OPINION RELATIVE TO MEDICINAL PRODUCTS

Rotavirus vaccine (live)

ROTATEQ

Oral solution

Inclusion on list

Adopted by the Transparency Committee on 29 June 2022

SUMMARY

The legally binding text is the original French opinion version

- **Vaccine**
- **Sectors: Retail and hospital**

Key points

Favourable opinion for reimbursement for the active immunisation of infants aged 6 to 32 weeks for prevention of gastro-enteritis due to rotavirus infection, in accordance with the current HAS recommendations issued on 23 June 2022.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

In June 2022, the HAS drew up recommendations for vaccination against rotavirus infections, updating the role of the ROTARIX and ROTATEQ vaccines in the preventive strategy.

In France, for the prevention of rotavirus infections, it is now recommended to perform vaccination using:

ROTARIX in infants aged 6 to 24 weeks;

ROTATEQ in infants aged 6 to 32 weeks.

According to the vaccination recommendations adopted by the HAS board on 23/06/2022, “the HAS recommends vaccination against rotavirus in all infants aged 6 weeks to 6 months, using a two-dose vaccination regimen (at 2 and 3 months of age) for the monovalent vaccine (ROTARIX) and a three-dose regimen (at 2, 3 and 4 months of age) for the pentavalent vaccine (ROTATEQ). Strict compliance with this vaccination schedule is essential to ensure a full vaccination regimen before the age limit is reached (6 months for ROTARIX and 8 months for ROTATEQ).

The HAS recommends that information on the risk of acute intestinal intussusception (AII) be systematically delivered by healthcare professionals to the parents of children to be vaccinated. This information should make it clear that AII is an intestinal obstruction that can occur spontaneously, in the absence of any rotavirus vaccination, but that there is a slight increase in the frequency of this phenomenon in the week following ingestion of these vaccines. This information should specifically mention the clinical signs suggestive of AII in infants (bouts of crying, refusal to eat or drink, repeated vomiting, pallor, hypotonia, prostration, presence of blood in the stools) and should encourage the parents of these infants to consult without delay for an early diagnosis (recourse to ultrasound) and urgent medical management (reduction of the intussusception by a simple enema), with the seriousness of this condition often being the result of late treatment.

The HAS recommends the development of information materials tailored to the different healthcare professionals involved in this vaccination (prescriber, healthcare provider and administrator). Healthcare professionals (emergency physicians, paediatricians, general practitioners, midwives, paediatric nurses, pharmacists) should be made aware of the occurrence of these symptoms in this age group, particularly within seven days of the first dose.

The reinforced pharmacovigilance relative to reporting of AII cases should be continued.

At this stage, the HAS considers that it would be premature to make this vaccination compulsory. The HAS stresses the fact that in order to rapidly obtain significant vaccination coverage rates, specific actions should be carried out with general practitioners who currently seem reluctant to offer this vaccination.

The HAS will reassess the relevance of compulsory vaccination based on the first vaccination coverage data.

These vaccines, which are administered orally, can be given at the same time as other vaccines in the infant’s vaccination schedule.

It is recommended that the full vaccination regimen be performed using the same vaccine.

It is recalled that their administration should be delayed in subjects with diarrhoea or vomiting, or with an acute severe febrile illness (taking care not to exceed the age limit).

In addition, the HAS recommends the continuation of strain monitoring, which it considers to be crucial in order to document a possible evolution in the prevalence of associated strains following the introduction of vaccination against rotavirus infections.

Specific work should be scheduled to discuss the relevance of an incomplete regimen.

It is highlighted that these live vaccines should be administered with caution (hygiene measures after each nappy change) in infants in close contact with immunocompromised patients, such as patients with malignant diseases or on immunosuppressive therapy.

The HAS points out that ROTARIX and ROTATEQ do not protect against acute gastro-enteritis due to other pathogens than rotavirus. The prevention of acute gastro-enteritis from all causes is based on the maintenance of hygiene measures (hand washing, cleaning of surfaces), breastfeeding and the administration of oral rehydration solutions to treat dehydration and prevent severe forms.

Role of the medicinal product in the care pathway

The Transparency Committee considers that ROTATEQ, rotavirus vaccine (live) must be used in accordance with its MA and in accordance with current vaccination recommendations, in particular complying with the vaccination regimen and the age limit for the last dose administered to infants.

The Committee considers that for this use, it is essential that the parents of infants eligible for vaccination be provided with prior information by healthcare professionals (pharmacists, general practitioners, paediatricians, etc.) about the transient risk of acute intestinal intussusception (AII) in the seven days following administration of the vaccine and the characteristic clinical signs of this (bouts of crying, refusal to eat or drink, repeated vomiting, pallor, hypotonia, prostration, presence of blood in the stools), which should lead to an emergency consultation and performance of an abdominal ultrasound.

