

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

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Product Name</u>	<u>Strength/ dextropropoxyphene/ paracetamol/ caffeine</u>	<u>Pharmaceutical Form</u>	<u>Route of Administration</u>
Greece	Stargen Ltd Favierou 48 Athens 10438 Greece	Romidon	75mg/2ml	Solution for injection	Intramuscular, intravenous use
Greece	Norma Hellas S.A. Menandrou 54 Athens 10431 Greece	Zideron	75mg/2ml	Solution for injection	Intramuscular, intravenous use

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR SUSPENSION 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.

The availability of a parenteral formulation might be viewed as providing a further therapeutic option, since it would arguably reduce the risk of an accidental overdose (by the patient taking more, because of lack of efficacy) and of intentional overdose (depending on where supplies were held). However, the CHMP considered that parenteral opioids carry further significant risks in themselves, such as abuse/dependence and diversion which are also of major concern.

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.

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.

Though a parenteral formulation of dextropropoxyphene might be viewed as providing a further therapeutic option, parenteral opioids carry further significant risks in themselves, such as abuse/dependence and diversion, which would appear difficult to justify in this instance given the lack of evidence of efficacy.

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.

Whilst there is a risk of fatal overdose, the CHMP considered that it is limited for the parenteral dextropropoxyphene medicinal products, given the administration under hospital setting (given by healthcare professionals) and the classification of these medicinal products as narcotic prescription (in the Member State where the product is authorised) and the lack of evidence of fatal overdose particularly of accidental overdose. Nevertheless, the CHMP also took the well-established narrow therapeutic index into account, as well as other known risks associated with the use of parenteral opioids and potentially associated with the use of parenteral dextropropoxyphene such as abuse and dependence and given that the efficacy of parenteral dextropropoxyphene containing medicinal products has not been established, the CHMP concluded that the benefit-risk balance for the parenteral dextropropoxyphene containing medicinal products was negative and recommended the suspension of the Marketing Authorisations to be effected within 15 months of the Commission Decision to allow healthcare professionals to prepare for a potential switch to using alternatives. For the suspension to be lifted, the Marketing Authorisation Holders would need to provide evidence of a patient population in which the benefit-risk balance of parenteral dextropropoxyphene medicinal products is positive.

GROUNDNS FOR SUSPENSION 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 the efficacy of parenteral dextropropoxyphene containing medicinal products has not been established;-
- The Committee considered the risk of fatal overdose with dextropropoxyphene. The Committee noted that this risk is limited for the parenteral dextropropoxyphene medicinal products, given the administration under hospital setting (given by healthcare professionals) and the classification of these medicinal products as narcotic prescription (in the Member State where the product is authorised). However, the CHMP took note of the narrow therapeutic index of dextropropoxyphen containing products. In addition, the CHMP considered other known risks associated with the use of parenteral opioids such as the risk of abuse and dependence.
- The Committee concluded that the risks associated with the use of parenteral dextropropoxyphene medicinal products in the treatment of symptomatic pain outweigh the potential benefit as the efficacy has not been demonstrated.

The CHMP, having considered the matter as set out in the appended referral assessment report recommended the suspension of the Marketing Authorisations for all parenteral medicinal products referred to in Annex I to be effected within 15 months of the Commission Decision in order to allow healthcare professionals to prepare for a potential switch to using alternatives.. For the suspension to be lifted the Marketing Authorisation Holders would need to provide evidence of a patient population in which the benefit-risk balance of parenteral dextropropoxyphene medicinal products is positive.

ANNEX III
CONDITION FOR THE LIFTING OF THE SUSPENSION

For the suspension to be lifted the Marketing Authorisation Holders would need to provide the National Competent Authorities with the following:

- Evidence of a patient population in which the benefit-risk balance of parenteral dextropropoxyphene medicinal products is positive.