Pemetrexed (as pemetrexed disodium) 2mg/mL and 13.5mg/mL in 100mL Sodium Chloride 0.9%w/v Intravenous Infusion Bags (Baxter Viaflo) LA2020001(4)

Justification of related substances levels reported – (unspecified impurities) which exceed ICH Q3(B) levels.

The report (LA2020001(4)) sets out the proposed acceptance criteria for a 21 day shelf life to be assigned for the ready to administer product between 2mg/ml and 13.5mg/ml. According to the data after 21 days at 2-8°C (the proposed maximum shelf life for the products under test within this report) we see the following approximate increases in related substances levels:

2mg/mL: Largest individual peak increase by 0.3%. Total increases by 0.8% (T=0 level < 0.1%) There was very little loss of active during the full study period of 28 days at 2 – 8°C followed by 24hrs at 25°C.

13.5mg/mL: Largest individual peak increases by 0.7%. Total increase by 1.5% (T=0 level < 0.1%) Loss of active totalled around 2.5% during the full study period of 28 days at 2 – 8°C followed by 24hrs at 25°C.

The degradation products detected have not been identified during the study but the degradation profile for pemetrexed disodium is well understood[1,2]. Oxidation is the main mechanism responsible for the degradation of pemetrexed in aqueous solutions.; three oxidative degradants, -hydroxy lactams, keto-pemetrexed, and oxidative dimers are formed by the oxidation pathway. Under acidic conditions, decarboxylation of glutamic acid is observed, and des-glutamate and glutamic acid are generated. Under alkaline conditions, degradation proceeds by hydrolysis of the side-chain amide, followed by deamination. Safety information on these degradation products is not readily available.

The British Pharmacopeia (BP) 2020 has a monograph for the API Pemetrexed Disodium Heptahydrate but not the injection dosage form. The API has the following limits for related substances

— impurity E: maximum 0.3 per cent (Enantiomeric purity)

— impurities A, D: for each impurity, maximum 0.15 per cent;

— unspecified impurities: for each impurity, maximum 0.10 per cent;

— total: maximum 0.6 per cent; (reporting threshold: 0.05 per cent)

The BP lists five potential impurities (A – E) for the API but from the studies referenced above none of these are likely degradation products from pemetrexed degradation in aqueous solution. Clearly though there are significant numbers of potential impurities and related substances for pemetrexed, for example, the SynZeal website lists 24 separate related substances.

The United States Pharmacopoeia (USP) – 40 has a monograph for Pemetrexed for injection defined as a sterile, lyophilized mixture of pemetrexed disodium and suitable added substances. Hence this

refers to the un-reconstituted powder. This has limits for related substances as set out in the below table.

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ketopemetrexed[a]	0.31	0.61	0.60
Pemetrexed	1.0	–	–
Any individual unspecified impurity	–	1.0	0.24
Total Impurities	–	–	1.30

[a] (4-{2-[(*RS*)-2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]ethyl}benzoyl)-L-glutamic acid.

ICH Q3B[3] states that specified degradation products can be identified or unidentified. A rationale for the inclusion or exclusion of degradation products in the specification should be presented. This rationale should include a discussion of the degradation profiles observed in the safety and clinical development batches and in stability studies together with a consideration of the degradation profile of batches manufactured by the proposed commercial process. For unidentified degradation products, the procedure used and assumptions made in establishing the level of the degradation product should be clearly stated.

A general acceptance criterion of not more than (≤) the identification threshold (see below) for any unspecified degradation product and an acceptance criterion for total degradation products should also be included.

Where there is no safety concern, degradation product acceptance criteria should be based on data generated from batches of the new drug product manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug product.

ICH Q3(B) is, of course, concerned with the regulatory filing of information for the licensing of pharmaceutical products. Although the principles are generally applicable to products prepared as Specials, there is no legal obligation to follow ICH for these products.

ICH M7 covering mutagenic impurities does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9. Exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities. This is safe to assume for pemetrexed degradation products and hence there needs to be no specific consideration of mutagenic potential.

The dose for Pemetrexed is usually 500mg/m^2 body surface area, hence approximately 1g maximum dose. For this dose the ICH Q3B identification threshold is 0.2% or 2 mg TDI (Total Daily Intake),

whichever is lower, in this case this is 0.2% (2mg) the qualification threshold is 0.2% or 3 mg TDI, whichever is lower and hence again this is 0.2% (2mg)

Where there is a degradation product greater than identification threshold which cannot be identified or reduced to below the threshold you are able to consider patient population and duration of use and consider conducting:

Genotoxicity studies (point mutation, chromosomal aberration)
General toxicity studies (one species, usually 14 to 90 days)
Other specific toxicity endpoints, as appropriate

The conduction of genotoxicity studies is not practical in this instance. Pemetrexed itself is used for cancer treatment and appears on the NIOSH hazardous drugs list 2020 Table 1. (Drugs that contain MSHI (Manufacturer Special Handling Information) in the package insert and/or meet the NIOSH definition of a hazardous drug and are classified by the NTP (National Toxicology Program) as "known to be a human carcinogen," and/or classified by the IARC (International Agency for Research on Cancer) as "carcinogenic" or "probably carcinogenic.")

Other studies published on the stability of pemetrexed in ready to use solutions have not measured or considered the degradation products in their assessment of shelf life[5,6,7,8]. These have recommended shelf lives of up to 31 days refrigerated or 48 hours at room temperature, although in one case[6] the shelf life was limited by micro-precipitate formation in PVC bags, a second paper[8] discounted this as a problem in polyolefin containers.

From the chromatographs in the report it is likely that the main degradant peak relates to Ketopemetrexed for which the retention time is not significantly dissimilar to that listed in the USP, although there were some small variations between the USP method and the method used in this study. The results accepted for the 13.5mg/ml concentration solution are higher than the USP limit when the relative response factor is taken into consideration (assuming that the main degradation peak is due to Ketopemetrexed), but they were not significantly so. Similarly, the total impurities level in the 13.5mg concentration solution was just above the USP acceptance criterion. The 2mg/ml concentration was totally compliant with the USP limits throughout the recommended shelf life.

Pemetrexed should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. Hence the total daily intake of related substances averaged over the 21-day period will be considerably lower and only that in a single dose of pemetrexed.

For the reasons outlined in this paper the use of limits above those listed for unidentified related substances in ICH Q3B and marginally above the USP monograph for the pemetrexed for injection in lyophilised powder form is fully justified for this study.

Assessment carried out by:

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