Medsafe report on fluocortolone for rectal use, October 2001

Proposal: An exemption be granted for Ultraproct to be dispensed as a Restricted Medicine in pack sizes not exceeding 35g for the ointment and packs of 12 for the suppositories.

Background: Both Ultraproct suppositories and ointment are classified as Prescription Only medicines and have been so since registration in New Zealand in 1969.
Currently only rectal medicines containing ≤ 1% hydrocortisone in combination with a local anaesthetic are classified as Restricted medicines.
At the 24th meeting (November 2000) of the Medicines Classification Committee, a policy statement was made that "1% hydrocortisone should be used as the benchmark for the OTC classification of topical corticosteroids for both potency and range of indications".

Recommendation: Decline

Investigation

1. **The proposed strength, quantity, dosage form, dose and route of administration of the medicine including indication**
   Strengths, dose forms and route of administration to be the same as those currently available. The sponsor's proposal is for maximum quantities of 35g of Ultraproct ointment and 12 Ultraproct suppositories be sold as Restricted medicines for the following indications: haemorrhoids, superficial anal fissures and proctitis. Currently these are the registered indications for Ultraproct as a Prescription medicine.

2. **Approved indication(s)**
   Haemorrhoids, superficial anal fissures and proctitis.

3. **How long has the particular product been marketed?**
   Since December 1969 in New Zealand.

4. **Overseas regulatory status**
   Prescription only.

5. **Demonstrated efficacy (i.e. its ability to produce a wanted pharmacological effect at the proposed dosage)**
   Fluocortolone caproate (also known as fluocortolone hexanoate) and fluocortolone pivalate are classed as moderately potent topical corticosteroids.[1] They are both fluorinated corticosteroids. The pivalate and hexanoate esters of fluocortolone have been used in combination for the local treatment of anorectal disorders.[1]
   Sponsor's submission included an article published in 1969, regarding a comparison trial between topical hydrocortisone 1% and fluocortolone 0.2% used on psoriasis and eczema. Ultraproct is not indicated for these conditions so the results of this trial are not particularly relevant.
   No clinical trials were performed by Schering prior to marketing Ultraproct, initially in 1966.

6. **Is the product intended for treatment of a minor ailment or symptom readily identifiable by the user, which is capable of rapid spontaneous resolution and for which a medical consultation is not necessary?**
   Ultraproct suppositories and ointment are intended for relief of symptoms associated with haemorrhoids, superficial anal fissures and proctitis. There are a number of anorectal products currently available for OTC purchase, but none contain corticosteroids more potent than hydrocortisone. The potency of the currently available OTC products makes them suitable for self-treatment of mild anorectal conditions. However, if a more potent topical corticosteroid is required, then medical consultation is necessary.
   Medical referral is also necessary if symptoms persist, complications arise or doubt exists about the diagnosis.[2]

7. **Likelihood of mis-diagnosing, masking or compromising the appropriate medical management of a disease**

   Differential diagnoses include carcinoma of the rectum or colon, inflammatory bowel disease, diverticular disease and rectal prolapse. [2]

   Recurrence of symptoms indicates that alternative causes and treatment needs to be considered. [2]

   Rectal bleeding must not be attributed to haemorrhoids unless more serious conditions have been excluded. Rarely, haemorrhoids can lead to anaemia or severe haemorrhage. [3]

   Corticosteroids have not been shown to be beneficial in anal fissures and theoretically can interfere with wound healing.[3]

8. **Requirement for professional advice from a medical practitioner, or pharmacist**

   If the currently available OTC products are not effective in relieving the indications, then medical advice must be sought. The causes of the symptoms need to be examined and addressed, including life-style factors such as diet.

   Pregnancy and straining at stool are common causes of haemorrhoids.[4] Topical corticosteroids should not be used during the first trimester.[5] Pregnant women with haemorrhoids should be referred to their doctor for treatment. Reasons for constipation and stool straining need to be addressed,[6] and some of these may be adequately dealt with by the pharmacist but further medical investigations are likely to be required.

9. **Requirement for supervision of sale by a pharmacist**

   If Ultraproct is to be reclassified as proposed, the sale would need to be supervised by a pharmacist to ensure the product is appropriate for the symptoms described, and to meet the legislative requirements of selling Restricted medicines.

