Submission for Reclassification of Hyalase as a Prescription Medicine.

Part A

1. International Non-proprietary Name of the medicine.

   Hyaluronidase.

2. Proprietary name(s).

   Hyalase

3. Name and contact details of the company / organisation / individual requesting a reclassification.

   New Zealand Society of Cosmetic Medicine. [redacted] ph [redacted]

   Cosmetic Nurse Network. [redacted] [redacted] ph [redacted]

   Note: Contact details will be removed from the form prior to publication on the Medsafe website.

4. Dose form(s) and strength(s) for which a change is sought.

   Hyalase® 1500 I.U. Powder for Solution for Injection / Infusion

5. Pack size, storage conditions and other qualifications.

   1ml neutral glass ampoule containing a plug of white freeze-dried powder.

   Pack size: 10 ampoules. Do not store above 25^{o}C.

6. Indications for which change is sought.

   The Medsafe data sheet states that hyaluronidase can be used to enhance permeation of subcutaneous or intramuscular injections, local anaesthetics and subcutaneous infusions and to promote resorption of excess fluids and blood in the tissues. (9)

   The hyaluronidase enzyme in Hyalase is extracted from ovine testicles in the UK. The mechanism of action of hyaluronidase is enzymatic cleavage of the B 1,4-glucosaminidic bond between the glucosamine and glucuronic acid constituents of the hyaluronic acid polymer. This action reduces the resistance of tissue to fluid spread. (2)

   Clinically in NZ, Hyalase is used most often by anaesthetists and ophthalmologists to enhance anaesthesia for operative procedures, especially those involving the eye. It is also used off label by plastic surgeons and cosmetic medicine doctors and nurses to dissolve dermal filler in the event of an adverse reaction.

7. Present classification of the medicine.

   General sale

8. Classification sought.

   Prescription medicine

9. Classification status in other countries (especially Australia, UK, USA, Canada).

   Hyalase is a prescription medicine in Australia, UK, Ireland, South Africa and Brazil.

   In the USA and Germany, the Hyalase brand is not available, but all brands of hyaluronidase (Vitrase, Hylenex, Hylase Dessau) are prescription medicines.

   In Switzerland, Sweden and Norway, an ordinary prescription is not sufficient for hyaluronidase, and a special prescription where the doctor takes more responsibility is required.

   Hyaluronidase is not an approved medicine in Canada, France and Taiwan.

   We were unable to find any country in the world where hyaluronidase is classified as anything less than a prescription medicine.

10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute.

    Hyalase was first approved on 31 December 1969. [9]

    It is distributed in NZ by Healthcare Logistics on behalf of Artex NZ Ltd. The majority of Hyalase is used by ophthalmologists, a much lesser amount goes to DHBs and there is small usage in cosmetic medicine.

    550 packs if Hyalase were sold in the last year. This has fallen from 750 per year because of a global supply shortage.

    The main wholesale supplier of Hyalase is CDC Pharmaceuticals, who supply 400 packs a year. CDC has been supplying Hyalase as a prescription medicine, assuming it was the same classification as other countries.

11. Local data or special considerations relating to New Zealand (if applicable).

    There are no local special considerations. NZ use does not appear to be any different from international use.

12. Labelling or draft labelling for the proposed new presentation(s).

    We are not aware that any change in labelling is necessary, given that Hyalase is a prescription medicine in other countries.

13. Proposed warning statements (if applicable).

    There are no proposed warnings

14. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

    No other products would be affected. Hyalase is the only approved brand of hyaluronidase in NZ.

    Due to a recent global shortage of Hyalase, wholesalers are now also offering an alternative brand of hyaluronidase, Hylenex. Hylenex is an unapproved medication in NZ and therefore requires a prescription.

Part B

1. Indications and dose

    We propose reclassification for all indications.

    The Medsafe datasheet for Hyalase states that hyaluronidase can be used to enhance permeation of subcutaneous or intramuscular injections, local anaesthetics and subcutaneous infusions and to promote resorption of excess fluids and blood in the tissues.[9]

    Clinically, Hyalase is used by anaesthetists and ophthalmologists to enhance anaesthesia for operative procedures, especially those involving the eye. It is also used off-label by plastic surgeons and cosmetic medicine doctors and nurses to dissolve dermal filler in the event of an adverse reaction.

