index.

Therefore, the CHMP concluded by majority that the benefit-risk balance of dextropropoxyphene containing medicinal products is negative and that its Opinion of 25 June 2009 should not be revised for oral/rectal dextropropoxyphene containing medicinal products and recommended the withdrawal of the Marketing Authorisations to be effective within the next 15 months of the Commission Decision in order to allow switching patients to safer alternatives, considering the extensive clinical use of dextropropoxyphene containing medicinal products and the wide patient exposure in some Member States.

GROUNDS FOR WITHDRAWAL OF THE MARKETING AUTHORISATIONS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended for medicinal products containing dextropropoxyphene;

- The Committee assessed the grounds for re-examination submitted by a group of MAHs on 15 July 2009, the information provided by the MAHs at an oral explanation on 20 October 2009 and the scientific discussion within the Committee;

- The Committee considered that dextropropoxyphene containing medicinal products showed only limited efficacy in the symptomatic treatment of pain;

- The Committee also considered that a significant number of deaths have been reported in which dextropropoxyphene is present at toxic levels confirming that the risk of accidental fatal overdose associated with dextropropoxyphene containing medicinal products and their narrow therapeutic index is of major concern;

- The Committee concluded, in view of the available data, that the risk of accidental fatal overdose associated with the use of dextropropoxyphene containing medicinal products in the symptomatic treatment of pain outweigh the limited benefits. In addition, the Committee considered that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

The CHMP, having considered the matter as set out in the appended referral assessment report recommended the withdrawal of all the Marketing Authorisations for all oral/rectal medicinal products referred to in Annex I to be effective within the next 15 months after Commission Decision in order to allow switching patients to safer alternatives in particular, considering the extensive clinical use of dextropropoxyphene containing medicinal products and the wide patient exposure in some Member States.