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Baxter

# SUBMISSION FOR RECLASSIFICATION OF MEDICINE

# Advate (octogog alfa)

250 IU, 500 IU, 1000 IU and 1500 IU
injection with diluent
TT50-7243, a, b,c

May 2007

## PART A

1. **International non-proprietary name**
   Octogog Alfa, Factor VIII coagulant

2. **Proprietary name**
   ADVATE Injection with dilutent (TT50-7243, a, b, c)

3. **Company requesting reclassification**
   Baxter Healthcare Limited

4. **Dose forms and strengths for which a reclassification is sought**
   250 IU, 500 IU, 1000 IU and 1500 IU

5. **Pack size and other qualifications**
   Single-dose 5 mL vials packaged together with 5 mL of sterilized water for injection, 1 BaxJect device for reconstitution, 1 mini-infusion set, 1 of 10 mL sterile disposable syringe for administration, 2 alcohol swabs and 2 plasters.

6. **Indications for which change is sought**
   All indications approved for use of Advate in New Zealand – ie for use in haemophilia A for prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with ADVATE as perioperative management.

7. **Present classification of medicine**
   Prescription Medicine

8. **Classification sought**
   General sale

9. **Classification status in other countries:**
   - Australia – General Sale
   - UK – Prescription only medicine
   - USA – Prescription only

10. **Extent of usage in NZ and elsewhere:**
    - NZ – only recently registered, and currently awaiting responses on various CMNs submitted post-registration, so currently no sales activity in New Zealand.

    - Please see Table 1 showing countries in which Advate has been authorised to date. More than 2 billion international units have been distributed to date.

**Table 1 – Countries in which Advate has been authorised**

| Country | Authorization Date | Authorization Number |
|---|---|---|
| USA | 25-Jul-03 | US License 140<br>STN: BL 125063/0 |
| Switzerland | 17-Feb-04 | 56352 01 (250 IU)<br>56352 02 (500 IU)<br>56352 03 (1000 IU)<br>56352 04 (1500 IU) |
| European Union | 2-Mar-04 | EU/1/03/271/001 (250 IU)<br>EU/1/03/271/002 (500 IU)<br>EU/1/03/271/003 (1000 IU)<br>EU/1/03/271/004 (1500 IU) |
| Norway | 29-Mar-04 | EU/1/03/271/001/NO (250 IU)<br>EU/1/03/271/002/NO (500 IU)<br>EU/1/03/271/003/NO (1000 IU)<br>EU/1/03/271/004/NO (1500 IU) |
| Iceland | 1-Apr-04 | EU/1/03/271/001/IS (250 IU)<br>EU/1/03/271/002/IS (500 IU)<br>EU/1/03/271/003/IS (1000 IU)<br>EU/1/03/271/004/IS (1500 IU) |
| Australia | 25-Feb-05 | AUST R 100384 (250 IU)<br>AUST R 100385 (500 IU)<br>AUST R 100386 (1000 IU)<br>AUST R 100387 (1500 IU) |
| Canada | 31-Jul-06 | DIN 02284138 (250 IU)<br>DIN 02284146 (500 IU)<br>DIN 02284154 (1000 IU)<br>DIN 02284162 (1500 IU) |
| Japan | 20-Oct-06 | 21800AMY10128000 (250 IU)<br>21800AMY10129000 (500 IU)<br>21800AMY10130000 (1000 IU) |
| Argentina | 15-Dec-06 | 53 464 (all potencies)<br>250, 500, 1000, 1500 IU |
| New Zealand | 25-Jan-07 | 250, 500, 1000, 1500 IU |
| Puerto Rico | 30-Jan-07 | No Number assigned<br>250, 500, 1000, 1500 IU |

11. **Labelling for the proposed new presentation(s)**
    See attached

12. **Proposed warning statements**
    - Label – “Keep out of reach of children” (which is on the current label).
    - Data sheet: Current warnings remain.

13. **Other products affected:** None

## PART B - Reasons for requesting classification change

14. **Benefits to the consumer and to the public expected from the proposed change**

    It will be easier for Haemophiliacs on Advate to access treatment. Many haemophiliac patients are required to take Factor VIII coagulants for an extended period of time. As a General Sales medicine, Baxter would be able to deliver the product directly to patients, who can then take it to their physician for administration. This is a similar service to that provided by Baxter Healthcare for its home dialysis and parenteral nutrition patients.

    There will be a general benefit to the public by reducing the administrative burden on DHBs and hospital pharmacies, which will no longer need to be the Prescribing Pharmacist under the Medicines Act. This will also reduce the need for the patient to continuously visit the hospital to collect Advate and receive the treatment.

    A further benefit is that as the Australian label can be used, without the need for overlabelling, supply of the product to the New Zealand market will be simpler, faster and more efficient. Should there ever be a shortage of supply in New Zealand, Baxter New Zealand will be able to obtain immediate supply from Baxter Australia.

    Looking forwards to the expected creation of ANZTPA, there is an expectation that products common to the Australian and New Zealand market will be harmonised. As the regulatory files for Advate in Australia and New Zealand are almost identical, it would also be logical that the medicine has the same classification in both countries.

15. **Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated**

    Haemophiliac patients who are prescribed Advate will in almost all cases require repeat prescriptions. There is no requirement for diagnosis by a pharmacist or self-diagnosis, rather the patient will receive repeated doses of Advate as required. Initially diagnosis and

determination of the required treatment regime will be made by a haemotoligist. From that moment on, the patient will continue to have Advate administered in accordance with the prescribed treatment regime.

