VI.2  Elements for a Public Summary

VI.2.1  Overview of disease epidemiology

The bacterium *N. Meningitidis* can cause infection in the blood. The infection may affect individuals of any age but is mostly a disease of children. Individuals with difficulty fighting infection and individuals traveling to areas where the disease happens commonly are also at risk for the disease. The infection is spread by close contact with an already infected individual. When this infection in the blood occurs, patients can become extremely ill and experience fever, headache and neck ache among other symptoms. If severe, the patient may experience low blood pressure which may be life-threatening. Patients with the disease may die; those who do not die, may be left with permanent disabilities.

VI.2.2  Summary of treatment benefits

Meningococcal vaccines are made up of parts of related, but slightly different, forms of the bacterium, called serogroups. Additional substances, such as proteins, may be added to the vaccine to increase the chance that the vaccine causes the body to produce substances that fight infection, called antibodies. Most healthy patients who receive the vaccine in the correct amount and at the correct times will be able to form antibodies.

Current (gold) standards of treatment

Patients who develop meningococcal infection in the blood are treated with medications known as antibiotics which act to kill the bacteria. In addition, patient may be treated with other medications to ensure normal blood pressure and function of important organs such as the heart. This treatment often takes place in a hospital intensive care unit.

Where the medicinal product fits in the therapeutical armamentarium (i.e. 1st line, relapse, etc.)

Menjugate is a vaccine which is used to prevent meningococcal C disease in the blood. Menjugate does not treat meningococcal C disease.

A brief statement of the standard against which the medicine was judged: number of patients in pivotal studies and treatment regimes

17,433 subjects were exposed to at least one dose of Menjugate either as investigational
or comparator vaccine in clinical trials conducted in infants, toddlers, children, adolescents and adults.

In general, Menjugate has shown to be safe, well tolerated, and capable of producing an immune response in vaccinated subjects against the meningococcal serotype C bacteria.

Note that the comparator, meningococcal polysaccharide (MenPS) vaccine was administered intramuscularly in these studies in order to maintain the blind. The MenPS vaccine, while licensed for a subcutaneous route of administration, has been reported to be safe and well tolerated when administered intramuscularly.

Serum bactericidal antibody responses are measured using human complement. In addition, a modified ELISA (developed and validated at Chiron), measuring high avidity serum IgG anti-capsular antibody responses against \textit{N. meningitidis} group C polysaccharide was also used to assess immunogenicity. In studies performed at the US Centers for Disease Control (CDC, Atlanta, GA), results of the Chiron ELISA have been shown to correlate with vaccine-induced bactericidal titres better than the standard ELISA.

Study V14_57 included 873 healthy toddlers aged 12 through 23 months randomized between MenC-CRM liquid (299 subjects), MenC-CRM ROS (268 subjects) and MenC-CRM EMV (306 subjects). On the top of the 873 subjects analyzed, 119 subjects who were initially enrolled into MenC-CRM ROS group but wrongly vaccinated with a second commercial lot of MenC-CRM EMV vaccine were analyzed also as a separate group call MenC-CRM ROS_EMV. Therefore, study V14_57 included a total of 992 subjects randomized: 989 subjects were included in the safety analysis as they were exposed at least at one dose of Menjugate.

Again Menjugate has shown to be safe, well tolerated, and immunogenic in the V14_57 study in all groups.

\textbf{Results in lay language}

Menjugate is a vaccine that was able to prevent disease caused by the bacterium \textit{Neisseria meningitidis} group C (also named meningococcal group C bacteria). The vaccine works by causing the body to make its own protection (called antibodies) against these meningococcal group C bacteria. \textit{Neisseria meningitidis} group C bacteria can cause serious and sometimes life-threatening infections, such as meningitis (infection of the tissue covering the spine) and septicaemia (blood poisoning).