    In the cosmetic arena, Hyalase is considered an essential medicine for safe use of dermal fillers. The most serious adverse event, inadvertent arterial obstruction with filler, is regarded as an emergency requiring prompt injection with Hyalase in order to save tissue or vision.

    There are no OTC indications and no uses for which the general public requires access to Hyalase.

    For anaesthesia, 1500 IU (one vial) is mixed with the volume of local anaesthetic to be administered by injection. In ophthalmology, 15 IU per ml is recommended for anaesthesia.

    In cosmetic medicine for dissolving filler, small doses (10-15 IU) are injected for dissolving small amounts of filler. For emergency use in managing adverse events such as arterial occlusion by dermal filler, 750-1500 IU is used per injection.

    For subcutaneous infusion of fluids, the dose of Hyalase is 1500 IU per 500-1000ml fluid. For extravasation and haematoma, a dose of 1500 IU is injected.

2. Presentation

    Hyalase is available in NZ as a 1500 IU vial for injection/infusion. This is the form we propose should be reclassified.

3. Consumer benefits

The general public does not require access to this drug. It has no over the counter indications.

Safe administration of Hyalase requires a clean clinical environment equipped with emergency equipment to manage potential anaphylaxis. It should be administered by a health professional with the knowledge and training to correctly diagnose the need for Hyalase, perform informed consent, dilute the medication correctly, perform anti-sepsis, perform and interpret a test patch where necessary, inject the correct dose safely avoiding IV injection, and appropriately diagnose and treat any adverse reactions including anaphylaxis. The used glass vial and needles must be disposed of into a sharps container. It is recommended that patients are observed by a health professional for 30-60 minutes following Hyalase administration [10].

It is not appropriate for the general public to administer this medicine as they do not have the knowledge, skill or equipment to use it safely.

4. Contraindications and precautions

The Medsafe data sheet gives a contraindication of hypersensitivity to hyaluronidase It is “not to be used for intravenous injections or to reduce the swelling of bites or stings or at sites where infection or malignancy is present. It is not to be used for anaesthetic procedures in cases of unexplained premature labour.” [9]

The Medsafe datasheet “special warnings and precautions” are:

1) Do not apply directly to the cornea.
2) Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs.
3) Solutions for subcutaneous administration should be isotonic with extracellular fluid. Hyaluronidase is physically compatible with the commonly used infusion fluids. Use in hypodermoclysis has been reported with 0.9% sodium chloride, 0.18% sodium chloride with 4% glucose, 0.45% sodium chloride with 2.5% glucose and 5% glucose.
4) Potassium 34mmol/litre has been administered by hypodermoclysis in isotonic glucose or saline with 1500 I.U/litre hyaluronidase. Electrolyte-free fluids are less preferable than those containing electrolytes and should not be given too rapidly. Hyaluronidase has also been mixed with morphine, diamorphine, hydromorphone, chlorpromazine, metoclopramide, promazine, dexamethasone, local anaesthetics and adrenaline (see 6.2. Incompatibilities). [9]

5. Undesirable effects

Anaphylaxis

The most serious adverse effect is anaphylaxis which is very rare but potentially fatal. There are a number of case reports in the literature of anaphylaxis following hyaluronidase administration. [1,2,NZ CARM data]

Concern has been expressed regarding use of hyaluronidase in those with a history of anaphylaxis to bee or wasp venom because of the presence of hyaluronidase in these venoms, although it is unclear whether this concern is fully justified [3]

Loss of Sight

A case report published in the literature described visual loss as a result of orbital inflammation caused by allergy to hyaluronidase used for cataract surgery. [4]

Urticaria and Angioedema

Local reactions such as urticaria or angioedema can occur, potentially fatal when administered near the oral cavity or airways. [5-8] The incidence is estimated at approximately 0.1% [2]

Local inflammation, oedema, infection, bleeding and bruising

Local symptoms at the site of injection are commonly experienced

NZ CARM data

There were 8 adverse events reported in NZ dating from April 2013 to July 2017. Two reports were of anaphylaxis, both in 2013, 1 report was of bronchospasm, rash and oedema, and 5 reports were of injection site oedema. All incidents occurred in hospital. More details of these cases are contained in the attached document from CARM.

The narrow window date of adverse events reported to CARM implies that there is underreporting of adverse events with Hyalase. NZSCM is aware of anecdotal reports of significant oedema of the test patch or injection site that have not been reported to CARM.

