

Circular No DH 70/05

Attention: Medical Officers
Dentists
Pharmacists

Dear Health Care Professional,

Update on medicinal products for human use

A. Marketing Authorisation

The aim of registration of medicinal products is to ensure that the products on the market are of the required quality, safety and efficacy. Moreover after the products receive a marketing authorisation, post-marketing surveillance is carried out for these products continuously.

Within the European Union the following procedures are currently in place for granting a marketing authorisation:

- I. Centrally authorised products are granted a market authorisation that allows placing on the market simultaneously all over the EU.
- II. For products approved through the Mutual Recognition Procedure, a product is authorised in one member state (the Reference Member State) and then this authorisation is mutually recognised in other Member States (the Concerned Member States) as applied for by the market authorisation holder. Malta has started participating as a concerned member state since 1st May 2004. More than 60 applications have been received.
- III. National applications (if a country approves national applications it will be responsible to become Reference Member State for that product within the EU). This procedure is used for third country products being licensed for the first time in Europe through the Maltese Medicines Authority or extensions of products already on the market e.g. new strengths or forms of the products.

As from 1st May 2004 these procedures started to apply in Malta as in the other EU member states.

During the negotiations for accession, Malta was granted a transition period up to December 2006, by which time the products that were on the transition list <http://www.health.gov.mt/mru/pub/derogationlist.pdf>, i.e. the products that could be placed on the market up to November 2002, could be granted a Marketing Authorisation (MA) in line with EU requirements. Out of a total 7,500 products on the transition list (not all of which were on the market because some were listed in order to be able to apply

for tenders of the Government Pharmaceutical Services), 5,500 products were from the EU and the rest were from non-EU countries. None of the products from non-EU countries have applied to receive a marketing authorisation in Malta. For the EU licensed products, market authorisation holders have applied to obtain marketing authorisations for around half of the products on the list. The fee for these applications was of Lm50. All applications have gone through the first phase of assessment and for most of the medicinal products the Marketing Authorisation Holder (MAH) is the mother company or its subsidiary abroad. 2,300 products from the transition list have been granted a provisional market authorisation (PMA). The list of products with a PMA can be accessed through <http://www.health.gov.mt/mru/pub/PMA%20List.pdf>. The list is regularly updated as applications are still being accepted.

Once a product is granted a PMA, the second phase – that of granting a MA will follow. The granting of the MA requires further assessment particularly that of ensuring that the product meets the EU requirements in terms of the Directives. Not all the products that were on the market before accession met these requirements. For example Malta was frequently being supplied with export packs as Malta was commercially considered part of the North African/Middle Eastern region for pharmaceuticals. The packaging and patient leaflet of export packs could be different from the EU licensed pack particularly in the information they contained. The list of products with a marketing authorisation together with their approved patient information leaflet (PL) and Summary of Product Characteristics (SmPC), which contain all the information about the product, including the approved indications and contra-indications, will start being published on the website of the Medicines Authority once the marketing authorisations are issued.

As from November 2004, only products with a PMA or a MA are authorised to be placed on the Maltese market. Stocks of products that were on the transition list and were placed on the market before November 2004 can remain on the market up to the end of December 2006. This means that in the meantime some products, that are not according to European requirements, for example products with information not in English or Maltese, may still be available on the market.

B. Qualified Licence

Article 126(a) of Directive 2004/27/EC has already been transposed into the local Marketing Authorisation Regulations (Legal Notice (L.N.) 387/2004 as amended by L.N. 465/2004 and L. N. 72/2005), which can be accessed on www.doi.gov.mt. This allows for products that are essential for “justified public health reasons” to be granted, following a more simplified registration process, a “Qualified licence” to be placed on the market. This qualified licence will be valid for one year and will be renewed until a suitable alternative is granted a marketing authorisation. The Superintendent of Public Health has set up a Committee with the remit of establishing the products eligible for this licence. For products to be accepted for a qualified licence, they must be already authorised in the European Union and therefore, will have been assessed for quality, safety and efficacy by other European Regulatory Authorities. The applicant will be

responsible for pharmacovigilance and post-authorisation surveillance as is the case for products issued with a marketing authorisation. All requirements relative to advertising, packaging and labelling must be in accordance with European legislation. A preliminary list of these products, which is updated periodically, can be found on our website on <http://www.health.gov.mt/mru/pub/listpdf.pdf>. Guidelines for applicants have also been published (<http://www.health.gov.mt/mru/pub/Qualified%20Licence.pdf>). Any recommendations to include products for which there is no authorised alternative on the local market will be taken into consideration by the committee for inclusion in this list, and these recommendations can be sent by e-mail to prelicensing.mru@gov.mt or posted to the Licensing Director, Medicines Authority, 198, Rue D'Argens, Gzira, GZR 03.

C. Products unlicensed in Malta

1. Products not licensed in Malta but licensed by other competent authorities of other European member states

These products have been assessed for quality, safety and efficacy and granted a marketing authorisation in one or more European countries, but not in Malta. These products can be made available to particular patients or hospital departments, using the procedure outlined in DH Circular 137/04 which can be accessed on the National Medicines Policy and Audit Unit website on http://www.health.gov.mt/circulars/2004/dh137_04.pdf.

2. "Special" medicinal products

"Specials" are unlicensed medicinal products prescribed by doctors when a licensed product for a particular indication does not exist. Such medicines can be supplied against an order or prescription by a hospital manufacturing unit or commercial manufacturer holding a "specials" manufacturing licence. These will be labelled with the manufacturing licence number. These products are not licensed in any EU country and whilst licensed medicinal products are subject to stringent control by national competent authorities, neither the prescriber nor the pharmacist can make the same assumptions of quality, safety and efficacy about "specials" products. The liability for the clinical use of "specials" products lies with the prescriber. These products can also be obtained through the system outlined in 1 above.

