QUERY ANSWER REPORT

What are the implications of the new licensed melatonin preparations?

BACKGROUND

Until recently, there was only one licensed melatonin product in the UK: Circadin tablets. This was (and is) often used off-licence in children with sleeping difficulties. Children requiring a liquid formulation were prescribed one of several unlicensed “special” products, e.g. KidNaps. There are now several licensed melatonin formulations:

- **Circadin 2mg MR tablets**, licensed for insomnia in patients 55 years of age and over. (1)
- **Slenyto 1mg and 5mg MR tablets** (3mm diameter – designed to be small enough for children to swallow whole). Licensed for treatment of insomnia in children and adolescents aged 2-18 with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. (2)
- **Melatonin 3mg film-coated tablets** (Colonis Pharma Ltd). Licensed for treatment of jet-lag in adults. (3)
- **Melatonin 1mg/1mL oral solution** (Colonis Pharma Ltd). Licensed for treatment of jet-lag in adults. (4)

It has been noted that obtaining a supply of the unlicensed oral solutions (e.g. KidNaps) has become more difficult.

This document aims to explain how the melatonin supply landscape has changed, and what this means for prescribing for individual patients.

ANSWER: SUMMARY

Supply of Unlicensed Melatonin Oral Solutions

Now that there is a licensed liquid formulation of melatonin (from Colonis Pharma Ltd), this will change the availability of the unlicensed liquid preparations:

- Manufacturers will need to make sure that the licensed product is not suitable for the patient, in order to fulfil their legal obligation not to supply an unlicensed product where a licensed product (even used off-licence) will do.
- Manufacturers of unlicensed melatonin oral solutions may reduce the quantities they make, which may mean delays in obtaining a supply for a particular patient.
Differences between the licensed melatonin oral solution from Colonis Pharma Ltd and the unlicensed products

- The Colonis melatonin 1mg/mL oral solution contains 150.37mg/mL propylene glycol. This should be borne in mind when prescribing for children under the age of 5 years; the product should not be used in neonates unless essential. The Colonis product contains some ethanol, but this is a tiny amount – far less than in the KidNaps product and not enough to cause a pharmacological effect even in small children.

- KidNaps melatonin 1mg/mL oral solution (unlicensed) contains 9-11% w/v ethanol as a cosolvent, rather than propylene glycol.

- There may be other unlicensed liquid formulations of melatonin available with varying quantities of ethanol and/or propylene glycol. Contact specials manufacturers directly for details.

Other options

There are also other licensed melatonin products available, including some tiny modified release tablets specifically formulated to be swallowed by children. Consider whether any of these formulations may be more appropriate for an individual patient.

**ANSWER: DETAIL**

**LICENSED VS UNLICENSED PRODUCTS**

**What is a licensed product?**

The Human Medicines Regulations 2012(5) provide that (subject to some exceptions) no medicine may be placed on the market without an authorisation. The authorisation guarantees the quality, safety, and efficacy of medicinal products. The centralised licensing system is administered by the European Medicines Agency (EMA) and enables the granting of an EU wide (centralised) marketing authorisation;(6) UK-only (decentralised) licences are administered by the Medicines and Healthcare Products Regulatory Agency (MHRA).(7)

A product licence - also called a ‘marketing authorisation’ can be regarded as permission to market a particular product, in a particular country (or group of countries) for use in a particular way.

A “licensed product” is a medicine which has been through the relevant regulatory approval process and has been granted a “product licence” (also known as a “manufacturing authorisation”). In order to obtain one of these, the manufacturer has to submit evidence of safety and efficacy.

**What is the difference between “off-licence” and “unlicensed”?**

A licensed medicine is usually used within the terms of its product licence. However, in some situations, either there is no medicine licensed for the intended use, or there is one but it is not suitable for the patient. Therefore, another product must be used instead.

- When a licensed product is used in a way that is not covered by the product licence, this is termed “off-licence” use (of a licensed product). For example, using Circadin tablets (licensed for insomnia in adults) to treat a child. “Off-licence” use is sometimes also called “Off-label” as the US term for a product licence is a “product label”.

- A product which does not have a licence at all is termed an “unlicensed” product, also called a “special” because it may have been “specially made” for the patient. An example is KidNaps melatonin oral solution, which does not have a product licence.
If there is no suitable licensed product, is it preferable to use a licensed product off-licence, or to use an unlicensed product?

The MHRA’s guidance on “special” products states:

Although MHRA does not recommend “off-label” (outside the licensed indications) use of products, if a UK licensed product can meet the clinical need, even off-label, it should be used instead of an unlicensed product (see Appendix 2).

This is because for a licensed product, the manufacturer has had to provide evidence for safety and efficacy, and has had to prove that the product is stable and has been produced in facilities reaching a high standard of Good Manufacturing Practice (GMP), before it can be marketed. This is not required for unlicensed products, although some of them are produced to GMP standards. Therefore, a suitable licensed product (even used off-licence) is regarded as being safer for the patient, and therefore preferred.

What are the implications of prescribing an off-licence or unlicensed product?

The MHRA and EMA regulate the sale and supply of medicines (and medical devices) but do not regulate the practise of medicine – doctors are free to prescribe an approved (licensed) drug for any purpose they deem necessary, or to prescribe an unlicensed drug (for non-medical prescribers it depends on what each class of prescriber is permitted to prescribe).

Although the guidance is aimed at doctors, it applies equally to non-medical prescribers.

