Carbetocin

Essential medicine status

Section: 22. Medicines for reproductive health and perinatal care > 22.3. Uterotonics

ATC codes: H01BB03

Indication	Postpartum haemorrhage ICD11 code: JA43.Z
INN	Carbetocin
Medicine type	Chemical agent
List type	Core
Formulations	Parenteral > General injections > IV: 100 µg per mL (heat stable)
EML status history	First added in 2019 (TRS 1021)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Carbetocin
DrugBank	Carbetocin

Expert Committee recommendation

The Committee recommended the addition of heat-stable carbetocin injection to the core list of the EML for the prevention of postpartum haemorrhage on the basis of similar effects compared to oxytocin for efficacy and safety outcomes. The Committee agreed that heat-stable carbitocin may offer advantages over oxytocin in some settings as it does not require cold chain transport or refridgerated storage. The Committee noted the current higher cost of carbetocin compared to other uterotonics and agreed with the context-specific recommendation in WHO guidelines for the prevention of PPH, that carbetocin be used where its cost is comparable to other effective uterotonics. The Committee also recommended that WHO facilitate increased access and affordability of carbitocin through inclusion in the WHO prequalification programme.

Background

The application requested the inclusion of heat-stable carbetocin on the EML for the prevention of postpartum haemorrhage (PPH). Carbetocin has not previously been considered for inclusion on the EML for prevention of PPH. Oxytocin, misoprostol and ergometrine are currently included on the EML for the prevention of PPH.

Public health relevance

Obstetric haemorrhage, especially PPH, is responsible for more than a quarter of all maternal deaths worldwide (1). In most low-income countries, PPH is the leading cause of maternal deaths. PPH is commonly defined as a blood loss of 500 mL or more within 24 hours after birth, and affects about 5% of all women giving birth around the world (2, 3). Uterine atony is the most common cause of PPH and a leading cause of PPH-related maternal mortality worldwide (1). PPH can be prevented if prophylactic uterotonics are administered during the third stage of labour, and by timely and appropriate management (4). Oxytocin is the first choice uterotonic drug recommended by WHO. However, oxytocin is sensitive to heat exposure and must be transported and store

at 2–8 °C continuously. This represents a problem in low-resource settings where the cold chain is difficult to maintain. Carbetocin, in its heat stable formulation, does not require cold chain transport and storage and can stay at room temperature for a long period of time (30°C for three years, 40°C for six months, 50°C for three months and 60°C for one month) (5). Based on the WHO CHAMPION trial results and on the updated WHO recommendations on uterotonics for the prevention of PPH, carbetocin is recommended for PPH prevention, especially in those settings where the cold storage of oxytocin is not possible.

Benefits

The application presented the findings of a Cochrane systematic review and network meta-analysis of seven uterotonic options (6), and GRADE tables extracted from the WHO recommendations on uterotonics for prevention of PPH (4). Carbetocin compared with placebo or no treatment was investigated in two randomized controlled trials (RCTs) involving 169 women in the network meta-analysis. There was moderate certainty evidence that carbetocin was associated with a substantial reduction in PPH ≥500 mL (RR 0.42, 95%CI 0.31 to 0.57), PPH ≥1000 mL (relative risk (RR) 0.52, 95%CI from 0.38 to 0.72), blood transfusion (RR 0.48, 95%CI from 0.26 to 0.89), and use of additional uterotonics (RR 0.19, 95%CI 0.13 to 0.27) when compared with placebo or no treatment. Evidence on whether the prophylactic use of carbetocin during the third stage of labour reduces maternal death when compared to placebo was of very low certainty. It was uncertain whether carbetocin reduced maternal intensive care unit (ICU) admissions due to the very low number of events. There was moderate certainty evidence that the use of prophylactic carbetocin probably reduces average blood loss compared with women receiving placebo or no treatment (mean difference: 138.37 ml, 95%CI 193.24 mL lower to 83.50 mL lower). There is moderate certainty evidence that carbetocin has similar effects to oxytocin for the outcomes of maternal death, blood transfusion and ICU admissions. Carbetocin may be superior to oxytocin for the outcomes of PPH ≥500 mL (41 few events per 1000 women – moderate certainty evidence), use of additional uterotonics (74 fewer per 1000 women – low certainty evidence) and blood loss after birth (82 mL less, on average – low certainty evidence). There was very low certainty evidence of a difference in effect between carbetocin and oxytocin for the outcome of PPH ≥1000 mL.

Harms

The application presented the findings of a Cochrane systematic review and network meta-analysis of seven uterotonic options (6), and GRADE tables extracted from the WHO recommendations on uterotonics for prevention of PPH (4). Compared to placebo or no treatment, carbetocin was associated with little or no difference to the risk of experiencing adverse effects (i.e. nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever and diarrhoea). Compared to oxytocin, there was no clear difference in terms of adverse effects. The certainty of the evidence ranged from very low to moderate.

Additional evidence

N/A

Cost / cost effectiveness

Ex-factory prices of carbetocin vary globally and range from € 8 to € 40 per unit (100 micrograms). In 2013, WHO was approached by Merck for Mothers (a philanthropic initiative of Merck, known outside the United States as Merck Sharpe & Dohme (MSD)) and Ferring Pharmaceuticals to explore the potential value of heat-stable carbetocin for reducing the incidence of maternal death. WHO convened an international panel of stakeholders who identified the need for demonstration of non-inferiority of heat-stable carbetocin before a change in guidance and practice could be considered. If non-inferior to oxytocin, the heat-stable formulation of carbetocin would be made available in public sector health care facilities in high-burden countries at an affordable and sustainable "access price" (comparable to the United Nations Population Fund (UNFPA) price of oxytocin), according to a memorandum of understanding signed by representatives of WHO, Ferring Pharmaceuticals and Merck (7). This price is a subsidized price of US$ 0.31 +/- 10% per ampoule of 100 µg heat-stable carbetocin (the UNFPA current price of Oxytocin is US$ 0.27 per unit (10 I.U.)). It was noted that the cost-effectiveness of carbetocin varies across settings (6, 8–12). The WHO recommendations for uterotonics state that "carbetocin would probably be cost-effective if the unit cost is comparable to other effective uterotonics and in settings where the cost of PPH care is substantial" (4).

WHO guidelines

The 2018 WHO recommendations for uterotonics for the prevention of PPH (4) recommend use of an effective uterotonic during

the third stage of labour for all births. Recommended uterotonics are oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine and oxytocin + ergometrine in fixed-dose combination. The Guidelines Development Group made a context-specific recommendation for carbetocin and recommended its use in contexts where its cost is comparable to other effective uterotonics, noting that the current cost of using carbetocin for PPH prevention was greater than the cost of using other effective uterotonics.

Availability

Carbetocin is approved in more than 80 countries worldwide, not including the United States and Japan. In most countries carbetocin is approved for prevention of uterine atony following delivery of the infant by caesarean section. In a few countries, primarily in Latin America and recently in Australia, it is also approved for prevention of uterine atony following vaginal delivery. The currently approved product is manufactured in Germany. The product Ferring will make available in low- and middle-income countries (LMICs) at access price will be manufactured in China and India. Ferring began the registration process in September 2018, where the first application was submitted to Swissmedic, via their procedure for Marketing Authorisation for Global Health Products (MAGHP). The approval by Swissmedic is anticipated in 2020, whereafter Ferring will pursue registrations in LMICs and seek WHO prequalification.

Other considerations

The heat-stable formulation of carbetocin does not need to be transported under cold chain conditions, nor does it require refrigerated storage. This may make carbetocin a preferred choice in settings where cold chain transport and storage of oxytocin is not possible.

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