Guideline
Legal status and pack size of opioid analgesics in Belgium

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Strategy for limiting the direct delivery of opioid analgesics to the patient

Table of contents

1. Introduction

The FAMHP strategy regarding the legal status of medicinal products indicates – as a general rule – that products with the same active ingredient, the same strength and the same pharmaceutical form should have the same legal status (FAMHP strategy on delivery, 29 October 2009).

Exceptions are made for therapeutic classes or medicinal products containing a specific active ingredient, whose pack size or the type of packaging may pose a significant risk to public health. These exceptions should be described in an FAMHP guideline published on the FAMHP website.

The current guideline concerns the legal status of opioid analgesics due to the important identified risk of abuse, misuse and addiction associated with their use (see Section 3). The objective of this guideline is to restrict the direct delivery of certain pack sizes or types of packaging to the patient in order to limit this risk in an outpatient setting.

Larger pack sizes and tablet containers can be accepted for use in hospitals or Individual Medical Preparation (IMP).

This guideline is applicable to the following opioids:

- morphine,
- diacetylmorphine (heroin),
- oxycodone,
- fentanyl,
- hydromorphone,
- buprenorphine,
- methadone,
- nalbuphine,
- piritramide,
- pentazocine,
- pethidine (= meperidine),
- tapentadol.

Some of these substances are also used as substitution treatments for opioid addiction. However, the use of these substances for that purpose lies outside the scope of this guideline.

2. Type of pack

Individual pack types are preferred to minimise the risk of overdose. Consequently, tablet containers are reserved for hospital use or IMP.

3. Justification

All opioids have a high affinity with mu receptors, which are responsible for the analgesic effects, but also for major side effects such as respiratory depression, euphoria, sedation and addiction.

The scientific literature describes abuse of all opioids, with the possible risk of (fatal) overdoses.

Strong, fast and short-acting opioids have higher abuse potential. Their use should therefore be closely monitored. The choice of a particular opioid analgesic is an important element in the prevention of addiction and abuse: whenever possible, the prescriber should opt for a slow and long-acting opioid, at the lowest effective dose and for the shortest possible period of time (NIHDI Consensus meeting, 2018).

Given the alarming data on the increasing use of opioids (associated with an often underestimated risk of psychological habituation) and the abuse and misuse issues that can result from it, the FAMHP reiterated how important it is that these substances be used in a rational manner (Flash VIG-news, 2020).

Limiting the size of packs for direct delivery to the patient and preventing unnecessary residual unused medicinal products is one of the measures of the framework to combat the abuse of these products.

Restricting the delivery of large packs directly to patients can also be considered as a measure to prevent accidental overdoses involving these types of products.

In addition to these safety considerations, adjusting the pack size also contributes to the amount of follow-up that needs to be carried out by healthcare providers when these products are being used for therapeutic purposes.

This strategy is supported by the recommendations of the Guideline on the risk management system for medicinal products for human use of the European Medicines Agency (EMA) (EMEA/CHMP/96268/2005, annex B, 1.4):
"by limiting the number of units, the patient will need to see a healthcare professional at defined intervals increasing the opportunity for testing and reducing the length of time a patient is without review…A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled."

4. Recommendations

4.1 Forms with extended release

All opioids listed in the introduction are used for the treatment of severe and very severe pain. For the treatment of continuous pain, opioids are provided in extended release dosage forms such as extended release tablets or capsules, or transdermal patches.

Patients suffering from severe pain should be monitored on a very regular basis and their analgesic treatment should be adjusted/titrated to the type and severity of the pain. **Smaller pack sizes prevent patients from being treated longer than the recommended periods of follow-up.**

Patients suffering from severe chronic pain should be seen by the healthcare provider two to four times per month so that the pain and their other symptoms, such as those caused by cancer, can be evaluated and the various treatments can then be adjusted or titrated. Potential interactions between medicinal products should also be regularly assessed.

In the case of chronic pain, it is sometimes necessary to switch between the available pharmaceutical forms (such as a switch between a transdermal patch and an oral system) and/or between molecules ("opioid rotation"). The objective of such a switch is to prevent the development of tolerance and to prevent side effects of the drugs. In case of such a switch, the quantity of residual material should be limited.

For non-cancer-related pain, the use of strong opioids should also be monitored regularly by the doctor to prevent overdosage.

The FAMHP recommends restricting the maximum pack size that can be delivered directly to the patient to the treatment for one month. This will therefore allow the doctor to monitor the patient sufficiently, while providing a suitable degree of flexibility.

4.2 Oral forms with immediate release

Oral forms with immediate release of strong opioids, such as immediate release tablets and capsules, and oral solutions, are used for dose titration and in the treatment of serious acute pain, when non-opioid analgesics or other opioids are insufficiently effective.