## 16. Local data or special considerations relating to NZ

There is significant precendent in New Zealand for Factor VIII coagulants to be classified as General Sale or Pharmacy Medicines. Baxter Healthcare's Recombinate is classified as a Pharmacy Medicine. By comparison, two competing products from different suppliers have been classified as General Sales medicines:

- ReFacto (Wyeth)
- Kogenate FS (Bayer)

In the interests of creating a level playing field in the healthcare industry in New Zealand, Advate should be assigned the same classification as ReFacto and Kogenate, with which it competed in the New Zealand market.

## 17. Comparison with other products in the New Zealand market

See attached Table 4.

## 18. Contraindications

Known hypersensitivity to any component or to mouse or hamster proteins.

## 19. Possible resistance

Under certain circumstances (presence of a low responder inhibitor) doses larger than the calculated doses may be necessary.

Patients should be evaluated for the development of factor VIII inhibitors, if the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia A.

## 20. Adverse events - nature, frequency etc.

Across all clinical studies, a total of 1304 adverse reactions were reported among 128 of the 150 subjects who received at least 1 infusion of ADVATE (rAHF-PFM). Of the 1304 adverse events, 696 were reported among 85 subjects >16 years of age and 608 were reported among 43 subjects ≤ 16 years of age. All adverse events (product related and unrelated) reported by at least 10% of subjects are shown in Table 2.

**Table 2:**
**Summary of all adverse reactions (product related and unrelated) that occurred in greater or equal to 10% of study subjects.**

| MedDRA System Organ Class | MedDRA Preferred Term | Number of Events | Number of Subjects | % of evaluable Subjects * |
|---|---|---|---|---|
| Gastrointestinal | Pharyngolaryngeal pain | 22 | 17 | 11.3 |
| General disorder and administration site conditions | Fall | 25 | 19 | 12.7 |
| | Pyrexia | 37 | 25 | 16.7 |
| Infections and infestations | Nasopharyingitis | 32 | 22 | 14.7 |
| Injury, poisoning, and procedural complications | Accidents nos | 62 | 26 | 17.3 |
| | Limb injury nos | 195 | 52 | 34.7 |
| Musculoskeletal and connective tissue disorder | Arthralgia | 74 | 35 | 23.3 |
| Nervous system disorder | Headaches nos | 138 | 44 | 29.3 |
| Respiratory, thoracic, mediastinal disorder | cough | 37 | 23 | 15.3 |

* Note: Percentage relative to 150, the total number of subjects across all the studies who received at least one infusion of ADVATE (rAHF-PFM).

Eighteen of the 1304 adverse events were regarded as serious; none were related to the study medication. There was no death. Among the 1286 non-serious adverse events, only 28 in 12 subjects were judged by the investigator to be related to the study drug. Severity ratings among the 28 events were mild in 8 cases, moderate in 16 cases, and severe in 4 cases as shown in Table 3.

The unexpected decreased coagulation factor VIII levels occurred in one subject during continuous infusion of rAHF- PFM following surgery (postoperative Days 10 – 14). Haemostasis was maintained at all times during this period and both plasma FVIII levels and clearance rates returned to appropriate levels by postoperative Day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative. Factor VIII inhibitor testing was performed throughout all the studies in the rAHF-PFM clinical program. Among 136 treated subjects ≥ 10 years of age, all of whom had ≥ 150 exposure days to Factor VIII products at the study entry, 102 had at least 75 exposure days to ADVATE (rAHF-PFM). None of these subjects developed an inhibitor. One subject who had < 50 exposure days to ADVATE (rAHF-PFM) while on study developed an inhibitor. This subject manifested a low titre inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE (rAHF-PFM) exposure days. Eight weeks later the inhibitor was no longer detectable, and in vivo recovery was normal at 1 and 3 hours after infusion of RECOMBINATE (rAHF). For the group comprising all subjects with at least 75 exposure days to ADVATE (rAHF-PFM) and the single subject who developed an inhibitor, the 95% confidence interval (Poisson distribution) for the risk of developing an inhibitor to Factor VIII was 0.02 to 5.4%.

**Table: 3**
**Summary of Non-serious, Study-Drug Related Adverse Events**

| **Severity** | **MedDRA Preferred Term** | **Number of Events** |
|---|---|---|
| | | |
| **Mild** | Dysgeusia | 3 |
| | Pruritis | 1 |
| | Dizziness | 1 |
| | Catheter-related infection | 1 |
| | Rigors | 1 |
| | Headaches | 1 |
| | **Total** | **8** |
| **Moderate** | Dysgeusia | 1 |
| | Dizziness | 2 |
| | Headache nos | 1 |
| | Hot flushes | 2 |
| | Diarrhoea nos | 1 |
| | Oedema lower limb | 1 |
| | Sweating increased | 1 |
| | Nausea | 1 |
| | Dyspnoea nos | 1 |
| | Abdominal pain upper | 1 |
| | Chest pain | 1 |
| | Bleeding tendency* | 1 |
| | Haematocrit decreased | 1 |
| | Joint swelling | 1 |
| | **Total** | **16** |

| Severity | MedDRA Preferred Term | Number of Events |
|---|---|---|
| | | |
| **Severe** | Headache | 1 |
| | Pyrexia | 1 |
| | Haematoma nos | 1 |
| | Coagulation factor VIII decreased | 1 |
| | **Total** | **4** |
| | *Recorded as a prolonged bleeding after postoperative drain removal on the case report form. | |

## 21. Potential for abuse or misuse

Advate is not an addictive pharmaceutical. It is not anticipated that there will be any potential for abuse or misuse.

For further information, please contact:

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