The price of enhanced half-life factor IX

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Dear Sir,

Factor VIII and IX products with enhanced half-life are being introduced into routine clinical practice1. Not unexpectedly, these new products have raised a number of questions that span from defining their place in therapy in clinical practice to issues of regulatory approval by national drug agencies or regional health systems. In this context, determining the price of these long-acting products is particularly difficult because a complex comparison is needed between the new products2 and those with "normal" half-life available as standard of care for more than two decades3. This communication is focused on factor IX and deals with innovative enhanced half-life products compared with "old" recombinant products characterised by standard pharmacokinetics.

Studying the pharmacokinetics of deficient factors in patients with haemophilia is based on well-standardised methods3,4. The methods are essentially the same as those used for more than 30 years for conducting pharmacokinetic investigations in all areas of clinical pharmacokinetics5. Drug clearance (CL) is recognised to be the main pharmacokinetic parameter; because CL is known to be directly related to concentrations, and so this parameter acts as the main determinant of the therapeutic effect.

As regards factor IX, all of these pharmacokinetic rules are entirely valid4. Using pharmacokinetic modelling is crucial to interpret the information on administered doses and measured plasma concentrations appropriately, particularly because the dosing regimens of factor IX are extremely variable, depending not only on the type of treatment (prophylaxis vs on-demand), but also on the dosing interval selected for individual patients (e.g. once weekly vs every other week). In other words, the use of pharmacokinetic modelling is advantageous for factor IX because a unified methodological approach can be applied despite the heterogeneity of dosing regimens.

The aim of this analysis was to compare the CL values of representative examples of a standard-half-life recombinant factor IX (BeneFix, Firm?, town?, country?) and an enhanced half-life recombinant factor IX (Alprolix, Firm?, town?, country?). All of the pharmacokinetic parameters regarding these two products were obtained from the European Medicines Agency (EMA) website (http://www.ema.europa.eu) in which all documents supporting the European approval decisions are available.

The EMA data on Benefix indicate that the CL is around 8.50 mL/h/kg (in more detail: CL=8.47 mL/h/kg in 24 subjects studied at baseline; CL=8.54 mL/h/kg in 23 subjects studied at 6 months). The CL of Alprolix is 3.17 mL/h/kg (data from 22 subjects). This information means that the new product has a CL of only 37% of that of the old product (relative reduction=63%). Hence, under identical conditions of dosage, concentrations are expected to be 2.7 fold higher with Alprolix than with Benefix.

The consequences of these findings in terms of drug pricing are simple. Since this theoretical approach assumes that the therapeutic effect is proportional to the plasma concentrations achieved, the above data suggest that the price per unit of Alprolix could be set at the price of Benefix multiplied by 2.7. A preliminary comparison based on countries in which both Benefix and Alprolix have been priced indicates that this ratio of 2.7:1 is close to the real prices. For example, in the USA the wholesale acquisition price of Alprolix, an estimate of the price paid by bulk purchasers, is $ 2.85 per unit, whereas that of Benefix is $ 1.19 per unit (ratio=2.4) (see https://www.bostonglobe.com). In Europe, the price of Alprolix has yet to be set in most countries, but its value in comparison with Benefix is likely to closely reflect the ratio mentioned above (Messori, unpublished observations).

The aim of this letter is to point out that, in determining the price of new products employed for replacement therapy and characterised by a better pharmacokinetic profile, pharmacokinetic principles can be used to make reliable suggestions on the price of the new product based on the price of the old one. However, it is known that the price of medicines is determined, in many cases, through a purely empiric approach (i.e. without using any pre-determined rule). Since the prices of long-acting products will likely be set empirically in many countries, it is worthwhile highlighting that rational principles for drug pricing exist particularly when pharmacokinetics is the key determinant of innovation. Using pharmacokinetic
rules could make the process of drug pricing more rational and more homogeneous across different countries than it currently is.

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**References**