SUPPLY OF UNLICENSED PRODUCTS

The MHRA’s guidance on “special” products states:

An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient. An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient … Examples of “special needs” include an intolerance or allergy to a particular ingredient, or an inability to ingest solid oral dosage forms. These examples are not exhaustive.

Thus, if there is an equivalent licensed formulation available, a specials manufacturer may not supply an unlicensed product. This applies regardless of whether the licensed product is licensed for the particular use to which the prescriber wishes to put it.

Some unlicensed preparations may therefore remain available, but it is likely that anyone ordering them will have to state why the licensed product is not suitable for the patient, in order to fulfil the special’s manufacturer’s obligation to only supply an unlicensed product where a suitable licensed product does not exist. For unlicensed preparations which were previously made in large quantities, the manufacturers may have to reduce their batch sizes, and/or frequency of production due to a reduction in demand. This may result in delays in obtaining the product for a particular patient.

ETHANOL AND PROPYLENE GLYCOL CONTENT OF MELATONIN SOLUTIONS

The Colonis licensed melatonin solution contains a very small amount of ethanol in the flavouring (0.00045mg per 1mL dose).

The KidNaps formulation contains 9-11%w/v ethanol, which is 90-100mg/mL. Thus, the KidNaps formulation contains significantly more ethanol than the new licensed formulation.

Why are ethanol and propylene glycol present in medicines?

Ethanol and propylene glycol are both often used as solvents or cosolvents for drugs which are insoluble in water. Melatonin is only slightly soluble in water, so will need a cosolvent to stay in aqueous solution.
If ethanol is not used, then something else must be used instead. In the case of the Colonis melatonin liquid, the cosolvent used is propylene glycol.(4)

**The Safety of Propylene Glycol in Medicines**

Propylene glycol is commonly used in liquid formulations of medicines (and also in foods) and is generally regarded as non-toxic; it is estimated to be one-third as intoxicating as ethanol. However, administration of large volumes is associated with adverse effects, most commonly on the central nervous system, especially in neonates and children. Adverse effects are more likely to occur following consumption of large quantities of propylene glycol or on administration to neonates, children under 4 years of age, pregnant women, and patients with hepatic or renal failure. Adverse events may also occur in patients treated with disulfiram or metronidazole.(13)

On the basis of metabolic and toxicological data, the WHO has set an acceptable daily intake of propylene glycol at up to 25mg/kg body-weight,(13) but this applies to use as a food additive. The European Medicines Agency(15) has set the following limits, advising that the product should be used with caution if they are likely to be exceeded in normal dosing:

- Adults and children over the age of 5 years: 500mg/kg/day.
- Children under 5 years of age: 50mg/kg/day.
- Neonates: 1mg/kg/day.

These are not “maximum safe limits”, but rather “caution in use”; if the required dose of medication would result in the patient receiving more than the above amount of propylene glycol, it is a signal to consider whether a different drug or different formulation would be more appropriate.

The Colonis melatonin solution contains propylene glycol 150.37mg/1mL dose. Thus, it should not be used in neonates unless essential and the benefits outweigh the risks. For older children under the age of 5 years, a maximum dose of 0.33mL/kg/day of the product should be used (again, unless the benefits outweigh the risks and there is no preferable alternative).

**The Safety of Ethanol in Medicines**

When considering the ethanol content of medicines, it should be remembered that the human body produces ethanol, resulting in a “natural” (endogenous) Blood Alcohol Concentration (BAC) of up to 0.15mg/100mL (1.5mg/L).(16)

The EMA requires that medicines containing ≥100mg ethanol per dose call attention to this in the product information, and provides for a stronger warning for medicines containing ethanol ≥3g/dose.(15) However, the EMA has not published guidelines on the limits for ethanol content of medicines for children, although there were proposals for such limits,(16) which do not appear to have made it into the finished document. The proposed limits (which were, again “caution in use” limits rather than “maximum safe limits”) followed those already in use in France, and were:

- 1mg/kg/day-<6mg/kg/day: The amount of alcohol in this dose range is not expected to product a Blood Alcohol Concentration (BAC) significantly greater than the endogenous BAC (1.5mg/L).
- 6mg/kg/day-<75mg/kg/day: In infants (<2 years old) and children 2-5 years old, use of the medicine should be justified and the benefit must outweigh the risks (including the risks posed by the ethanol content).
- ≥75mg/kg/day: provided BAC does not exceed 12.5mg/100mL in patients 6 years old and above, this amount of ethanol is unlikely to produce any effects. It should not be used in children <6 years old.

It is also worth noting that the American Academy of Pediatrics has also produced guidance regarding acceptable levels of ethanol content for formulations intended for use in children.(17) They recommend various limits on the alcohol content of medicines intended for use in children, and recommend that children
should not be prescribed a formulation that would result in a blood alcohol level of 25mg/100ml (rather than the European 12.5mg/100mL) after a single dose.

**Choosing a Formulation**

There may be other unlicensed melatonin liquid formulations available with varying quantities of propylene glycol and ethanol. If the licensed Colonis preparation is unsuitable for a particular patient, then it is worth contacting different specials manufacturers to find out the details of their formulations. The pertinent information to obtain includes:

- Alcohol content
- Propylene glycol content
- Storage requirements (before and after opening)
- Shelf life (total and once opened)
- Pack size
- Price.

**REFERENCES**


12. Personal communication, Veriton Pharma. 03/07/2019.

**Note:** this report is based on the information available to us on the date of preparation: it is not valid indefinitely. Please contact us for the most recent information if necessary.


Note: this report is based on the information available to us on the date of preparation: it is not valid indefinitely. Please contact us for the most recent information if necessary.