10. **Proposed labelling and warning statements**

    The sponsor does not propose to alter the labelling or package insert unless requested to by the Medicines Classification Committee.

11. **Hazard potential, including likelihood for any adverse effects**

    The sponsor submitted a **Safety Summary Report** (collated in May 1997) covering the period January 1990 – March 1997. Up until collation date, the total number of patients exposed to Ultraproct suppositories or ointment was just over 26 million. During this time, there were seven spontaneous adverse reaction reports. All were allergic-type reactions and four of these were found to be attributable to the cinchocaine component of Ultraproct. The Report stated that there were no adverse reaction or interaction case reports published in the literature during this period.

    Evaluator's comment: The sponsor does not appear to have sought a more current Safety Summary Report of recent data. Not sure whether this is because the data is not available, or has no contributing value, or perhaps contains unfavourable data.

    Also, it is well known that only a small number of adverse reactions to medicines are ever reported. It is also likely that the occurrence of side effects has been limited as a result of Ultraproct being used under medical supervision.

In 1995, a **warning statement** to avoid contact of the medicine with eyes was added to the Core Text (data sheet). The reason given was "due to the irritative effects of these kinds of products when coming into contact with the eyes".
Evaluator's comment: More serious ocular adverse effects of topical corticosteroids are raised intra-ocular pressure and cataract formation.[1]

Adverse effects: Absorption of corticosteroids through the skin can cause pituitary-adrenal axis suppression and Cushing's Syndrome. Absorption is greatest from areas of thin skin, raw surfaces and intertriginous areas, and is also increased by occlusion. Local side effects include striae and contact dermatitis.[7]
Corticosteroid-containing topical preparations for anal and rectal disorders are suitable for occasional short-term use after exclusion of infections such as herpes simplex. Prolonged use can cause atrophy of the anal skin.[8]
Cinchocaine is more irritant than lignocaine. Local anaesthetics can be absorbed through the rectal mucosa therefore only short-term use is recommended; they can also cause sensitisation of the anal skin.[8]

12. **Any relevant data on post-marketing experience**
See 11 above.

13. **Potential for inappropriate use of the medicine**
If the condition is not correctly diagnosed, there is potential for Ultraproct to be used inappropriately. The affected area does not lend itself to examination in a pharmacy setting. Pharmacists are not trained to carry out differential diagnoses of the conditions given in 7 above.
The pack sizes would restrict duration of use, unless users made repeat purchases.

14. **Potential for abuse of the medicine (e.g. non-therapeutic use of the medicine for self-gratification)**
The ingredients in Ultraproct are unlikely to be abused. The dose forms are such that extraction of the ingredients is difficult and again unlikely.
The 1997 Safety Summary Report (1990-1997) stated that no information had been received about abuse of Ultraproct.

15. **Current availability of other products with similar benefits**
The other products currently available for the relief of symptoms associated with anorectal conditions are:
- **Anusol** ointment and suppositories (*General Sales medicine*): contains zinc oxide, balsam Peru and benzyl benzoate.
- **Proctosedyl** ointment and suppositories (≤ 35g oint or 12 supps *Restricted medicine*): contains hydrocortisone and cinchocaine.
- **Xyloproct** ointment and suppositories (≤ 35g oint or 12 supps *Restricted medicine*): contains hydrocortisone acetate, lignocaine, aluminium acetate and zinc oxide.
- **Kenoid** ointment (*Prescription Only medicine*): contains triamcinolone acetonide, lignocaine and nystatin.

16. **Any public health advantage associated with the availability of these medicines**

None. The number and range of products currently available for OTC purchase (listed in 15 above) more than adequately provide sufficient treatment options for self-medication. If these products do not effectively relieve the condition/s, then it is essential that medical advice be sought.

No other moderately potent topical corticosteroids (including fluocortolone) for dermatological or rectal use are available as OTC medicines in New Zealand. Increased potency does not mean that the corticosteroid is better than a less potent one; instead less of the steroid is required to achieve the same therapeutic response. Given the concerns previously expressed[9,10] by both the Medicines Classification Committee (MCC) and the Dermatological Society, it would not be appropriate to set a precedent of reclassifying the more potent topical corticosteroids as anything less than Prescription Only medicines.

