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Committee for Human Medicinal Products

CHMP/BWP report to the CMDh on pancreatin-containing products[1]

Assessment of the viral safety of the products and the need for a warning statement in SmPC

Summary

At the request of the CMDh, the Biologics Working Party (BWP) and the Committee for Medicinal Products for Human Use (CHMP) assessed the viral risk of pancreatin products and expressed their view on whether the SmPCs of these products should include a harmonised warning about their viral safety.

Pancreatin is manufactured from porcine pancreatic tissue from animals that have been declared suitable for human consumption. The risk of transmission of infectious agents, which may be present in the raw material, is reduced by measures taken during the manufacturing process. Despite this, the possibility of transmitting infectious agents cannot be totally excluded.

The CHMP discussed the possible impact of a SmPC warning and also took into account the potential viral risk from food intake and the fact that there have been to date no confirmed cases of virus transmission from pancreatin known to CHMP. The CHMP, taking into account the viral risk assessment by the BWP, concluded that a harmonised warning statement in the SmPCs of all products across the EU was not required as the viral risk is theoretical (i.e. not empirically proven) and a warning would be of limited value to prescribers and could deter patients from taking needed medication in the absence of any evidence of harm.

In addition, the BWP concluded that the manufacturing process for these medicines is effective in inactivating or removing enveloped viruses but that measures to further improve the viral safety of pancreatin with respect to non-enveloped viruses should continue to be encouraged.

The CMDh has endorsed the report of the CHMP and BWP. This public version of the report explains the basis of the CHMP/BWP recommendations.

[1] Public version of report Ref: EMEA/CHMP/BWP/64982/2012 with confidential information removed.

Introduction

In June 2011, the CMDh requested the opinion of the BWP with regard to the issue of warning statements for pancreatin containing products.

The following questions were addressed to BWP:

- Does the BWP concur on the need for a European harmonisation of the warning statements on viral safety in the SmPC of Pancreatin containing medicinal products?
- If yes, the BWP is asked to assist the CMDh in the review of the safety profile (quality related) in terms of viral safety of the various products and the advice of the BWP is requested on the wording of such a warning statement.

The BWP formed a drafting group to address these questions, following which a report was drafted and discussed at BWP. The report was adopted by BWP in October 2012 and presented to CHMP in December 2012. The outcome of the CHMP discussion is also included in this report.

Situation in 2012

According to a BWP survey completed by mid-2012, France is the only Member State in which a warning statement is obligatory. In addition, several Member States have accepted a voluntary proposal from MAHs to include such a warning statement. Other Member States have either not received any such proposals, or have received proposals and have refused them or put them on hold pending the outcome of the current discussion. A significant lack of harmonisation, both within and between member states, is therefore present.

General principles to be applied

It was broadly recognised that a warning statement should reflect an identified, specific, and distinct risk, related to a specific product or class of products. General warning statements, which do not relate to a specific risk, but are meant only as a disclaimer or to gain market advantage, should not be included in the SmPC.

As reflected in the title of section 4.4 of the SmPC, “Special warnings and special precautions for use”, this section is intended for clinically important warnings and precautions for use.

Viral risk assessment

Pancreatin is a pancreatic extract containing several digestive enzymes, whose properties are defined by Ph. Eur. (monograph 350 pancreas powder). General requirements for viral safety of medicinal products whose manufacture has involved the use of materials of animal origin is addressed in Ph. Eur. general chapter 5.1.7 Viral Safety. In addition, scientific principles described in guidelines dealing with viral safety for recombinant and plasma-derived products may be applied, although pancreatin is formally not within the scope of these guidelines. Based on this, the viral safety can be assessed based on the complementary approaches of selection of source materials, testing for viral contaminants, and inactivation/removal steps during the manufacturing process. Pancreatin is taken orally.

