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EMA/805330/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation EC (No) 726/2004

Procedure no: EMEA/H/A-5(3)/1468

INN/active substance: gentamicin (solution for infusion/solution for injection)

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1. Information on the procedure

On 10 April 2018, the Executive Director of the European Medicines Agency requested the Committee for Medicinal Products for Human Use (CHMP) for a scientific opinion under Article 5(3) of Regulation (EC) No 726/2004 concerning human medicinal products containing gentamicin (solution for infusion/solution for injection).

Considering that the underlining cause is the same for medicinal products for human and veterinary use, a parallel request was made for a CVMP Opinion under Article 30(3) of Regulation (EC) No 726/2004.

2. Scientific Discussion

2.1. Background information

Gentamicin is a broad-spectrum antibiotic of the aminoglycoside group. It exerts its bactericidal effect by interfering with normal bacterial protein synthesis and has a sustained post-antibiotic effect against susceptible pathogens. Gentamicin is indicated for the treatment of infections caused by gentamicin-sensitive germs in adults and paediatric patients.

Gentamicin is currently authorised in more than 25 countries worldwide and it is a medically necessary product [1]. Known adverse drug reactions of systemic treatment with gentamicin include nephrotoxicity, ototoxicity, nervous system disorders, hypersensitivity, anaphylactic reactions, blood and lymphatic system disorders, gastrointestinal disorders, hypotension, skin and subcutaneous tissue disorders.

This CHMP review concerns the human medicinal products containing gentamicin for systemic use only (solutions for infusion/solution for injection).

The gentamicin active pharmaceutical ingredient (API) is manufactured via a standard fermentation process.

Since December 2015, an increase in the number of adverse drug reactions (ADRs) relating to gentamicin-containing solutions for injections were reported in several Member States, firstly in horses and later in humans. In humans, the main ADRs observed were decreased blood pressure and allergic reactions, including one fatality (in Italy). In horses, anaphylactic type reactions; colic; excessive sweating; tachycardia; tachypnoea; dyspnoea; shivering; groaning; pawing; rolling; flehmen and restlessness were observed with several fatal outcomes.

All drug product batches leading to these ADRs were manufactured using active substance batches sourced from the same Active Ingredient Manufacturer (AIM). However, not all active substance batches were affected.

The German veterinary laboratory involved in testing the product suspected that histamine was the cause of the ADRs and found clear correlation between histamine concentration in drug product batches and adverse events observed. The amounts of histamine found were very low (about 100 ppm in batches leading to adverse events and about 6 ppm in unobtrusive ones).

Histamine is known to trigger reactions even in very low concentrations and it is reported that an amount of 7 µg administered intravenously can cause a measurable effect in humans [2].

Elevated levels of histamine in gentamicin APIs were linked to fish peptone raw material utilised in the fermentation process sourced from a certain supplier between the second half of 2014 until June 2017. Fish (used to produce the peptone) were inadequately stored at the manufacturing site of this supplier prior to production of fish peptone resulting in a greater level of fish decomposition. This decomposition allowed the bacteria present in the fish to produce additional histamine from free histidine present in the material. Histamine is a product of enzymatic conversion of histidine by histamine decarboxylase.

The AIM reverted to their previous supplier of fish peptone from June 2017. The newly manufactured active substance batches (using the previous supplier stock) since June 2017 have lower levels of histamine detected in active substance batches (3 - 12 ppm).

An acceptable specification for histamine in fish peptone has not yet been established. Another supplier of gentamicin sulphate does not use fish peptone and consequently residual histamine was not detected in their active substance batches. Therefore, it may be possible to prevent the risk by using an alternative source of peptone (e.g. vegetable origin rather than animal origin).

As a short-term risk management measure the European Directorate for the Quality of Medicines *&* Healthcare (EDQM) has rapidly revised the relevant certificate of suitability (CEP) for gentamicin sulphate to include an interim histamine limit of 16 ppm.

The European pharmacopoeia does not currently require the control of the level of histamine in the drug substance gentamicin. However, due to the public health risk associated with histamine contamination, further requirements related to the quality of raw materials have been added to the raw materials section of the monograph on Products of fermentation (1468) in April 2018.

In light of the above, it was considered necessary to ask the Committee for Medicinal Products for Human Use (CHMP) to give an opinion under Article 5(3) of Regulation (EC) No 726/2004 on whether a specification should be introduced regarding the limit of histamine for the active substance gentamicin and/or the medicinal products (solution for infusion/solution for injection) containing gentamicin for human use.

