MALTA MEDICINES AUTHORITY

NATIONAL GUIDELINE FOR THE RECLASSIFICATION OF A MEDICINAL PRODUCT FOR HUMAN USE FROM "SUBJECT TO MEDICAL PRESCRIPTION" TO "NOT SUBJECT TO A MEDICAL PRESCRIPTION"

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1. Introduction

The Malta Medicines Authority evaluates whether a medicinal product would be better available as a prescription or non-prescription medicine.

When the Malta Medicines Authority receives a new marketing authorisation application for a medicinal product, in addition to evaluating the data to determine whether the product should be authorised for sale in Malta, it also considers whether a product is best dispensed as a prescription or non-prescription medicine. Legal classification is a national decision.

Subsequent to the classification of a product, the Malta Medicines Authority may receive, or may itself request the submission, on the basis of more information that has come to light, an application to change the prescription status of a product, normally from prescription only to non-prescription. Occasionally, a medicine, which was previously classified as having non-prescription status may be reclassified to prescription only status if new risks are identified which alter the benefit/risk ratio and it is established that it is no longer safe to supply without the supervision of a doctor.

2. Legal Framework

Article 70 of Directive 2001/83/EC (Article 29 of the Medicines Act, 2003 and Regulation 26 of the Medicines (Marketing Authorisation) Regulations) provides two classifications for the supply of medicinal products for human use in the Community:-

- "medicinal products subject to medical prescription"
- "medicinal products not subject to medical prescription"

Article 71 of Directive 2001/83/EC (Regulation 27 of the Medicines (Marketing Authorisation) Regulations) provides the criteria for classifying a medicinal product as subject to medical prescription. Thus a medicinal product which meets these criteria is subject to a medical prescription and a medicinal product which does not meet these criteria is not subject to a medical prescription, as stated in Article 72.

According to Article 71(4) of Directive 2001/83/EC a medicinal product, which meets any of the criteria for supply subject to medical prescription, may be classified for supply not subject to medical prescription if: "*the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging and/or other circumstances of use, can make supply without medical prescription appropriate."*
This may result in the same products with different presentations having both a prescription and non-prescription status. In this case separate marketing authorisations are issued.

3. Scope

This guideline is to help marketing authorisation holders to apply for a national change in the legal classification for supply of a medicinal product from "subject to medical prescription" to "not subject to a medical prescription". This guideline applies **only** to nationally approved products in Malta. These include products authorised via the Decentralised/Mutual Recognition Procedures and National Marketing Authorisation Procedures including Parallel Import products and products authorised via Article 126(a) of Directive 2001/83/EC. However, requests for switching of products that have been authorised through a mutual recognition (MR) or decentralised (DC) procedure require special consideration and should be discussed with the MMA in advance of a submission. Where Malta is

either the Reference Member State (RMS) or a Concerned Member State (CMS), the MMA will need to determine whether the change can be processed nationally or whether the change in legal status needs to be submitted through an MR or DC procedure.

The change of classification of centrally authorised products is outside the scope of this guideline.

4. Principles and procedure

In general, switching applications are only considered for products that have a well-known, long established safety profile as a prescription only medicine. A variation to change the legal status is required.

An updated expert report in order to switch a medicinal product from "subject to medical prescription" to "not subject to a medical prescription" is also required. The updated expert overview should be submitted in line with the requirements described later on in this guideline.

Mock-ups of the product information and the proposed name (if applicable) should be submitted with the initial application. In the case of shared packs with other member states (MS), any pending variations relating to name changes in these MS should be finalised before submission of a reclassification in Malta.

It should also be highlighted that a change of legal status may concern only certain pharmaceutical forms/strengths/presentations within the same marketing authorisation. In cases where both the "subject to medical prescription" and "not subject to a medical prescription" are to remain on the market then a new MA number (and separate marketing authorisation) is assigned to each product and these products may be required to have distinct and separate packaging.

Examples of products that are normally classified as *prescription only*:
- Medicines containing new chemical entities that were authorised less than five years ago
- Medicinal products that are administered parenterally (by injection)
- Psychotropics or narcotics listed in any of the schedules to the Single Convention on Narcotic Drugs or the Convention on Psychotropic Drugs, products with a risk of misuse, abuse, dependence or withdrawal syndrome – requiring frequent monitoring by physician
-Antidepressants, antipsychotics, anxiolytics not listed in schedules of the Convention on Psychotropic Drugs
-Products with specific follow up measures required in their risk management plans (RMP) to address on-going safety concerns
- Antimicrobial agents with potential for development of resistance if used extensively without medical supervision

5. Criteria for classifying a medicinal product as subject to a <u>medical prescription or not</u> subject to a medical prescription

The information below should be taken into consideration by the applicant when applying for a switch:

Safety

Medicinal products shall be *subject to medical prescription* when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision. A direct danger when the product is used correctly and in accordance with the patient information encompasses toxicity, interactions and adverse reactions.