17. **Patient convenience including geographical factors**

If Ultraproct is to be reclassified as a Restricted medicine (quantities limited as proposed), then patients currently obtaining this medicine by prescription will still be able to access it when it is no longer subsidised by Pharmac. Also medical consultation would not be necessary in order to obtain Ultraproct. However, patients currently using Ultraproct regularly are likely to have conditions that require medical supervision and will use larger quantities than the limited amount proposed to be available for OTC purchase.

As a result of Pharmac's sole supply tender process, from 1st December 2001, one brand (Proctosedyl ointment and suppositories) will remain as a fully subsidised prescription medicine on the Pharmaceutical Schedule. In it's fax to Suppliers, Wholesalers and the Pharmacy Guild (dated 30 May 2001), outlining tender results, Pharmac incorrectly advised that "Ultraproct, Xyloproct or Kenoid will continue to be available for purchase over-the-counter from pharmacies". Of these three brands, at the time of the fax, only Xyloproct could be purchased over-the-counter. Medsafe has not received a reclassification submission for Kenoid.

The on-going supply of Ultraproct cannot be solely determined by its medicine classification status. The decision to continue providing stock is up to the sponsor. If Ultraproct were to be removed from the market, there is a sufficient number of alternative and suitable products available, both on prescription and over-the-counter. Thus patient convenience is unlikely to be compromised.

18. **Monitoring**

The safety profile of Ultraproct suggests that monitoring is not necessary when these products are prescribed and used appropriately. However, the low number of adverse reactions reported may possibly be attributed to other factors. It is likely that because these products have been used under medical supervision, the occurrence of side effects has either been managed or minimised through prescriber awareness and patient education. Another contributing factor is that for any medicine, only a small proportion of adverse reactions are ever reported to monitoring centres. Hence absence of data does not necessarily indicate absence of problems.

19. **Education**

Ultraproct has been available in New Zealand for over 30 years. Consequently, both prescribers and consumers of these products are likely to be sufficiently informed about them. Both products have package inserts, albeit brief.

20. **Comments from other interested parties**

Both the Pharmacy Guild and Pharmaceutical Society support the reclassification of Ultraproct products to Restricted medicines, however their reasons lack strong justification.

Conclusion

There is no justification for reclassifying Ultraproct suppositories and ointment as Restricted medicines. Martindale classifies the fluocortolone esters as moderately potent. In New Zealand, no other moderately potent topical corticosteroids for dermatological or rectal use are presently available for purchase over-the-counter in pharmacies. At the 24th MCC meeting (November 2000), the Committee made a policy statement that "1% hydrocortisone should be used as the benchmark for the OTC classification of topical corticosteroids for both potency and range of indications".[10] The anti-haemorrhoidal Restricted medicines presently available contain hydrocortisone or hydrocortisone acetate, whose potencies are classed as mild.[1] If a more potent corticosteroid is required, then medical advice should be sought.

The MCC has previously expressed concerns that the public has become blasé about the use of hydrocortisone since reclassification to make it available over-the-counter.[9] MCC is aware that there could be a tendency for consumers to perceive that the more potent corticosteroids are better, therefore initiating a change in pattern of use towards products that are not necessarily appropriate.[10] The Dermatological Society recently questioned the ability of pharmacists to diagnose conditions for which the more potent corticosteroids may need needed.[10] The potential for increased adverse effects cannot be excluded, particularly when the more potent corticosteroids are applied to areas of high systemic absorption such as broken skin and occluded areas.[1] The fact that Ultraproct has a good safety profile to date, may be attributed to its current classification of Prescription Only, which means it has been used in a controlled and appropriate manner under medical supervision.

As a result of Pharmac's sole supply tender process for the corticosteroid-containing anti-haemorrhoidal preparations (effective from 1st September 2001), patients' choice of fully funded products has been reduced to just one brand (Proctosedyl: contains hydrocortisone and cinchocaine). Patients regularly using these preparations will be under medical care, therefore a switch to another brand will be carried out under the supervision of their doctor. Reclassifying Ultraproct as Restricted medicines will not benefit patients wishing to remain on Ultraproct as they will be limited by the quantity they can obtain at one time.

With regard to continued availability of the Ultraproct products, it is up to the sponsor to ensure on-going supplies of stock to meet consumer demand. If Ultraproct were to

be removed from the market, there are a sufficient alternative products available, both on prescription and over-the-counter. Thus patient convenience is unlikely to be compromised.

References

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