In order to review the referred issue the CHMP requested information to the active substance manufacturers and the MAHs of gentamicin-containing products. One active substance manufacturer and several MAHs have given responses to the CHMP questions and information on their data. Below the overall summary of the responses and assessment is presented.

Responses to the CHMP questions were provided by one active substance manufacturer hereinafter 'the active substance supplier' (Fujian Fukang Pharmaceutical Co., Ltd) and several MAHs (Belupo D.D., Laboratorio Farmacologico Milanese S.r.l., Sopharma AD and SIA Briz, Labesfal Laboratorios Almiro, S.A., Italfarmaco S.p.A, Aventis Pharma, Sanofi–Aventis, Sanofi and Winthrop Pharmaceuticals, Panpharma and Rotexmedica, Biologi Italia Laboratories S.r.l (Recipharm), Fisiopharma S.r.l).

KrKA and Infectopharm Arzneimittel Und Consilium Gmbh informed EMA that they would not provide responses.

A summary of the responses and the CHMP assessment is presented below.

2.2. Quality aspects

i. Initial source of raw material

Manufacturers of medicinal products are obliged to control the GMP compliance of each active substance manufacturer and consequently provide competent authorities with qualified person (QP) declarations concerning good manufacturing practice compliance of active substance manufacture (the 'QP declaration'). However, the change to a new source of peptone, particularly when it is of animal origin (e.g. fish peptone), without notifying the finished product manufacturer complexify the control of the GMP compliance of the active substance and the related QP declaration. Drug substance and drug product manufacturers need to ensure the appropriate control of the raw materials as part of their auditing strategy. In the case of the gentamicin source of peptone, it is considered important that the source of peptone (e.g. animal or vegetable origin) is clearly documented by the active substance manufacturer.

Furthermore, the names and addresses of all peptone suppliers should be adequately documented, in line with section 13 of ICH Q7 GMP '*Guide for Active Pharmaceutical Ingredients*' which considers the requirements for changing the source of supply of *critical* raw materials.

Where appropriate, the active substance manufacturer should declare that fish peptone has been used in the manufacture of the active substance and that histamine is a specified and controlled impurity in the specifications.

Whilst, the European Pharmacopoeia does not currently require the control of the level of histamine in the active substance gentamicin, requirements related to the quality of raw materials as per the raw materials section of the monograph on Products of Fermentation (1468) needs to be complied with [3]. The implementation date for the last revision of this monograph was 1st April 2018.

For a future revision of this monograph on Products of Fermentation (1468), EDQM might consider including, in cases where fish peptone is used, a requirement for a risk assessment, limits for histamine levels in the fish peptone fermentation nutrient, a histamine removal step (if possible) in the manufacturing process and a limit test for residual histamine levels in the drug substance.

ii. Manufacturing process steps for reducing the histamine

The CHMP evaluated data provided by the active substance supplier who replied to the CHMP questions on the attempts to purge histamine from the active substance batches. Various laboratory experiments were performed to confirm the capacity of removing histamine after preparing gentamicin sulfate according to the current extraction process.

These studies showed that the current extraction process has the capacity to remove histamine and that the histamine residues present in gentamicin sulfate produced using peptone containing 800 ppm histamine do not exceed the interim specification of 16 ppm. The purge studies were only performed for the whole extraction process rather than each step due to the lack of an analytical method for determining histamine amounts in each in-process sample. Therefore, it was not possible to determine which steps of the manufacturing process were most efficacious in the removal of histamine.

To verify the process capacity of the charcoal decolorization step, gentamicin sulphate with known histamine residues was dissolved in water, histamine standard was added to prepare a solution, equivalent to gentamicin sulphate containing 130 ppm histamine. According to the current production process, the histamine spiked solution went through the charcoal decolorization step and subsequent process to prepare gentamicin sulphate. It is shown in the results that the residual histamine in all 3

samples was 9 ppm, suggesting that the current charcoal decolorization step can reduce histamine to a certain extent.

Nevertheless, the data does show that the manufacturing process is able to purge histamine from the fermentation broth. The results show that the process is able to reliably reduce the levels of histamine to below 9 ppm in lab scale batches provided that the histamine levels in the fermentation broth are ≤ 800 ppm.