The most common side effects reported during studies involving human volunteers usually lasted only one-to-two days and were not usually severe. The side effects were:

\textbf{Very common (may affect more than 1 in 10 people)}:

- In all age groups: redness, swelling and tenderness/pain at the injection site but these did not usually require further medical attention. Redness or swelling of at least 3 cm and tenderness causing discomfort with movement were rarely observed for more than 48 hours.
- Infants: being sick (vomiting)
- Infants and toddlers: irritability, drowsiness, difficulty sleeping, loss of appetite and diarrhea.
- Secondary school children: headache
- Older children and adults: feeling generally unwell
- Adults: muscle and joint pains, feeling sick (nauseous)

\textbf{Common (may affect up to 1 in 10 people)}:

- In all age groups: Fever (but rarely severe)
- Infants and toddlers: crying
- Toddlers: being sick (vomiting)
- Primary school children: headache
• Other side effects reported during routine vaccination programs included

**Very rare (may affect up to 1 in 10,000 people):**

Different age groups:

• Enlarged lymph glands
• Dizziness
• Faints
• Numbness
• Tingling sensation or pins and needles feeling
• Temporarily reduced muscle tone
• Visual disturbances and sensitivity to light. These have usually occurred together with headache and dizziness.

Although fits (also called seizures or convulsions) have been reported very rarely after vaccination with Menjugate, it is thought that some of these reports in teenagers and adults may have been fainted. In infants and young children, fits were usually associated with high fever. The majority of people affected have recovered rapidly.

**Post-authorization data which impacts on efficacy**

There has been no evidence thus far that the vaccine does not work as well in the public (after more than 88 million of doses distributed worldwide since 2000) as it did in individuals in the studies.

**VI.2.3 Unknowns relating to treatment benefits**

Studies of Menjugate were conducted in healthy persons. For that reason, the safety and the vaccine’s ability to cause the body to make antibodies in persons who have disorders of their immune system which result in impaired ability to fight infection is unknown.

Because there were no subjects in this age group in the studies conducted for approval for Menjugate, there is no information on the vaccine’s safety and ability to cause antibodies to be produced in persons greater than 65 years of age.

**VI.2.4 Summary of safety concerns**

**Important identified risks**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>In general these events are rare. Patients vaccinated with Menjugate are not known to be at increased risk of these events as a result of vaccination. However they have been reported from the public using Menjugate and are considered as possibly related to the vaccine.</td>
<td>Anaphylaxis and fever can be treated as soon as it started clinically. Vaccination failure has to be considered as more likely in subjects with disorders of their immune system which result in impaired ability to fight infection.</td>
</tr>
<tr>
<td>Convulsions, Febrile convulsions</td>
<td></td>
<td></td>
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<tr>
<td>Vaccination failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Important potential risks**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
**Missing information**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety During Pregnancy or lactation</td>
<td>Individuals with these conditions were specifically excluded from the clinical studies of Menjugate. As such, there is no information on the safety of Menjugate or the vaccine's ability to cause the body to make protective antibodies against Meningitis C in these people. Similarly, there is no data on persons greater than 65 years of age.</td>
</tr>
<tr>
<td>Subjects with disorders of their immune system which result in impaired ability to fight infection</td>
<td></td>
</tr>
<tr>
<td>Safety and immunogenicity in elderly</td>
<td></td>
</tr>
<tr>
<td>Potential for Medication Errors Resulting From Confusion in the Two Formulations</td>
<td>There were no errors in CDP and there has been no signal for reconstitution errors in the post marketing period.</td>
</tr>
</tbody>
</table>

**VI.2.5 Summary of additional risk minimisation measures by safety concern**

Not applicable.

**VI.2.6 Planned post authorisation development plan**

No post authorization efficacy studies are planned. See Module SV.2. This vaccine has been studied extensively in e.g. the UK after its introduction into the National Immunization Programme and there was no evidence for an association with certain safety events or mortality.

**VI.2.7 Summary of changes to the Risk Management Plan over time**

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Safety Concerns</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>31/10/2013</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2.0</td>
<td>26/09/2014</td>
<td>Addition of the potential for Medication error arising from two marketed product formulations as Missing Information</td>
<td>None</td>
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<tr>
<td>3.0</td>
<td>22/12/2015</td>
<td>No changes in the classification of the Safety concerns</td>
<td>N/A</td>
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</tbody>
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