A medicinal product *not subject to a medical prescription* should have low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties. The medicinal product should also have no interactions with commonly used medicines which can produce serious adverse reactions. The safety of a medicinal product is relative to that of the alternative treatment.

An example of indirect danger, even when the product is used correctly in line with the patient information leaflet, would be where symptomatic treatment might mask/hide an underlying condition requiring medical attention and supervision. Use of the medicine might delay diagnosis and definitive treatment and jeopardise the chance of more successful therapy. A time limit beyond which, if symptoms persist, medical advice should be sought should be included in the product information. Medicinal products not subject to a medical prescription should be approved primarily for short term treatment, e.g. when the possibility of "masking" could occur.

An indirect danger is also present if wider use of a medicinal product would increase the risk of resistance to the product, in particular in the general population, to such an extent that the usefulness of any medicinal product is likely to be compromised; or if the symptom is commonly the outward manifestation of a diverse range of underlying pathologies and where the patient cannot easily discern the underlying disease.

Self-assessment

(a) It is important that the condition or symptoms, for which a medicinal product *not subject to a medical prescription* is indicated, can be correctly assessed by the patient and that the product can be used without medical supervision. This means that the patient should be capable of excluding conditions which could appear to be similar to the indications but unsuitable for treatment with the medicine in question.

Account may be taken of the availability of appropriate information sources that would assist the patient in achieving this, including written information or the advice of pharmacist and other health care professionals.

(b) The natural course of the disease, the condition, the duration of symptoms and their reoccurrence and consequences due to this should be correctly self-assessable.

(c) Contraindications, interactions, warnings and precautions should be those which can be understood by the patient.

Risk and consequences of incorrect use

It is important that the danger to health is small, if the patient uses the product where it is not indicated, uses it for a longer period than recommended**,** exceeds the recommended dose or fails to heed warnings or contraindications. Consideration of the consequences of misuse is an important component of the overall safety profile of the medicinal product which should be reflected in the label (as provided for in Article 54 (g) and (n) of Directive 2001/83/EC (Regulation 3 (g) and (n) of the Medicinal Products (Labelling and Packaging) Regulations) and/or the package leaflet.

6. Data requirements

a) Products authorised in Malta as "*subject to a medical prescription"* and already authorised in another EU state as "*not subject to a medical prescription*"

In cases where the product is already approved as "*not subject to a medical prescription*" in another EU state then a type II simple national variation may be submitted in line with the requirements established below;

- An updated expert overview with a critical analysis of the proposed availability of the product without a medical prescription with the dose and indications as already authorised, unless the pack size or the strength is decreasing. The safety profile of the drug should be discussed and reports from post-marketing surveillance studies, clinical trials and published literature should be presented, unless otherwise justified. Information on adverse drug reactions should be provided including experience of use without medical supervision in other EU Member state/s.

- The product information including mock-ups should be presented with all the points listed in the section "*ii) Product information*" of this guideline clearly adhered to.

- Proof of the legal status as "not subject to a medical prescription" in the EU country/ies should also be provided.

The variation will follow the type II simple timetable and the same fees apply.

Applications that are based on an approved switch of a reference medicinal product (generic/hybrid medicinal products) can be submitted as Type IB variation if the products have the same indication, posology, route of administration, risk minimisation measures and pharmaceutical form as the reference product.

b) Products authorised in Malta as "*subject to a medical prescription*" for which a switch to "not subject to a medical prescription" is requested

The submission should be classified as a type II complex variation which will follow the same timeline and the same fee requisites. In order to facilitate the evaluation of safety in relation to benefit it should be presented in a logical and concise manner as shown below.

- *An updated expert overview*

The expert should provide a critical analysis of the proposed availability of the product without a medical prescription with the dose and indications as already authorised, unless the pack size or the strength is decreasing. The expert should take a clear position, support the switch in light of current scientific knowledge and demonstrate why none of the criteria (with respect to safety) that determine classification for supply subject to a medical prescription apply to the product.

Data be taken into consideration and discussed in the expert overview:

i) **Safety**

(a) Experience in terms of patient exposure to the substance needs to be considerable and should be outlined. Normally, active substances which are suitable for supply without a medical prescription will have been in widespread use for five to ten years in EU countries, in medicinal products subject to a medical prescription. Adverse reactions related to the pharmaceutical form and/or posology and strength proposed for supply not subject to a medical prescription should in normal conditions be minor and should cease on discontinuing therapy.

(b) Information on adverse reactions should be provided, including experience of use without medical supervision, for example in another Member State or in a third country.

Variables such as numbers of patients treated, demographic details, indications for use and dose should be provided and taken into account in providing and interpreting the data.

