AWMSG Secretariat Assessment Report – Limited submission

Ipilimumab (Yervoy®) 5 mg/ml concentrate for solution for infusion

Company: Bristol-Myers Squibb Pharmaceuticals Limited

Licensed indication under consideration: Monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age to < 18 years of age

Date of licence extension: 18 January 2018

Comparator(s)

- Ipilimumab (Yervoy®) is the first licensed treatment for advanced (unresectable or metastatic) melanoma in adolescents. For this rare disease, clinical experts have indicated that if they were to see a case in adolescents, adult treatments would likely be used off-label.

Limited submission details

- The limited submission criteria were met based on a new minor licence extension and an anticipated minimal budgetary impact.

Clinical effectiveness

- Ipilimumab has previously been recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of previously untreated (TA319) and treated (TA268) advanced (unresectable or metastatic) melanoma in adults, and is available in NHS Wales for adults under a Department of Health Patient Access Scheme (PAS).
- This submission covers the licence extension to include adolescents aged 12 years to < 18 years.
- The company submission includes a summary of data from adult clinical studies used in the European Medicines Agency regulatory filing of ipilimumab, and paediatric data from two additional studies (phase I: CA184-070 and phase II: CA184-178) to evaluate the efficacy and safety of ipilimumab in the adolescent population.
- Study CA184-070 was designed to assess tolerance and pharmacokinetics of different ipilimumab doses in paediatric patients in a number of tumours including melanoma. The study included patients outside of the age range under consideration and no patients received the licensed dose of ipilimumab. Study CA184-178 was designed to assess the survival rate, safety and tolerability of ipilimumab 10 mg/kg. The study dose was amended to include the 3 mg/kg dose to ensure consistency with the adult licensed dose. Only four patients in study CA184-178 received the licensed dose of ipilimumab. No definitive conclusions can be drawn from the studies due to the small patient numbers. However, the

Committee for Medicinal Products for Human Use (CHMP) states that the data appear to follow a similar trend as observed in the adult population.

- In studies CA184-070 and CA184-178, no new safety concerns and no new adverse drug reactions were reported in adolescents 12 years of age and older (n = 30). However, CHMP highlights that ipilimumab does seem to be less well tolerated in adolescents compared to adults. Toxicity is substantial with severe and life threatening adverse events, which is already known for adults. The applicant company has committed to implement post-marketing collection of paediatric safety data to further characterise the safety profile in children and mitigate the uncertainties surrounding a negative effect of ipilimumab on endocrine-related adverse drug reactions, which may affect hormonal and sexual development in adolescents.

Budget impact

- Based on Welsh Cancer Intelligence and Surveillance Unit melanoma specific incidence figures for 2011–2015, and assuming 10% of patients develop metastatic disease (assumption previously accepted by NICE), the company estimates that two adolescents would receive treatment with ipilimumab in the next five years.
- The acquisition cost of treating each patient with ipilimumab, inclusive of drug wastage and based on the PAS price, is [commercial in confidence figure removed]. Based on two patients receiving treatment with ipilimumab over the five year period, the budget impact is [commercial in confidence figure removed].

Consideration of All Wales Medicines Strategy Group (AWMSG) policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

- The applicant company estimates that the whole licensed indication for adolescent and adult patients in Wales with advanced or metastatic disease would account for 6.5% of 824 incident cases of melanoma, and therefore calculates the maximum total number of people eligible for treatment with ipilimumab in Wales is 54.
- AWTTC considers ipilimumab eligible to be appraised as an ultra-orphan equivalent medicine because although the medicine has not been granted European Medicines Agency designated orphan status, the full population of the licensed indications is ≤ 1 in 50,000 people and is therefore equivalent to ultra-orphan. The New Medicines Group and AWMSG will consider additional criteria (see Table 1) if they consider ipilimumab meets the criteria to be appraised in line with the policy for orphan, ultra-orphan and medicines developed specifically for rare diseases.

Table 1. Evidence considered by NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers	Melanoma is the third most common skin cancer in the UK and leads to more years of life lost overall than many more common cancers. Only 0.7–2% of all melanoma cases occur in patients below the age of 20 years, but melanoma is the most common form of skin cancer in the paediatric population. For paediatric patients, 5-year disease-specific survival is 57% in the case of distant disease. Advanced/metastatic melanoma is a terminal illness with current treatment options providing limited survival.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Ipilimumab is the first licensed treatment for advanced (unresectable or metastatic) melanoma in adolescents aged 12 to < 18 years. CHMP highlighted that advanced melanoma in the paediatric population is challenging to treat with very limited licensed therapeutic options and therefore an unmet need exists.
Whether the medicine can reverse or cure, rather than stabilise the condition	Advanced melanoma cannot be cured.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	There is no evidence that ipilimumab bridges the gap to a "definitive" therapy.
The innovative nature of the medicine	Ipilimumab is the first of a new class of immunotherapy that has a novel mode of action, blocking CTLA-4. This results in T-cell activation, proliferation and lymphocyte infiltration into tumours, which leads to tumour cell death. The company highlights that the innovative mode of action goes beyond that of traditional cytotoxic agents that directly target the tumour itself. Consequently, patients treated with ipilimumab do not generally follow conventional response patterns, but show extended response over time.
Added value to the patient (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	CHMP stated that it is very likely that paediatric patients may derive the same beneficial treatment effect as for adults. Any survival benefit would allow patients to resume normal activities such as education and work. The company also highlights the benefit of reduced frequency of administration on everyday life.
Added value to the patient's family (e.g. impact on a carer or family life)	Cancer management is associated with a high burden of lay care which impacts upon the carer and the family itself. An effective treatment is expected to result in a reduction of lay care necessary for patients, allowing family members and carers to resume daily activities and increase the likelihood of re-engaging with work. Therefore, additional benefits from a societal perspective are anticipated.

AWMSG: All Wales Medicines Strategy Group; CHMP: Committee for Medicinal Products for Human Use; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; NMG: New Medicines Group.

End of life

- Life expectancy with advanced melanoma is limited. Based on adult studies of ipilimumab in advanced melanoma, NICE considers ipilimumab to be a life-extending end-of-life treatment. Life expectancy was < 24 months and NICE felt the medicine offers an extension to life of at least three months.
- Median overall survival in adolescent patients with advanced melanoma receiving the licensed dose of ipilimumab was 18.2 months (n = 4) in study CA184-178.

Additional information

- AWTTC is of the opinion that, if recommended, ipilimumab (Yervoy®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Evidence search

Date of evidence search: 29 May 2018
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Ipilimumab (Yervoy®) 5 mg/ml concentrate for solution for infusion. Reference number: 3604. September 2018.