Special recommendations

Although vaccination against rotavirus is not compulsory, the Committee stresses the fact that, with the objective of rapidly achieving significant vaccination coverage, specific actions encouraging healthcare professionals (emergency physicians, paediatricians, general practitioners, midwives, paediatric nurses, pharmacists) to offer this vaccination to parents are required, taking into account:

- firstly, the available updated data on the real-world use of these vaccinations, demonstrating:
  - a good efficacy in terms of preventing RVGE leading to outpatient consultations, hospitalisations and/or emergency department visits and nosocomial infections due to rotavirus;
  - an impact on the organisation of care in countries having introduced universal vaccination and with good vaccination coverage in terms of a reduction in RVGE-related hospitalisations in eligible infants in the post-vaccination period of between 65% and 84%;
- and, secondly, the new applicable vaccination recommendations, which specify, in particular, the optimal conditions for use of these vaccines, particularly in the event of suspected AII within seven days following vaccination.

In addition, the Committee reiterates that the prevention of GE from all causes is based on the maintenance of hygiene measures (hand washing, cleaning of surfaces), breastfeeding and the administration of oral rehydration solutions to treat dehydration and prevent severe forms.

Committee's conclusions

Considering all of this information and further to debate and voting, the Committee considers:

Actual clinical benefit

- In metropolitan France, gastro-enteritis due to rotavirus infection accounts for 14 to 35% of acute viral gastro-enteritis cases in infants and young children, predominantly during the winter period. It is primarily manifested by diarrhoea and vomiting of variable intensity, generally moderate but which may, in rare cases, lead to severe dehydration and, exceptionally, acute intestinal intussusception. According to the available data, the number of deaths related to rotavirus gastro-enteritis in children under 3 years of age is estimated to be 16 over the period from 2014 to 2019, i.e. 3.2 deaths per season attributable to rotavirus.
- The proprietary medicinal product ROTATEQ, rotavirus vaccine (live) is a preventive treatment.
- The efficacy (immunogenicity)/adverse effects ratio is high in infants aged 6 to 32 weeks, provided that the optimal use conditions are complied with, in accordance with current recommendations.
- There is an alternative vaccine: ROTARIX, monovalent rotavirus vaccine, indicated in infants aged 6 to 24 weeks.
- ROTATEQ, rotavirus vaccine (live), can be used in accordance with its MA and within the framework of current vaccine recommendations from the age of 6 weeks.

Public health benefit

Considering:

- the seriousness of gastro-enteritis due to rotavirus, leading to 28,000 emergency department visits and the hospitalisation of around 20,000 infants per infant season in France. The number of rotavirus-attributable deaths is estimated to be 3.2 per season;
- the unmet medical need, apart from symptomatic treatments using oral rehydration solutions, breastfeeding and hygiene measures (hand washing, cleaning of surfaces);
- an additional impact of the proprietary medicinal product ROTATEQ on the reduction of severe RVGE and all-cause GE in view of clinical trials and real-world efficacy data;
- an additional impact on the organisation of care (reduction in outpatient consultations, hospitalisations and/or emergency department visits and nosocomial rotavirus infections) and on the care and life pathway (indirect immunity conferred by vaccination in infants not eligible for vaccination and in adults aged 65 years and over);

ROTATEQ, rotavirus vaccine (live) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ROTATEQ is SUBSTANTIAL in the active immunisation of infants aged 6 to 32 weeks for prevention of gastro-enteritis due to rotavirus infection and only in the populations recommended by the HAS on 23/06/2022.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the active immunisation of infants aged 6 to 32 weeks for prevention of gastro-enteritis due to rotavirus infection and only in the populations recommended by the HAS on 23/06/2022, and at the MA dosages.

Recommended reimbursement rate: 65%

Clinical Added Value

Considering:

- **clinical data having demonstrated a vaccine efficacy (97 % reduction in the risk of severe rotavirus gastro-enteritis [RVGE] in children under 1 year of age);**
- **data in the literature having demonstrated a real-world efficacy in terms of prevention of RVGE leading to outpatient consultations, hospitalisations and/or emergency department visits and nosocomial infections due to rotavirus, as well as an efficacy against the six most common genotype combinations circulating in France at present (G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8]);**
- **the impact on the organisation of care in countries having introduced universal vaccination and with good vaccination coverage in terms of a reduction in RVGE-related hospitalisations in eligible infants in the post-vaccination period of between 65% and 84%;**
- **a globally favourable safety profile despite a transient additional risk of acute intestinal intussusception (AII) primarily occurring in the seven days following administration of the first dose of vaccine (up to 6 cases per 100,000 vaccinated infants);**

But:

- **the absence of a demonstrated impact on the reduction of deaths attributable to gastro-enteritis (low risk in France).**

the Transparency Committee considers that the proprietary medicinal product ROTATEQ, rotavirus vaccine (live) provides a minor clinical added value (CAV IV) in the prevention of gastro-enteritis due to rotavirus infection in infants aged 6 to 32 weeks.