Pancreatin is manufactured from porcine pancreases. Pigs should be fit for human consumption, and slaughtered in authorised slaughterhouses under veterinary control. Inspection at slaughter will however not exclude animals with non-apparent or subclinical infections, and no screening for viruses is performed on the starting material, as this is not practically feasible.

Pancreatin is manufactured by a combination of simple extraction and digestion steps without further purification; digestion is mostly based on the autocatalytic effect of the digestive enzymes (lipases, proteases) in the starting materials. The exact manufacturing process differs between manufacturers.

Available data from the MA dossiers/CTDs, which is further supported by publicly available information, sufficiently demonstrates the following:

- The manufacturing process (probably because of the extraction solvent used and the effects of the digestive enzymes of pancreatin itself) and/or the pancreatin itself (because of its intrinsic lipolytic properties) will effectively inactivate or remove any enveloped viruses. Therefore, viral safety with respect to enveloped viruses is assured.
- The manufacturing process has limited capacity to inactivate or remove non-enveloped viruses. Therefore viruses such as porcine parvovirus (PPV) and porcine circovirus (PCV) – both considered to be non-pathogenic in humans and are ubiquitous in swine – may be present in drug product[2]. Their presence in the finished product is a marker of the possible persistence of other resistant non-enveloped viruses found in pigs. Furthermore, pigs may carry the zoonotic agent hepatitis E virus (HEV, a non-enveloped virus), which is transmissible by the oral route; the risk that HEV-contaminated pancreas glands are entering the manufacturing process cannot be excluded, as virus testing of the starting material is not practically feasible. Testing at a later stage, e.g. on the level of drug substance, would represent a less-than-ideal situation and is currently not a regulatory requirement, although manufacturers have been developing and implementing tests.

Several national competent authorities have repeatedly urged pancreatin manufacturers to improve the virus inactivation/removal capacities; however, up until now attempts at improvement have met with limited success, due to the fact that most conditions which would remove/inactivate adventitious agents will also result in an inactive product.

The following important parameters for a risk assessment for HEV are not known at present:

1. The extent of contamination of pancreas glands and the HEV virus burden entering the manufacturing process is not currently known.
2. How much virus would be required for effective transmission after oral intake?

From the above analysis, the assessment of the risk with HEV leads to the conclusion that its presence in the drug substance batches cannot be excluded. Considering the poor sensitivity of the method applicable to the pancreatin, the level of HEV RNA may be relatively high. The methods to detect the virus itself are still in development.

Measures to improve the viral safety of pancreatin with respect to non-enveloped viruses should continue to be encouraged based on the complementary approaches of selection of source materials, testing for viral contaminants, and inactivation/removal steps during the manufacturing process. Reference is made to CPMP Note for Guidance on virus validation studies the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95).

It is proposed that the BWP further discuss whether testing for HEV NAT testing can be considered suitable to reduce the risk and is feasible for routine testing of Pancreatin-batches. If BWP concludes that such testing for HEV is appropriate, it will liaise with the EDQM to propose consideration of a revision of the pancreas powder monograph.

The BWP is not aware of any recorded cases of virus transmission associated with pancreatin-containing products. This is supported by consultation with national competent authorities and publicly

[2] Presentation of B. Cherney, FDA, to the Antiviral Drugs Advisory Committee, December 2008 http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4402s1-02-FDA-Cherney%20.pdf

available information from Solvay provided to the FDA in 2008 (http://www.fda.gov/ohrms/dockets/AC/08/slides/2008-4402s1-03-Solvay.pdf).

Further information should become available in the future since FDA has a post-marketing requirement for MAHs to undertake an observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking pancreatin[3].

Should a warning statement be included in SmPCs?

The drafting group discussed the scientific data related to viral safety and considered that there are two positions regarding a warning statement. The two positions are either to advise against a warning statement, or to advise to implement a general warning statement (precise text to be considered, but the warning statement required by France would be a suitable starting point).