When the product is used for titration, the immediate release formulation is used to find the dose that sufficiently relieves the pain. The patient will then be given the same daily dose, but in the form of extended release tablets.

Based on these considerations, the FAMHP recommends **restricting the maximum pack size of the oral immediate-release form for delivery directly to the patient to one week of treatment**.

Multi-dose oral solutions form an additional risk for accidental overdose. Further limitations can be applied to these products.

4.3 Products for systemic absorption via oral and/or nasal mucous membranes

Products for systemic absorption via oral and/or nasal mucous membranes are developed for rapid absorption via the oral mucous membrane (such as a nasal spray, lozenge, tablet for sublingual use or buccal tablet) for the management of breakthrough pain.

Breakthrough pain is a temporary exacerbation of otherwise controlled chronic background pain.

Patients can use these products, which have been specially developed for combating breakthrough pain, no more than four times daily. More frequent use often indicates that the dose of the long-acting opioid needs to be increased.

In view of their very rapid effect (after only a few minutes), these agents are the most dangerous and could lead to the death of unsuspecting patients (or a child) within a few minutes of taking only one tablet.

The package sizes should, therefore, be **as small as possible**. The FAMHP recommends that the largest pack size delivered directly to the patient should not contain more than twenty units. This limited size makes it possible for the patient to have enough tablets for a weekend without having to contact the doctor again.

4.4 Parenteral forms of administration

To prevent abuse, for example as a result of residues of unused products, the maximum pack size to be delivered directly to the patient for parenteral administration forms is limited to **ten units**.

A more stringent limitation or restriction to hospital use is applicable to specific products, for example, due to a high quantity of active ingredient per unit, a high potential of abuse, or when use outside the hospital/monitored setting is contra-indicated (see 5. Practical application).

5. Practical application

In the case of new marketing authorisation (MA) applications, the legal status is evaluated during the procedure, using the recommendations described in chapters 2 and 4.

Table 1 illustrates how these recommendations can be applied. The posology is based on the approved summary of product characteristics (SmPC).

Table 1. Recommended maximum pack sizes of individual forms of packaging that can be directly delivered to the patient (tablet containers are reserved for use in hospitals and/or IMP).

Active substance Pharmaceutical formulations	Posology	Pack size (maximum)
Morphine		
Tablets/capsules with extended release	Maximum dose – 2 per day	60 units
	Maximum dose – 1 per day	30 units
Tablets/capsules with immediate release		50 Units
Mono-dose oral solution		50 units
Multi-dose oral solution	2 mg/ml	100 ml
	20 mg/ml	20 ml
Parenteral		10 units (if product contains not more than 50 mg/unit)
		1 unit (if product contains more than 50 mg/unit)
Oxycodone		
Tablets/capsules with extended release	Maximum dose – 2 per day	60 units
Tablets/capsules with immediate release		50 units
Multi-dose oral solution	1 mg/ml	250 ml
	10 mg/ml	50 ml
Fentanyl		
Transdermal patch	Maximum dose – every three days	10 units
Buccal tablet, lozenge, sublingual tablet, nasal spray (= products for breakthrough pain)		20 units
Parenteral		(*hospital use only*)
Hydromorphone		
Tablets/capsules with extended release	Maximum dose – 2 per day	60 units
Tablets/capsules with immediate release		50 units
Parenteral		10 units
Buprenorphine (use for analgesia)		
Transdermal patch	Maximum dose – every 7 days	5 units
	Maximum dose – 2 times per week	10 units
Parenteral		10 units
Sublingual tablet		50 units
Methadone (use for analgesia)		
Parenteral		10 units
Piritramide		
Parenteral		(*hospital use only*)
Pethidine		
Parenteral		(*hospital use only*)
Tapentadol		
Tablets/capsules with extended release	Maximum dose – 2 per day	60 units
Tablets/capsules with immediate release		50 units
Multi-dose oral solution	4 mg/ml	250 ml
	20 mg/ml	100 ml
Nalbuphine		
Parenteral		10 units
Pentazocine		
Tablets/capsules with immediate release		50 units
Suppositories		50 units

6. References

- FAMHP strategy on delivery, 29 October 2009.
- Guideline on the risk management system for medicinal products for human use of the European Medicines Agency (EMA, European Medicines Agency) (EMEA/CHMP/96268/2005, Annex B, 1.4)
- National Institute for Health and Disability Insurance (NIHDI) Consensus meeting – The rational use of opioids in the treatment of chronic pain, 6 December 2018
- Flash VIG-news: abuse of opioid analgesics – for rational use of opioids, 6 January 2020
- De Mooter E, Maebe J, Willems H, Lys C, Hans G. Verbruik en mogelijk misbruik van opioïden in België. Evolutie van 2006 tot 2017. Tijdschrift voor Geneeskunde, 2019 75 (11): 709-716