Moreover, the gentamicin sulphate batches produced in the last two years by the active substance supplier who replied to the CHMP questions contain residual histamine below 16 ppm, and the supplier states that no adverse effect has been reported for active substances produced since September 2016. The histamine present in the batches is well- controlled below 16 ppm as per the current CEP, and each batch is tested for histamine residues prior to release. Batch data provided since reverting to the previous fish peptone supplier in June 2017 showed that levels of histamine are consistently below 5 ppm with only few results between 5-8 ppm. This further supports the conclusion of the purge study results that the current manufacturing process has the capacity to adequately reduce histamine.

Further studies were initiated to explore the possibility of introducing manufacturing process improvements. Up to now, available results indicate that with the current manufacturing process, histamine was significantly reduced, and the adjusted process did not show obvious advantages over the current one.

The active substance manufacturer stated that more studies will be conducted. For the charcoal decolorization step, the adequate temperature and the charcoal quantity will be further investigated. For the process steps of resin absorption and ammonia washing, the process parameters, e.g. pH, process time or washing agent volume, will be studied. It is expected that the study will be completed by end March 2019.

The CHMP concluded that the additional histamine purge studies for the charcoal decolorization step, resin absorption step and the ammonia washing step that are expected to be completed by March 2019 should be submitted to the competent authorities as soon as available with a view to updating the manufacturing process of the API to introduce process improvements regarding the reduction of residual histamine, as well as tightening of the histamine limit in the API.

Satisfactory validation data has been provided by API manufacturer for the in-house liquid chromatography- mass spectrometry (LC-MS) analytical procedure for determining residual histamine in the drug substance. The validation data shows that the limit of detection (LoD) for the method is 0.2 ppm and the limit of quantification (LoQ) is 1 ppm.

iii. Residual histamine limit

The CHMP requested also the active substance manufacturer who replied to the CHMP questions to explore the feasibility of a residual histamine limit tighter than 16 ppm which was provisionally proposed in April 2018.

The active substance manufacturer acknowledged that the majority of the histamine content results for recently produced batches of gentamicin sulphate are within 8 ppm, but the histamine results of some batches are close to 8 ppm. Therefore, the API manufacturer considered that the histamine limit of 8 ppm (or the lower 3 ppm) is not currently feasible. They consider that no tightening of the limit is possible at this stage and they also consider it unnecessary on the basis that the limit of 16 ppm is considered to be safe.

This was not accepted by the CHMP as the calculation used to establish 16 ppm as a safe limit was not formally endorsed. Furthermore, whilst at this stage the batch data does not fully support a limit less than 5 ppm of histamine in the active substance, a limit of 8 ppm is well within the current manufacturing capability of the manufacturer and it is considered to be acceptable for all patient populations from a safety point of view.

Indeed, for humans, the recommended daily dose of gentamicin is 3-6 mg/kg given in divided doses or 160 mg/Kg (about 2.5 mg/kg for 70kg patient where renal function is not impaired) administered as a single dose. Taking the upper limit of the recommended daily dose for an adult with a bodyweight of 70kg, is 350 mg (5 mg/kg x 70kg).

However, this dose may be administered in divided doses at six or eight hourly intervals. Taking the worst case scenario of eight hourly intervals, the maximum single dose is 350 mg/3 = 116.6667 mg. This is lower than the maximum recommended dose of 160 mg once daily given to patients with a urinary tract infection without renal function impairment. Therefore, the maximum single human dose should be taken as 160 mg to represent worst case scenario.

If we consider that 1 mg gentamicin base is equivalent to 1.69 mg gentamicin sulphate, the level of histamine can be calculated as follows:

Maximum adult dose = 160 mg

160 mg (gentamicin) x 1.69 = 270.4 mg (gentamicin sulphate)

270.4 mg (gentamicin sulphate) x 16 ppm = 4.326 µg histamine

As 4.326 µg is not sufficiently below the quantity of histamine which is known to cause hypotension (7 µg), a significantly lower limit needs to be considered to ensure a suitable safety margin.

However, by restricting the maximum limit of histamine in the API to 8 ppm the total amount of histamine in the highest adult dose is (270.4 mg gentamicin sulphate x 8ppm =) 2.163 µg of histamine.

This quantity of 2.163 µg is significantly below the quantity of histamine which is known to cause hypotension (7 µg).