The following arguments were brought forward in favour of not implementing a warning statement:

- The risk of viral transmission is considered theoretical at this point in time as the experts are not aware of any recorded cases of viral transmission (especially taking into account the long history of use of pancreatin products).
- The oral route of administration diminishes (although it does not exclude) the risk of transmission.
- The risk might be compared to the risk of consuming raw/undercooked pork, or raw/undercooked meat in general.
- Warning on theoretical or remote risk should be avoided in the Product Information, in order to avoid weakening the warnings. Warning statements should be reserved for actual risks, in order to preserve the strength of the warnings.

The following arguments were brought forward in favour of implementing a general warning statement:

- Although pancreatin is manufactured from pigs fit for human consumption, this does not guarantee that pigs are free from adventitious agents. No screening for adventitious viruses is performed on the starting material.
- The manufacturing process is relatively mild. Enveloped viruses are efficiently inactivated or removed but non-enveloped viruses are able to withstand these conditions.
- Tests for viruses in pancreatin have limited sensitivity. Infectivity assays are hampered by the interference or cytotoxicity of the pancreatin itself. Although manufacturers are implementing tests for viruses (especially HEV), these tests may not be sensitive enough to rule out the presence of adventitious agents in the drug substance batch and final product.
- Scientific studies using infectivity assays have proven that non-enveloped viruses (PPV) are indeed present in batches of pancreatin.
- HEV is a human pathogen which might be transmitted through this route. It should be noted that HEV is common in swine, and available data provide strong evidence that HEV has been transmitted by the consumption of raw liver sausage. It should be noted in this context that generally requirements for medicinal products are not the same as those for food, and standards

[3] Antiviral FDA Drugs Advisory Committee Meeting – December 2, 2008 (http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiviralDrugs)

are higher for medicinal products. The extent of HEV virus burden entering the manufacturing process is not known.

- It cannot be sufficiently excluded that HEV may be present in the final product and patients and physicians should be informed of this risk. Careful wording is needed so as not to deter patients from taking needed medication.

BWP Conclusion

BWP considered the two questions raised by CMDh and concluded as follows:

Does the BWP concur on the need for a European harmonisation of the warning statements on viral safety in the SmPC of pancreatin containing medicinal products? If yes, the BWP is asked to assist the CMDh in the review of the safety profile (quality related) in terms of viral safety of the various products and the advice of the BWP is requested on the wording of such a warning statement.

There are two positions regarding a warning statement, either to advise against a warning statement, or to advise to implement a general warning statement.

The pertinent scientific considerations (quality related) are outlined in the report. CMD(h) should especially consider the following:

- on the one hand the risk of virus transmission is theoretical, i.e. the risk of virus transmission is not proven by documented cases. BWP is not aware of any recorded cases of virus transmission associated with pancreatin containing products.
- on the other hand non-enveloped porcine viruses are present in pancreatin and a risk of transmission of hepatitis E virus, a known human pathogen, cannot be excluded.

If CMDh decides to implement a general warning statement, the warning required in France would be a suitable starting point for developing an appropriate warning statement.

Measures to further improve the viral safety of pancreatin with respect to non-enveloped viruses should continue to be encouraged based on the complementary approaches of selection of source materials, testing for viral contaminants, and inactivation/removal steps during the manufacturing process.

CHMP December 2012

The BWP Chair presented the BWP report on pancreatin containing products: viral safety of the products and whether a warning statement should be included in SmPCs.

The members discussed the impact of a warning in the SmPC and also took into consideration the potential risk by food intake (e.g. raw pork meat) and that no confirmed cases of virus transmission from pancreatin were known to date by CHMP.

The CHMP agreed by consensus that there was no need for a harmonised warning statement in the SmPC of all products across the EU. The basis for the decision was that the risk is theoretical (i.e. not empirically proven) and a warning would be of limited value to prescribers and could deter patients from taking needed medication in the absence of any evidence of harm.