Briefing document on generic clopidogrel

What is the background to this?

- Generic clopidogrel tablets are now available in the UK.
- The generic preparations contain different salts to that in *Plavix*.
- *Plavix* contains clopidogrel hydrogen sulphate; generic tablets are either
    - clopidogrel hydrochloride
    - clopidogrel besilate

What preparations are available?

Clopidogrel hydrogen sulphate

- Marketed as *Plavix*.
- *Sanofi Aventis* and *Bristol Myers Squibb Pharmaceuticals* are the market authorisation (MA) holders.
- *Plavix* was first marketed in 1998.

Clopidogrel hydrochloride

- Generic preparations are available from *Teva UK and Consilient Health.*
- Both preparations were marketed in July 2009.
- *Consilient Health* is the MA holder for the *Consilient Health* and *Teva UK* products.
- *Consilient Health* obtained market authorisation through the MHRA.

Clopidogrel besilate

- Generic preparations are available from *Arrow Generics* and *Beacon Pharmaceuticals.*
- Both preparations were marketed in July 2009.
- The MA holder for the *Arrow Generics* product is *Specifar.*
- The MA holder for the *Beacon Pharmaceuticals* product is *Pharmathen*; brand name *Grepid.* As far as we are aware, this is the only branded generic product currently available.
- *Specifar* and *Pharmathen* are based in Greece. MAs were obtained through the EMEA

What are the cost implications?

- Clopidogrel is listed in category C of the Drug Tariff. While it remains in category C, community pharmacists will be reimbursed at the Tariff price for *Plavix* (currently £36.35 for 30 tablets) regardless of which preparation is dispensed. Clopidogrel is expected to move to category A in December 2009.

- The list price of generic clopidogrel is as follows:

Company	Salt	28 tablets*	30 tablets*
Teva UK	Hydrochloride	**£29.52**	*≅ £31.63*
Consilient Health	Hydrochloride	**£33.94**	*≅ £36.36*
Arrow Generics	Besilate		TBC
Beacon Pharmaceuticals	Besilate		**£36.35**

*These prices may be subject to discount.

Do the licensed indications differ?

All of the clopidogrel salts are bioequivalent and are licensed throughout Europe, including the UK, for all the same indications as the branded product, Plavix.

The two licensed indications for clopidogrel are:

(i) As monotherapy, for the prevention of atherothrombotic events in patients following a myocardial infarction or ischaemic stroke or for patients with established peripheral arterial disease

(ii) In combination with aspirin, for patients following an acute coronary syndrome (ACS)

Although all the clopidogrel salts are licensed for both these indications, there are some restrictions on the marketing of the generic agents for the ACS indication in the UK. As a result, some manufacturers have chosen not to list this as an indication in the Summary of Product Characteristics and / or the patient information leaflet.

How was generic clopidogrel licensed?

- Generic clopidogrel products have been licensed, via the abridged MA application process, on the basis of clinical trial data submitted to the regulatory authorities for *Plavix* by the original MA holder. No additional clinical trial data were required.
- Generic companies have had only to demonstrate that their product is bioequivalent to the reference product – or as stated on the MHRA website, ensure that patients can be switched between the brand leader product and a generic version without causing any therapeutic problems. In general these are small studies conducted in healthy volunteers to compare pharmacokinetic parameters of the generic medicine to the branded product.
- Clinical trial data submitted for regulatory purposes are protected by a period of 'data exclusivity'. During this time other companies cannot use the data in support of a licence for a generic product.
- The 'data exclusivity' period for clinical trial data for all indications for *Plavix* has expired. As a consequence, generic companies can submit an abridged MA application, and can be awarded a licence, for all the indications for which *Plavix* is licensed.
- Several generic companies have submitted an abridged MA application for the full complement of *Plavix* indications, and have been granted a positive opinion by the CHMP/EMEA.
- However, because the combination of aspirin with *Plavix* for the treatment of ACS has a patent protection, companies cannot market generic clopidogrel for the ACS indication even if they have a licence.

What are the concerns?

- Due to the restricted marketing authorisation for generic preparations in the UK the patient information leaflets for the generic products do not include ACS and could be a source of confusion to patients.

- Again largely due to the restricted marketing authorisationThe *Summary of Product Characteristics* for generic clopidogrel products differ from that for *Plavix*. The principal differences are in:
    - Section 4.1 Therapeutic indications – the ACS indication is not included.
    - Section 5.1 Pharmacodynamic properties – the paragraphs on ACS are omitted.
    - Section 6.1 List of excipients - there are some differences in tablet excipients.

What may change in the future?

- The Drug Tariff will be updated in December 2009 to take into account the availability of generic products. Cost saving will only be realised when the Drug Tariff is updated and if the prices of the generic products fall as current prices are mostly comparable with Plavix.

- It is anticipated that PASA and the local procurement consortia will consider the implications of the availability of generic clopidogrel in due course

Recommendations

- Prescribe the agent generically (clopidogrel 75mg tablets) for all indications
- For the secondary prevention of atherothrombotic event, aspirin 75mg daily remains the preferred agent. In patients with aspirin allergy (usually bronchospasm) clopidogrel should be considered as an alternative. In patients with GI adverse effects with aspirin, consider co-prescription of a PPI in the first instance.
- For patients following an acute coronary syndrome the usual duration of clopidogrel therapy is 12 months, after which time the drug should be stopped. Aspirin should be prescribed throughout the course and should be continued long-term

Acknowledgements:
Chris Proudlove & Karoline Brennan
North West Medicines Information Centre (druginfo@liv.ac.uk).
and
Vanessa Chapman & Peter Golightly
Trent Medicines Information Service (medicines.info@uhl-tr.nhs.uk)

Local decisions November 2009:

NHS Surrey Heart & Stroke Clinical Reference Group	The use of generic clopidogrel was supported by the group on 04/09/09
K&M APC and WK PCT	Discussed at the K&M APC and WKPCT prescribing group and agreed to support prescribing of generic. In addition they have put it on the risk register as corporate risk (ie risk of litigation in promoting a product with no marketing authorisation-as per guidance circulated by Jim from barrister in North) as opposed to clinical. It was felt important that a policy is developed for prescribing of unlicensed meds which incorporates situations such as this, when a drug may have good evidence to support its use but for commercial or other legal (patent) reasons remains unlicensed.
South London Cardiac and Stroke Networks	**Key Local Messages:** (i) Prescribe the agent generically (clopidogrel 75mg tablets) for all indications (ii) For the secondary prevention of atherothrombotic event, aspirin 75mg daily remains the preferred agent. In patients with aspirin allergy (usually bronchospasm) clopidogrel should be considered as an alternative. In patients with GI adverse effects with aspirin, consider co-prescription of a PPI in the first instance. (iii) For patients following an acute coronary syndrome the usual duration of clopidogrel therapy is 12 months, after which time the drug should be stopped. Aspirin should be prescribed throughout the course and should be continued long-term
Joint statement between the Medicines Management team (West Sussex PCT), AAW PBC leads and Cardiology Department at Western Sussex Hospitals NHS Trust	"We advise that clopidogrel should continue to be prescribed generically as clopidogrel tablets (not as the proprietary brand Plavix or hydrogen sulphate salt) for all indications."