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EXPERT OPINION

Comment on: A record number of fatalities in many categories of patients treated with deferasirox: loopholes in regulatory and marketing procedures undermine patient safety and misguide public funds?

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The editorial by GJ Kontoghiorghe [1] contains significant factual inaccuracies, selectively omits important information about deferasirox and lacks the robust epidemiological methodology typical for analysis of pharmacovigilance data for safety signals. The aim of this letter is to correct these inaccuracies, providing correct information for doctors and patients.

Several key references in the editorial do not meet the criteria for scientific data integrity. For example, data are cited from *ehealthme.com*, a website that includes social media among its data sources, and *fda-reports.com*, the website of a US personal injury law firm. In addition, data cited from the Institute for Safe Medication Practices (ISMP) report are interpreted out of context, cover a 4-year time period and are highly flawed as a result of a reporting problem acknowledged by ISMP itself [2]. Several other references cited are the author's own opinion/review articles and many reflect treatment practices in place over 5 years ago, when less was known about available iron chelators. Furthermore, the author, a chemist, is the inventor of the drug deferiprone (a fact which is not disclosed). We believe that peer-reviewed, published clinical trial data and health authority reports provide far more reliable information.

The article lacks robust epidemiological methodology, as shown in Figure 1 [1]. Four mortality data sets are drawn upon to allegedly demonstrate a progressive increase in the number of fatalities among patients treated with deferasirox. The author compares 1-year data with cumulative data obtained since deferasirox FDA approval, from different and highly unreliable sources. Several of the cited references do not report the data referenced. The author also wrongly cites an EMA 'warning' 'issued for increasing the dose from 30 to 40 mg/kg per day'. The actual EMA Report approves the 40 mg/kg/day dose and states that 'increased risk of renal adverse events with Exjade doses above 30 mg/kg cannot be excluded'.

Deferasirox has been approved in 117 countries. Since first approval in 2005, over 5900 patients have been enrolled in trials with up to 5 years of follow-up, and there have been over 150,000 patient-years of exposure. The author's claim that reporting of 'mortality and morbidity incidence [...] is scarce' and suggestion that Novartis would 'promote only positive aspects of the drug but downplay

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serious toxicities' are unfounded and unsupported, as are claims regarding the lack of monitoring of side effects. Efficacy and safety data have been published extensively [3-5]. Novartis is fully committed to meeting international guidelines ensuring quality and transparency of industry-sponsored clinical trial reporting, and to Good Publication Practice. The deferasirox label clearly identifies appropriate safety-monitoring measures. Novartis submits annual safety reports to health authorities; relevant findings are reflected in label updates and promptly communicated to healthcare professionals.

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Author's response

Novartis should publish all their own first-hand extensive epidemiological and pharmacovigilance updated data on morbidity, mortality and treatment outcomes of deferasirox, which are necessary and essential information required by doctors and patients. Such data should include all the fatal toxicity cases of renal, hepatic and bone marrow failure, gastric haemorrhage etc. as described in the label updates, instead of avoiding such issues and criticising four different independent organisations, which released FDA- and EMA-based information on fatalities, which reached 4113 cases by the end of 2012 [1]. Novartis has not included any reference or criticism of NeLM, which is the largest medicines information portal for healthcare professionals in the UK National Health Service, which has reported an 11.7% mortality (1935 cases out of 16,514) by EMA by the end of 2009 and is higher to that reported by ISMP earlier that same year (1320) [1,2]. It should be noted that this rate of fatalities is one of the highest ever reported for a new patented drug.

Novartis sponsored publications, highlighting that positive effects of deferasirox are questioned, especially since fatal and other toxicity incidences are not mentioned and the need for prophylactic measures ignored. Similarly, the approach and policies adopted by Novartis and the regulatory authorities are misleading and may undermine patient safety, especially

Novartis has been helping patients with iron overload since 1962, when deferoxamine became available. We are committed to ensuring that patients with iron overload continue to have access to effective and safe chelation, and that healthcare professionals have up-to-date and accurate information about the risks and benefits of our drugs.

Declaration of interest

A Riva is an employee of Novartis.

when considering the reporting of > 500 fatalities for the off-label use of deferasirox in many non-iron-loaded conditions [1]. Who is really responsible for the off-label use of deferasirox and should such cases not have been reported? [1].

My status as the inventor of the generic drug deferiprone is public knowledge cited in many publications since the 1980s [3]. Similarly, I am the inventor of many other chelators, of deferoxamine suppositories, of the combination of deferoxamine and deferiprone that changed thalassaemia from a fatal to a chronic disease and the ICOC deferoxamine/deferiprone combination that resulted in the normalisation of the iron stores in thalassaemia patients [3-5]. These projects were part of academic research and as in the case of deferiprone, they did not involve any pharmaceutical or other commercial companies. In contrast to the 'golden era' of chelation therapy which has been attained by some of these inventions, it would appear that not only is deferasirox ineffective in reaching these goals but it also comes with an increasing rate of morbidity and mortality in the cohort of patients using it [1-5].

As a chemist, among other specialisations, I have the means to question how a drug costing around 200 US dollars to produce is sold by Novartis at 80,000 US dollars per patient per year, which under the present financial circumstances is a major impact on public expenditure. Within this context and also the necessity for transparency, pharmaceutical companies should declare the income and profits from drug

sales and specify the individual amounts spent on 'lobbying' health and regulatory authorities, physicians, patient organisations etc., which may be compromising patient safety as described in Figure 2 [1].

Declaration of interest

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