Whilst no data exist to show whether ≈ 2 µg of histamine administered parenterally is capable of causing hypotension, the suitability of an 8 ppm limit can be justified considering the Ph. Eur. 2.6.11 Depressor Substances test. The Ph. Eur. 2.6.11 Depressor Substances test is an old Ph. Eur. test for finished product batches likely to be contaminated with depressor substances such as histamine. A finished product would fail the Ph. Eur. 2.6.11 Depressor Substances test if the depressor response of the test dose is greater than the reference dose of 0.1 µg/kg histamine (0.1 ppm of histamine).

Based on the calculations using this test, a histamine limit of 8 ppm is considered acceptable for all patient populations including the paediatric population albeit without a safety margin. Therefore, it is strongly recommended that the limit is tightened to at least 8 ppm and that further tightening of the limit should be considered in March 2019 when data on additional histamine purge studies will become available for the charcoal decolorization step, resin absorption and ammonia washing.

Following the data assessment a limit of 8 ppm can be considered appropriate and proportionate to the risk for the time being, until further data becomes available from ongoing purge studies of the active substance manufacturer which aim to reduce histamine levels in the active substance to a lower level (i.e. < 1 ppm).

The CHMP therefore concluded that the interim limit approved in the current CEP for gentamicin sulphate should be reduced to as low as reasonably practicable in line with manufacturing capability and batch data. A limit of 8 ppm is considered to be within the current manufacturing capability of the API manufacturer based on current batch data and is within the validated range of the analytical method. Further tightening of the limit (i.e. 1 ppm) should be considered in March 2019 when data on additional histamine purge studies will become available for the charcoal decolorization step, resin absorption and ammonia washing.

iv. Alternative peptone sources such as those of vegetable origin (i.e. soy peptone)

To evaluate the possibility to replace fish peptone with vegetable origin peptone in the gentamicin production process, a lab trial was conducted in late 2017 and 2018, by the active substance manufacturer.

During the gentamicin fermentation process, fish peptone provides a nitrogen source which is required for growth and metabolism of the production strain. Among the compositions in the fermentation media, the other main nitrogen source is soybean meal of vegetable origin. Therefore, soybean meal or soy peptone was used to replace fish peptone and productivity tests in shaking flasks were performed.

The results of this investigation showed that the productivity of the strain was decreased by over 35%. The active substance manufacturer stated that possibly, there were aminoacids of different type and content in the fish peptone and soybean meal or soy peptone. Although fish peptone was substituted by a suitable amount of soybean meal or soy peptone to obtain equivalent nitrogen source in the fermentation media, the growth and metabolism of the production strain was impacted. As a result, the productivity was also affected and became lower.

In conclusion, with the same production strain and fermentation process, the laboratory trial using soybean meal or soy peptone obtained a much lower productivity than that using fish peptone. The active substance manufacturer plans to compare the relevant components of fish peptone and soybean peptone, especially the type and contents of aminoacids, and adjust medium proportion accordingly. It is expected that the study results will be available by the end of March 2019. The study results should be submitted to the competent authorities as soon as they become available.

Therefore, the results from the new laboratory trials using soybean peptone that are expected to be completed by March 2019 should be submitted to the competent authorities as soon as available with a view to updating the manufacturing process of the active substance to include process improvements that could potentially eliminate residual histamine from the active substance.

2.3. Clinical aspects - Safety

The CHMP requested from the MAHs to do an analysis of available data on levels of histamine known to have been associated with hypotension and hypersensitivity reactions in more sensitive individuals and the paediatric population.

In most cases the MAHs have not presented any information to propose limits for acceptable levels of histamine in the final products that are known to be safe in more sensitive individuals and the paediatric population.

Nevertheless, some MAHs have presented relevant information from medical literature.

Whilst data submitted does not allow concluding on the safety of intramuscular and topical histamine administration in humans, the literature reference provided suggested that human subjects can tolerate up to 180 mg of pure histamine orally without having evident AEs, whereas IV administration of 0.007 mg of histamine produces vasodilatation and an increase in heart rate. When injected, this could potentially lead to adverse reactions comparable with those experienced during life-threatening allergic reactions. This suggests that histamine is not efficiently absorbed from the gastrointestinal tract and is postulated that the histamine-metabolising enzymes present in the intestinal tract prevent the absorption of ingested histamine into the circulatory system [2].