D. Clinical Trials

As from 1st May 2004 a new EU directive (Directive 2001/20/EC) has been issued regarding clinical trials. All new clinical trials to be undertaken in Malta will henceforth have to be approved by an Ethics Committee and by the Medicines Authority. No clinical trials can be undertaken unless an authorisation has been issued (L.N. 490/04). Medicines

inspectors will conduct inspections at all trial sites to verify compliance with EU Good Clinical Practice (GCP).

E. Post-Licensing Activities

Once products receive a marketing authorisation in Malta, they are subject to post marketing surveillance with regards to their quality, safety and efficacy. The Medicines Authority is responsible for all activities related to the post-marketing phase of medicinal products for human use. These activities include pharmacovigilance (for example: the review of adverse drug reactions (ADRs) occurring locally; the withdrawal or suspension of marketing authorisations; the approval of Dear Doctor and Health Care Professional letters), processing of variations to marketing authorisations, as well as the regulation of promotional material on medicinal products for human use.

The local legislation codifying the responsibilities of both market authorisation holders and prescribers on medicinal products are found in the regulations governing pharmacovigilance (L.N. 22 of 2004) and L.N. 400/2003 as amended by L.N. 269/2004, which can be accessed on www.doi.gov.mt of medicinal products.

The Medicines Authority reminds all health care professionals about the importance of reporting any suspected serious or unexpected ADRs to the Medicines Authority, as outlined in article 4 of the Pharmacovigilance Regulations, 2004 (L.N. 22 of 2004) by filling the attached ADR reporting card. Furthermore ADR reporting cards can be downloaded from the Medicines Authority's website http://www.health.gov.mt/mru/pub/ADR_reportform.pdf.

Since the launch of the ADR reporting system in May 2004, 45 ADR reports have been reported locally to the Medicines Authority, 50% of which were reported by health care professionals and the remainder by market authorisation holders. Updates of the Medicines Authority website (www.health.gov.mt/mru) are made to provide the latest information directly to patients and health care professionals.

It is important to point out that, crucial to the proper use and safety of medicines licensed in Malta is the Summary of Product Characteristics (SmPC) published on the Medicines Authority website for each licensed medicinal product in Malta. Once market authorisations start being issued the patient information leaflet (PL) and the SmPC will be published on the Medicines Authority website. The SmPC contains the approved information which prescribers and dispensers should consult and follow when prescribing/dispensing medicines to patients. In addition to the SmPC and PL, the Medicines Authority also publishes prescribing information on licensed products on its website and on the Medicines Authority Drug Safety Bulletin. Attached please find a copy of the second issue of the Drug Safety Bulletin relating to post-marketing issues of medicinal products. If you as a health care professional would like to ask a question regarding the information in this circular or would like updated SmPCs/PLs and

statements on prescribing information of medicines sent to you electronically, please e-mail to the Post Licensing Director of the Medicines Authority at postlicensing.mru@gov.mt.

F. Summary

1. For medicinal products placed on the market before 1st May 2004:
 - a. If a product was included on the transition list, the product could apply for a provisional market authorisation, which will proceed to a market authorisation on submission of the EU dossier as already submitted in other EU member states. Fee for national registration Lm 50.
 - b. If product cannot apply through PMA/MA route or was not on the transition list and there is no alternative on the market on public health grounds the product can apply for a qualified licence. Healthcare professionals can send recommendations for such products to be included on the list of chemical entities that are eligible for a qualified licence.
2. Products placed on the EU market after 1st May 2004 are to be registered in Malta through the same procedure (mainly the Mutual Recognition Procedure with Malta as a concerned member state) as applied for registration in other EU countries.
3. All products registered in the EU through the centralised procedure, (for example biotechnology, oncology, diabetes products and new chemical entities) are automatically registered in Malta (no fee).
4. There can be parallel importation of products, which have an authorisation (but not for products with a qualified licence) in Malta.
5. Products unlicensed in Malta
 - a. Specific medicinal products that are not licensed in Malta but licensed in other EU member states - a doctor can apply to make a medicinal product available for a particular patient or for use within a hospital department or clinic.
 - b. “Specials” – Medicinal products not licensed in Europe but available in another country under a “specials” manufacturing licence – prescriber to take clinical responsibility for use of the product.
6. Health care professionals are encouraged to help increase the accessibility of medicinal products for patients through the recommendation of alternative products when a product is no longer available on the market e.g. by generic substitution. As per Medicines Act, 2003 (Article 80(2)) a pharmacist may perform generic substitution unless a prescriber specifies the brand to be used.

7. Clinical Trials

All clinical trials conducted in Malta as from 1st May 2004 must be in line with L. N. 490/04 and must be registered and authorised by the Medicines Authority and the Health Ethics Committee. Any ongoing clinical trials must come in line with these requirements. A seminar for interested parties will be held soon and will be advertised on the Medicines Authority's website.

8. Post-Licensing activity

Healthcare professionals are obliged to report any suspected serious and unexpected adverse drug reactions to the Medicines Authority. Stamped addressed ADR cards are now available (attached).

Contacting the Medicines Authority

More information on the activities of the Medicines Authority can be obtained by accessing our website on <http://www.health.gov.mt/mru/>. Health care professionals, who wish to receive any information, including press releases directly via e-mail, are to contact the Medicines Authority on e-mail address info.mru@gov.mt.