

Generic Clopidogrel – An Update for HSC

Summary

- *Plavix* (clopidogrel hydrogen sulphate) tablets were launched in the UK in 1998. Since 2009, generic versions (either clopidogrel besilate or clopidogrel hydrochloride) have been available. They are licensed on the basis that they are bioequivalent to the reference product, *Plavix*.
- Generic preparations available in the UK and *Plavix* differ in their licensed indications with only *Plavix* being licensed for use in acute coronary syndrome (ACS). Although some generic clopidogrel preparations have been granted EU or UK approval for ACS, these products cannot currently be marketed for this indication in the UK due to a patent protection issue.
- Generic prescribing is encouraged and delivers cost savings to the NHS. The use of generic clopidogrel for ACS in the UK is 'off-label' and prescribers should be aware of the implications.
- The MHRA considers that the generic versions of *Plavix* are fully therapeutically equivalent in all indications approved for *Plavix*, but some clinical indications have been omitted from the SmPC of generics for legal reasons related to patent protection. As such, they can be considered therapeutically interchangeable. In view of this, many Primary Care and NHS Acute Trusts advocate the use of generic clopidogrel for all the indications for which *Plavix* is licensed, including ACS.

Recommendation

As all clopidogrel preparations are deemed to be bioequivalent, the Northern Ireland Medicines Management Forum recommends that prescribers should continue to prescribe generically for all indications in both primary and secondary care.

Background Information

How generic products are approved

Generics companies can apply for regulatory approval from the Medicines and Healthcare products Regulatory Agency (MHRA) for the UK, or from the European Medicines Agency (EMA) for Europe. If approved, the product is awarded a Marketing Authorisation (MA).

Under both the EU and UK systems, generic companies are able to apply for a MA under an abridged application process whereby the company demonstrates their product is bioequivalent to the reference product. Using this process, the generic company does not need to provide its own clinical or pre-clinical trial data; the MA is granted on the basis of data submitted for the reference product.

Plavix (clopidogrel hydrogen sulphate) is the reference product for all generic clopidogrel tablets, including those comprising other salts. For all generic preparations approved under the abridged process, the regulatory authority must be satisfied that the products are bioequivalent in order that patients can be switched between the branded product and a generic version without causing any therapeutic problems.

Licensed indications *Plavix*, the reference product, is licensed for the prevention of atherothrombotic events in:¹

- patients suffering from myocardial infarction (within 35 days), ischaemic stroke (within 6 months) or established peripheral arterial disease;
- patients suffering from Acute Coronary Syndrome (ACS): non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with aspirin.

Most generic clopidogrel tablets with UK or EU regulatory approval have been granted a MA for only the first of these indications. There are a number of generic clopidogrel preparations with EU approval²⁻⁶ and one with UK approval⁷ for both these indications. However, these products cannot currently be marketed for ACS in the UK (see below).

Usage patents

New branded medicines are covered by patents that prevent generics being marketed for a specified period of time, allowing the drug company to recover the costs of research and development. In addition to product patents, medicines can be protected by 'usage patents' that cover aspects such as a particular indication, dosage schedule or patient population.

Although a product patent for *Plavix* has expired (allowing generic clopidogrel to be marketed), it appears there is a usage patent applicable in the UK covering the use of clopidogrel and aspirin in combination in patients with ACS thus preventing generic clopidogrel tablets from being marketed in the UK for this indication.⁸⁻¹⁰

Patent infringement is linked to marketing. Despite the term 'Marketing Authorisation', regulatory approval of medicines is distinct and not related to patent issues. Consequently, as is the case for some generic clopidogrel tablets, medicines can receive a MA that includes an indication that is covered by a usage patent.

Until the UK usage patent expires, which some sources suggest will not be until February 2017, generic clopidogrel tablets cannot be marketed for ACS in this country, even if the MA covers that indication.

Generic Prescribing: clinical and other considerations

Generic prescribing is encouraged in the UK. It is generally more cost-effective than prescribing by brand name and, because it allows any suitable product to be dispensed, can reduce delays in supplying medicines to the patient. Increasing the level of generic prescribing has been a long-term DHSSPS and HSCB objective. A measure of generic prescribing in primary care is reported as a prescribing indicator.

The EU and UK licensing authorities are satisfied that available generic clopidogrel products are bioequivalent to the reference product, *Plavix*, and should not differ significantly in terms of efficacy and safety. They should therefore be considered to be therapeutically equivalent.

The licensed indications for generic preparations do not always reflect those of the established product. Examples include omeprazole and amitriptyline. In the case of clopidogrel, only the branded product *Plavix* is licensed for ACS; the use of generic clopidogrel for this indication would be 'off-label'. Further information on the licensing of clopidogrel is available at <http://www.medicines.org.uk>.

It is acknowledged that prescribers assume greater responsibility when using medicines 'off-label'. Due to the demonstrated bioequivalence and the existence of regulatory approval for ACS for some preparations, the risk associated with 'off-label' prescribing of generic clopidogrel for ACS is low. Many Primary Care and NHS Acute Trusts advocate the use of generic clopidogrel for all the indications for which *Plavix* is licensed, including ACS.

One concern of off-label use of medicines is that the patient information leaflet supplied with the medicine may not include appropriate information about the indication being treated. The PIL for some generic clopidogrel tablets include the phrase "Clopidogrel may also be authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions."¹¹

Further information regarding the implications of off-label prescribing and dispensing can be obtained from the appropriate professional regulator (http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_fags.asp#10, <http://www.rpsgb.org/pdfs/factsheet5.pdf>).

Cost Implications

The price for 30 clopidogrel 75mg tablets (December 2010) is £3.40 (net); the cost of *Plavix* is £35.64¹². NHS healthcare professionals have a duty to make the best use of public resources; cost as well as clinical suitability and product quality must be considered when choosing appropriate preparations.

References

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