Global CARM Data

There were 693 reports globally of adverse reactions to Hyalase.

NZSCM Safety Measures

To mitigate the risks of Hyalase administration, NZSCM members are required to follow a safety protocol for using Hyalase that includes access to emergency equipment and a test patch of Hyalase in the forearm prior to treatment. If there is significant wheal and flare in the test area, Hyalase is not injected into the face/lips due to the risk of swelling compromising the airway.

6. Overdose

Overdose with Hyalase has not been reported.

7. Medication errors and abuse/misuse potential

If the medicine is not reclassified, there are significant risks if it is freely accessed by the general public.

Safe administration of Hyalase requires a clean clinical environment equipped with emergency equipment to manage anaphylaxis. It should be administered by a health professional with the knowledge and training to correctly diagnose the need for Hyalase, perform informed consent, dilute the medication correctly, perform anti-

sepsis, perform and interpret a test patch where necessary, inject the correct dose safely avoiding IV injection, and appropriately diagnose and treat any adverse reactions including anaphylaxis. The used glass vial and needles must be disposed of into a sharps container. It is recommended that patients are observed by a health professional for 30-60 minutes following Hyalase administration [(4).]

The general public does not have the knowledge, skill or equipment to perform these tasks and therefore cannot use this medicine safely.

8. Communal harm and / or benefit

Use of Hyalase by the general public poses a number of risks including damage or death arising from infection, IV injection, oedema obstructing an airway, or anaphylaxis.

There are internet forums created by distressed patients who believe that Hyalase injected into their face has permanently damaged their appearance. Although the evidence does not support that Hyalase is causative, their distress is nevertheless real. Hyalase should not be used without proper informed consent, support and ongoing counselling in patients who may be at risk of such distress.

NZSCM believes that once the general public becomes aware that Hyalase is not a prescription medicine, there is a risk of use by lay people, because of its association with dermal fillers. We have observed that the desire for cosmetic improvement of the face can drive hazardous behaviour. There is a underground international online community exploring and encouraging this behaviour.

In 2014, dermal fillers were reclassified from prescription medicines to medical devices, creating an unintended loophole that allows them to be self-injected by lay people. Since then, members of the public have presented to NZSCM members requesting help after self-injecting dermal filler ordered off the internet with predictably adverse consequences. We have witnessed unaesthetic results, infection, granuloma formation and the presence of undisclosed foreign material in the injected product.

The risk of self-injection of Hyalase by lay people, with subsequent potentially fatal anaphylaxis, is not trivial. We therefore believe there is a significant risk of use by laypeople should Hyalase remain unrestricted.

9. Integrated benefit-risk statement

Reclassification of Hyalase as a prescription medicine would prevent the general public having free access, significantly reducing the risk of inappropriate use by an untrained layperson. The risks of damage or death arising from infection, IV injection, oedema obstructing an airway, or anaphylaxis would be much reduced.

Reclassification would bring NZ in line with the classification of Hyalase in all other countries. We have been unable to find a country where hyaluronidase is not a prescription medicine.

There do not appear to be any risks of harm arising from reclassification. Currently, systems are in place for use as a prescription medicine by both wholesalers and health professionals, because both assumed it was a prescription medicine, as in other countries.

Hyalase is largely used by specialist ophthalmologists and anaesthetists for anaesthesia, particularly for procedures around the eye. The DHBs are the next biggest user and there is a small amount of use in Cosmetic Medicine. Access to Hyalase for these users is unlikely to be impeded by reclassification.

Without reclassification, Hyalase will become more freely available to the general public. The systems developed by suppliers and users who assumed Hyalase was a prescription medicine are not necessary and will now likely be discarded. This will remove a restriction to access that has almost certainly been reducing the chance of adverse events associated with Hyalase.

10. Risk mitigating strategies

No risk mitigation strategy is needed if Hyalase is reclassified as a prescription medicine. If it is not reclassified, we propose that a risk mitigation strategy would be needed to prevent potential harm to the general public.

The proposed reclassification is supported by the NZ Society of Cosmetic Medicine and the Cosmetic Appearance Nurses Network.

The wholesaler of Hyalase, CDC Pharmaceuticals, also supports the reclassification. They believed it was already a prescription medicine and had been supplying it as such.

We believe the Colleges of Ophthalmologists, Anaesthetists and Plastic Surgeons would also support reclassification.

References.

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