Although relatively uncommon, histamine intolerance is a well-known syndrome and results from disequilibrium between accumulated histamine and the capacity for histamine degradation in the body [4]. Many individuals with histamine intolerance are unaware of the condition and practitioners are not likely to identify these individuals before the administration of therapy. In theory, these individuals with histamine intolerance are likely to be at higher risk to develop allergic-mediated AEs when inadvertently exposed to trace quantities of histamine. It is also well-known that medications commonly used during the administration of general anaesthesia including certain muscle relaxants, narcotics, analgesics, local anaesthetics and anti-hypnotics may inhibit the clearance of histamine and thereby increase the risk of adverse reactions to histamine [4]. In addition, opioids commonly used in hospital and during anaesthesia, such as morphine and fentanyl, directly stimulate mast cells to release histamine, but the relationship between the appearance of these effects and the histamine plasma concentration is complex, and there is no direct and invariable relationship between them [5].

The data submitted by the MAHs show that there are multiple factors (e.g. concomitant medication, age, level of health, histamine tolerance etc.) that have the potential to influence the sensitivity of the patient to histamine. However, only one MAH has proposed a limit of 10 ppm as the maximum amount of histamine that should be allowed in the API. The varying information available in medical literature suggests that there is a probability of increased risk of histamine type adverse events (AEs) in certain special populations and therefore it would be prudent to ensure that the histamine levels in the API are limited to as low as reasonably racticable (ALARP) to ensure that risk is kept to a minimum.

Reports from medical literature showed that the normal basal plasma histamine concentrations are 0.3 to 1.0 ng/mL. Histamine produces dose-related effects such as increased gastric secretion and increased heart rate at a plasma concentration of 1 to 2 ng/mL; tachycardia, headache, flush, urticaria and pruritus are observed at levels ranging from 3 to 5 ng/mL; a fall in arterial pressure may occur at a plasma concentration of 6 to 8 ng/mL; bronchospasm may occur at a plasma concentration of 7 to 12 ng/mL; and cardiac arrest has been associated with a plasma concentration of ≥100 ng/mL [6].

In contrast to healthy volunteers, patients receiving gentamicin are likely to have underlying severe bacterial infections including sepsis and pre-existing clinical instability of circulatory status and will be at a higher risk of AEs possibly associated with histamine exposure.

A study that compared the levels of plasma histamine required to elicit symptoms in the presence or absence of anti-histamines reported that adult patients experienced symptoms such as flushing and headache at a plasma concentration of 2.39 ± 0.52 ng/mL, an increased heart rate at a plasma concentration of 1.61 ± 0.30 ng/mL and widened pulse pressure at a plasma concentration of 2.45 ± 0.13 ng/mL after a sequential infusion of histamine at doses ranging from 0.05 to 1.0 µg/kg/min for 30 minutes [7]. Another published study suggested that in adult subjects, a single intravenous injection of 0.007 mg of histamine could result in vasodilatation and an increase in heart rate. Furthermore, the maximum dose that can be tolerated and would produce a marked circulatory response with mild toxic manifestation ranges from 0.2 to 0.3 mg.

Patients with histamine intolerance represent approximately 1% of the population. The use of gentamicin-containing products with elevated levels of histamine residue may be associated with limited AEs such as increased gastric secretion, increased heart rate, headache and flush; moderate AEs such as fall in arterial pressure, urticaria and pruritus; and a less likely albeit real possibility of causing life-threatening AEs such as bronchospasm and cardiac arrest.

Of note, gentamicin sulphate is often used during surgical procedures along with the concomitant use of medications known to impair the clearance of histamine or directly release histamine from mast cells (e.g. certain muscle relaxants, narcotics, analgesics, local anaesthetics and anti-hypnotics; opioids such as morphine and fentanyl). In the clinical setting, all patients exposed will be at an increased risk of the occurrence of mild, moderate and severe life-threatening AEs.

Prospective monitoring

Having considered the available data, the CHMP requests the MAHs to closely monitor as part of their routine pharmacovigilance activities any new reports of hypersensitivity and hypotension related to the use of gentamicin-containing medicinal products and to notify the regulatory authorities accordingly. A cumulative update of cases should be performed in the next PSUR, including details of histamine levels in respective batches if known. This requirement will also apply for generic products and products authorised under 'well-established use'.

The EURD list is to be amended to decrease the PSUR submission frequency from 5 years to 3 years; the next data lock point is 31 March 2020, for all gentamicin containing products for systemic use.

