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Human Medicines Research and Development Support Division

Summary of the evaluation of the proposed paediatric investigation plan

Daclatasvir (dihydrochloride) / asunaprevir / (1ar,12bs)-8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((1R,5S)-3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide hydrochloride (BMS-791325) for the treatment of chronic hepatitis C

On 20 June 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for the medicine mentioned above for the treatment of chronic hepatitis C.

What is daclatasvir / asunaprevir / BMS-791325, and how is it expected to work?

Daclatasvir / asunaprevir / BMS-791325 contains three active substances. Daclatasvir blocks the action of a viral protein called 'NS5A', asunaprevir blocks the action of a viral protein called 'NS3/4A protease', and BMS-791325 blocks the action of a viral protein called 'NS5B RNA-dependent RNA polymerase'. These three proteins are essential for HCV to multiply. By inhibiting these three proteins, daclatasvir / asunaprevir / BMS-791325 prevents the virus from multiplying and infecting new cells.

This medicine is proposed in adults for the treatment of chronic infection with genotype (GT)-1 hepatitis C virus (HCV) in patients with compensated liver disease, including cirrhosis, who are either treatment-naïve or who have received prior HCV therapy. Daclatasvir / asunaprevir / BMS-791325 is not authorised in the European Union. Studies in adults are currently on-going.

What was the proposal from the applicant?

For children, the applicant proposed to study the medicine in children from 3 years to less than 18 years of age with chronic GT 1 or GT 4 HCV infection, who are either treatment-naïve or who have received prior HCV therapy, in the framework of aa paediatric investigation plan*. The plan includes the development of an age-appropriate dosage form to be used in children*. It also includes a proposal to determine the right dose and to show efficacy and safety of the medicine in non-clinical and clinical studies.

The future indication proposed for children is "daclatasvir/asunaprevir/BMS-791325 as a fixed-dose combination is indicated for the treatment of children and adolescents from 3 years to less than 18

years of age infected with GT-1 or GT-4 chronic hepatitis C who are treatment-naïve or treatment-experienced."

Is there a need to treat children affected by a similar disease?

Taking into account the proposed indication in adults, and the characteristics of the medicine, the Paediatric Committee considered this medicine of potential use for the treatment of chronic hepatitis C in children. This condition occurs also in children, who can be infected from their mothers at birth. However, a significant proportion of children infected at birth can clear the infection in the first years of life without treatment, and even in those that do not clear the virus the disease progresses only slowly. Therefore, treatment is not normally considered necessary for children below 3 years of age.

What did the Paediatric Committee conclude on the potential use of this medicine in children?

At present, some treatments are available for the treatment of chronic hepatitis C in children in the European Union, such as peginterferon alfa-2a or peginterferon alfa-2b in combination with ribavirin, but these treatment regimens may cause serious side effects and are not well tolerated by many patients.

Therefore there is a need for more medicines for the treatment of chronic hepatitis C in children daclatasvir / asunaprevir / BMS-791325 has a potential interest for children. However, the Committee considered that new data were required to decide whether the use of this medicine will bring a benefit to the children affected by the condition, and to understand any potential risks.

The Committee considered that there is a need to develop an age-appropriate pharmaceutical form* of this medicine, which would allow to use the medicine safely and accurately in young children, and whose composition* must only include components that are known to be safe in children.

The Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults, before starting the paediatric studies.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- studies are not necessary in children below 3 years of age because treatment is not normally considered necessary in this age group due to the slow disease progression and high rate of spontaneous clearance of the virus.
- An age-appropriate pharmaceutical form* was needed for children unable to swallow the film-coated tablet. This age-appropriate pharmaceutical form will be developed by the applicant.
- Determination of the best dose should be made in a study of the medicine's behaviour in the body.
- It is necessary to show efficacy in the treatment of the disease in children. This will be done in a single-arm study. The Committee did not request the medicine to be compared with the only treatment currently licensed in children (peginterferon alfa/ribavirin), as the response rate to this treatment is known from several published studies, and studies of interferon-containing regimens are no longer recommended in children due to their side effects.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur.

What happens next?

The applicant has now received the EMA Decision* (P/0182/2014) on this medicine. The Decision itself is necessary for the applicant to request in the future a marketing authorisation* for this medicine in adults and/or in children.

The Decision* on the agreed Paediatric Investigation Plan means that the applicant will perform the studies and trials in the next months or years. In case of difficulties, or a change in current knowledge or availability of new data, the applicant may request changes to the plan at a later stage. This can be done through a modification of the PIP.

The agreed completion of all the studies and trials included in the Paediatric Investigation Plan is December 2023.

The results of the studies conducted in accordance with the agreed Paediatric Investigation Plan will be assessed, and any relevant information will be included in the Product Information (summary of product characteristics, package leaflet). If the medicine proves to be efficacious and safe to use in children, it can be authorised for paediatric use, with appropriate recommendations on the dose and on necessary precautions. The product information will also describe which adverse effects are expected with the medicine, and wherever possible, how to prevent or reduce these effects.

Subsequent modifications of the agreed Paediatric Investigation Plan

On 19 September 2014, Bristol-Myers Squibb International Corporation proposed to change some of the details of the previously agreed Plan.

The Paediatric Committee, after examining the request, agreed to modify the following details:

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- Details in the pre-clinical measures have been modified. The modifications are minor and do not impact the study conduct or conclusions.

An updated Decision on the Plan has therefore been published on the EMA website (P/0002/2015).

*Definitions:

Applicant	The pharmaceutical company or person proposing the Paediatric Investigation Plan or requesting the Product-Specific Waiver
Children	All children, from birth to the day of the 18th birthday.
Paediatric investigation plan (PIP)	Set of studies and measures, usually including clinical studies in children, to evaluate the benefits and the risks of the use of a medicine in children, for a given disease or condition. A PIP may include "partial" waivers (for example, for younger children) and/or a deferral (see below).
Waiver	An exemption from conducting studies in children, for a given disease or condition. This can be granted for all children (product-specific waiver), or in specific subsets (partial waiver): for example, in boys or in children below a given age.
Deferral	The possibility to request marketing authorisation for the use of the medicine in adults, before completing one or more of the studies /measures included in a PIP. The Paediatric Committee may grant a deferral to avoid a delay in the availability of the medicine for adults.
Opinion	The result of the evaluation by the Paediatric Committee of the European Medicines Agency. The opinion may grant a product-specific waiver, or agree a PIP.
Decision	The legal act issued by the European Medicines Agency, which puts into effect the Opinion of the Paediatric Committee.
Pharmaceutical form	The physical aspect of the medicine (the form in which it is presented), for example: a tablet, capsule, powder, solution for injection, etc. A medicine can have more than one pharmaceutical form.
Route of administration	How a medicine is given to the patient. For example: for oral use, for intramuscular use, for intravenous use, etc. The same medicine, or the same pharmaceutical form, may be given through more than one route of administration.
Patent	A form of protection of intellectual property rights. If a medicinal product is protected by a patent, the patent holder has the sole right to make, use, and sell the product, for a limited period. In certain circumstances, a patent for a medicinal product may be extended for a variable period by a Supplementary Protection Certificate.
Marketing Authorisation	When a Marketing Authorisation is granted, the pharmaceutical company may start selling the medicine in the relevant country (in the whole European Union, if the procedure was a centralised one).