(c) The safety profile should be summarised according to EU guidelines, including reports of and data from post-marketing surveillance studies, clinical trials and recent published literature presenting the issue of drug safety. Information concerning serious adverse reactions should be given and discussed. The problems of extrapolating data from the population, using the active substance supplied only on a medical prescription, to the population using it without a medical prescription should be presented and discussed.

(d) The application should consider the potential for and consequences of drug interactions, in particular with commonly prescribed drugs.

(e) The application should consider the consequences concerning misuse, e.g. use for longer periods than recommended, as well as accidental or intended overdose and the use of higher doses, should be discussed.

(f) The application should consider the consequences of the use of the product by a patient who has incorrectly assessed his condition or symptoms.

(g) The application should consider the consequences of incorrect or delayed diagnosis of a patient's condition or symptoms due to self medication with the product.

(h) A suitable time-period for treatment of the suggested indication(s) should be justified and given together with a proposed pack size.

ii) **Product information**

The way in which a medicinal product not subject to medical prescription is used is likely to differ from the way the same product was used when available only on prescription, even when the indications are the same or in the same therapeutic area. There is also the risk that the patient will consider the medicinal product not subject to a medical prescription as being safer than when the same product is subject to a medical prescription.

For a medicinal product classified for supply without a medical prescription, the proposed labelling and package leaflet are important elements of the application and will be closely examined for comprehensive information and effectiveness in protecting patients from any safety hazards. For this reason:

(a) The written information (package leaflet and label) must contribute effectively to safe and effective use of the medicine. The correct use of the medicine should be explained in the information. It is necessary to consider if the information is clear enough for the patients to use the medicine appropriately. This information should be sufficient so that it substitutes for the absence of medical supervision.

(b) The written information supplied with the medicine, in addition to the supervision

of the pharmacist when applicable, should be adequate to guard against a risk of using the product where it is contraindicated or unsafe. Contraindications, interactions, warnings and precautions need to be clearly described in layman's terms and prominently presented in the leaflet. The package leaflet must reflect the current safety knowledge of the active pharmaceutical ingredient concerned.

(c) In order to minimise risk and maximise benefit, the leaflet and the label should describe the situations where the product should not be used, in at least as much detail and prominence as to when it may be used and in accordance with the summary of product characteristics.

(d) Package leaflets should provide information on/ appropriately describe the use of the product and the circumstances when referral for medical advice is appropriate.

(e)The outer packaging or, where there is no outer carton, the immediate packaging should include instructions for use in the case of non-prescription medicinal products, as required by Article 54 (n) of Directive 2001/83/EC (Regulation 3 (n) of the Medicinal Products (Labelling and Packaging) Regulations).

(f) Contraindications and warnings, such as advice limiting duration of treatment or the need to consult a doctor in certain situations, should be provided as appropriate.

(g) This product information, on the label and in the leaflet, should be readable, see the *Guideline on the readability of the label and package leaflet.* If the MAH has carried out a user testing on the package leaflet to be used for the "not subject to a medical prescription" medicine then it is recommended to submit this report for evaluation.

Pack size and package form (container)
(a) The pack size should be decided in relation to the intended length of the treatment. Restricting the availability of a medicinal product to a small pack size is a possible safeguard against misuse, particularly overdose, or a delay in seeking medical attention.
(b) Medicinal products should have a container which as far as possible prevents children gaining access to the medicine, if they get hold of the container.

Maximum dose, maximum daily dose
Restricting the maximum dose or maximum daily dose may protect against potential danger whether the medicine is used correctly or incorrectly. However, it is necessary to confirm that the reduced dose retains the efficacy.

Other
A related change of container or packaging material should be discussed when applicable, together with necessary documentation.

Name of the product
It is up to the applicant in the case of a switch from 'prescription' to 'non-prescription' status of an already authorised medicinal product to choose whether to retain the same invented name or to choose a new invented name. If a new invented name is to be used it is important not to have suffixes and prefixes included in the proposed name that imply an advantage or enhanced mode of action or efficacy which is not in accordance with the approved summary of the product characteristics.

Other considerations:

Applicants are encouraged to contact the Malta Medicines Authority in advance of any given application for specific advice if required. Applications may be reviewed by external experts and advisory committees during the assessment procedure.

There may be instances where, the Malta Medicines Authority, requests the change of legal classification for a category of products or for products have particular active substance/s, in the interest of widening access for patients.

7. References

Medicines Act 2003: (Chapter 458 of the Laws of Malta)

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use.

European Commission: A guideline on changing the classification for the supply of a medicinal product for human use.

Conventions (unodc.org)

CMDh Best Practice Guide for authorisation of Non-Prescription Medicines in the Decentralised and Mutual Recognition Procedures

8. Revision History

Issue	Effective Date	Reason for revision
1.	March 2014	New Guideline
2.	July 2014	Removal of the type IB variation reference as there is no allowance for this in the national legislation
3.	September 2022	Update of the guideline in line with current practice, as per QIF 049-2022

Signatures on File