The EURD list is also to be updated to require products registered under Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC to submit PSURs for gentamicin-containing products for systemic use (injectables) and follow the same PSUR submission frequency of 3 years; the next data lock point is 31 March 2020.

2.4. Conclusions

The CHMP assessed all data submitted by one API manufacturer and nine MAHs. This included CMC processes, published literature and pharmacovigilance data, and made its conclusions on the presence of histamine in gentamicin-containing products for solution for infusion/solution for injection.

The CHMP recommendations are being summarised here. The source of peptone used (e.g. animal or vegetable origin) should be clearly declared by the API manufacturer. The names and addresses of all peptone suppliers must be documented in the dossier and if any changes are made to these, the supplier should immediately notify the finished product manufacturers, MAHs and the competent authorities accordingly, including the EDQM when the drug substance is covered by a certificate of suitability (CEP). Where appropriate, the drug substance label should declare that fish peptone has been used in the manufacture of the drug substance.

The CHMP concluded that the interim limit approved in the current CEP for gentamicin sulphate should be reduced to as low as reasonably practicable in line with manufacturing capability and batch data. A limit of 8 ppm is considered to be within the current manufacturing capability of the active substance manufacturer based on current batch data and is also within the validated range of the analytical method.

The histamine content of incoming peptone is currently controlled at a level of max 800 ppm. The active substance manufacturer did not have any data to show that a tighter control on histamine in the fish peptone would result in consistently lower levels of residual histamine in the final drug substance. Therefore, at this stage it is not possible to conclude that the levels of residual histamine in the final drug substance can be consistently reduced (<1 ppm) by using fish peptone with tighter limits (< 800 ppm) of histamine. As it will take some time for this data to become available and the fact that the drug substance is covered by an EDQM certificate of suitability, this issue would be best pursued between the active substance manufacturer and the EDQM certification department.

The additional histamine purge studies for the charcoal decolorization step, resin absorption step and the ammonia washing step that are expected to be completed by March 2019, should be provided with a view to updating the manufacturing process of the active substance, with any process improvements that consistently minimize residual histamine, and subsequent reducing even further of the histamine limit in the active substance.

The results from the new laboratory trials by the active substance manufacturer using soybean peptone that are expected to be completed by March 2019, should also be provided when available with a view to updating the manufacturing process of the API, with any process improvements that could potentially eliminate residual histamine from the API.

So, further investigation will be necessary to explore the possibility of further reducing the levels of residual histamine in final drug substance (<1 ppm) by using fish peptone with tighter limits (<800 ppm) of histamine.

This CHMP report will be shared with EDQM for their consideration.

Whilst this procedure assessed the impact on histamine impurities in gentamicin-containing medicinal products, manufacturers of other active substances obtained by fermentation should take due into account of this evaluation.

Summarising also the clinical data assessed mainly from public literature and the reported ADRs, the CHMP noted that intravenous administration of 0.007 mg of histamine produces vasodilatation and an increase in heart rate. When injected, this could potentially lead to adverse reactions comparable with those experienced during life-threatening allergic reactions. Histamine intolerance is a well-known syndrome and results from disequilibrium between accumulated histamine and the capacity for histamine degradation in the body. In theory, these individuals with histamine intolerance are likely to be at higher risk to develop allergic-mediated AEs when inadvertently exposed to trace quantities of histamine. It is also well-known that medications commonly used during the administration of general anaesthesia including certain muscle relaxants, narcotics, analgesics, local anaesthetics and anti-hypnotics may inhibit the clearance of histamine and thereby increase the risk of adverse reactions to histamine. In addition, opioids commonly used in hospital and during anaesthesia, such as morphine and fentanyl, directly stimulate mast cells to release histamine. So in the clinical setting, all patients exposed will be at an increased risk of the occurrence of mild, moderate and severe life-threatening AEs. The MAHs are requested to keep monitoring the AEs closely.

In order to strengthen the monitoring of the gentamicin-containing products for systemic use, the CHMP recommended that the EURD list should be updated to require products registered under Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC to submit PSURs for gentamicin-containing products for systemic use (injectables) and additionally to change the PSUR submission frequency from 5 years to 3 years; the next data lock point is 31 March 2020.Whilst this procedure assessed the impact on histamine impurities in gentamicin-containing medicinal products, manufacturers of other active substances obtained by fermentation should take into account this evaluation.

3. References

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