2.5 CLINICAL OVERVIEW ADDENDUM

(ALL STRENGTHS)

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List of Abbreviations and Definitions of Terms

CCSI	Company Core Safety Information
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
e-GFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HDL-C	High Density Lipoprotein Cholesterol
HR	Hazard ratio
MDRD	Modification of Diet in renal Disease
MRP	Mutual Recognition Procedure
PSUR	Period Safety Update Report
QRD	Quality Review of Document
SmPC	Summary of Product Characteristics
T2DM	Type 2 Diabetes Mellitus

2.5.1 INTRODUCTION

This Clinical Overview describes the evidence related to fenofibrate causing or aggravating serious skin reaction like Stevens-Johnson syndrome, and toxic epidermal necrolysis.

In addition, some editorial adaptations and changes for consistent wording are proposed for implementation.

2.5.2 BIOPHARMACEUTICS

2.5.2.1 Proposed update to Section Posology and Method of Administration

2.5.2.1.1 Geriatric population

Current wording:

In elderly patients, the usual adult dose is recommended.

Proposed wording:

In elderly patients, *without renal impairment*, the usual adult dose is recommended.

Justification for the addition:

This editorial change has been requested by Irish authorities during the previous MRP safety variation to give more clarity to the prescribers.

2.5.3 PHARMACOLOGY

2.5.3.1 Proposed update to Section Interactions

2.5.3.1.1 Other concomitant therapy

Current wording:

The potential for fenofibrate/fenofibric acid to affect the metabolism of other drugs has not been fully investigated in vitro or in vivo. Interactions cannot be predicted, and therefore, caution is recommended if fenofibrate is combined with other drugs.

In vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites.

Proposed wording:

We propose to delete this section.

Justification for the deletion:

Phenylbutazone was discontinued for human use because of its harmful side effects; in addition, the paragraph concerns "in vitro" data which should not be included in SPC. For both reasons, we would like to delete this additional interaction warning. Moreover, Irish authorities asked to delete this section during the previous MRP safety variation.

2.5.3.2 Proposed update to Section Pharmacodynamic properties

Current wording:

Because of its effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus.

Proposed wording:

We propose to delete this section.

Justification for the deletion:

This wording is no more in line with indications approved during the referral procedure and with the supportive wording on ACCORD data in section 5.1. Moreover, Irish authorities asked to delete this section during the previous MRP safety variation.

2.5.4 EFFICACY

This section is not applicable for this submission.

2.5.5 SAFETY

2.5.5.1 Clinical Information Related to Safety

There are differences between the master SmPC and the US label for fenofibrate and for fenofibric acid.

The master SmPC for fenofibrate lists *cutaneous hypersensitivity (e.g. Rashes, pruritus, urticaria), alopecia and photosensitivity reactions* as undesirable effects.

The US labels for fenofibrate and fenofibric acid list under precautions: *Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis.*

As the SmPC wording does not cover severe cutaneous reactions like toxic epidermal necrolysis and Stevens - Johnson syndrome, an overall assessment was done to clarifythe relationship between serious skin reaction and fenofibrate.

2.5.5.2 Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are characterized by typical skin lesions. The pathology of the disorders is not completely understood but viewed as a cytotoxic immune reaction aimed at the destruction of keratinocytes expressing foreign (drug-related) antigens. Drugs are regarded as the most important etiologic factors for these reactions. SJS and TEN are regarded as the same drug-induced or idiopathic reaction.

SJS and TEN are characterized by skin tenderness and erythema of skin and mucosa, followed by extensive cutaneous and mucosal epidermal necrosis and sloughing. They are potentially life-threatening due to multisystem involvement. In SJS less than 10% of patients suffer from detachment, in SJS/TEN from 10 to 30%, and in TEN more than 30% suffer from detachment. The patients present with an acute onset of symptoms like painful skin lesions, high fever, sore throat, mucous membrane involvement and ocular lesions. The clinical picture resembles an extensive second-degree burn. Since the condition becomes serious within a few hours it is a medical emergency. Unless the offending agent is discontinued immediately, the outcome may be fatal in the course of a few days. Many drugs are known to cause SJS and TEN, including allopurinol, ampicillin, amoxicillin, pyrazolons, sulfonamides, lamotrigene, certain anticonvulsants, and various NSAIDs.

2.5.5.3 Clinical Trials Safety Data

In the Integrated Safety Database 2344 patients were treated with fenofibrate in placebo controlled studies.

In the FIELD study 9 reports referring to severe cutaneous reactions could be identified, 3 in women and 6 in men. All reports were serious, none resulted in death.

					according to investigator [illegible] to surgery.
			necrosis, Vomiting, Breast cancer		the recurrence of breast [illegible].
					probably due to underlying [illegible] or psoriasis.
			Pain in extremity, Erythema, Leg amputation		according to investigator due to underlying peripheral artery disease.

	(Real)				
			control, Hypoglycaemia, Skin necrosis, Blood glucose increased		toe likely due to underlying iabetes mellitus.
					ulcer likely due to underlying diabetes mellitus and peripherally enous disease.
					contributed to by underlying diabetic europathy.
			ulcer, Femoral arterial stenosis	discontinuation	left 2nd toe likely due to underlying ellitus.
			disorder, Skin necrosis		probably due to underlying eripheral arterial disease.

None of these nine reports were considered related to study medication by the investigator. None of the reports is suggestive of TEN or SJS but rather more likely due to underlying disease.

2.5.5.4 Literature

A search of the published literature was conducted for articles of severe cutaneous reactions (TEN and SJS) coincident with fenofibrate or fenofibric acid from 01 January 1900 until 31 August 2011. Two articles with significant safety information were identified.

A review by Florentin et al (2008) describes fibrate adverse effects beyond liver and muscle toxicity. Regarding skin reaction the article mentions that there have been case reports of chronic radiotermatitis, phototoxicity, lichenoid , lichenoid photodermatitis, erythema multiforme, skin eruptions, Stevens - Johnson syndrome, pigmented purpuric dermatosis, vesicular or papular dermatitis, alopecia, pruritus, rash and urticarial lesions. The authors conclude that allergic or idiosyncratic reactions may represent the underlying mechanism for these side effects. Regarding fenofibrate photosensitivity reactions, erythematous rash, vesicular or papular dermatitis were specifically mentioned none of them severe. SJS was not reported for fenofibrate

Rojeau et al. (1995) did a case-control study on Medication Use and the Risk of SJS or TEN. Data were obtained through surveillance networks in France, Germany, Italy, and Portugal. Drug use before the onset of disease was compared in 245 people who were hospitalized because of TEN or SJS and 1147 patients hospitalized for other reasons (controls). Crude relative risks were calculated and adjusted for confounding by multivariate methods when numbers were large

enough. For fibrates (7 reports, 10 controls), they found a multivariate relative risk of 1.0 (0.4 - 2.8).

Comment: Both articles do not support an association between fenofibrate use and occurrence of SJS or TEN.

2.5.5.5 Background Epidemiology

Chan et al. (1990) evaluated the hospital discharge diagnoses of patients with erythema multiforme, SJS, or TEN during a 14-year period. The overall incidence of hospitalization for EM, SJS, or TEN due to all causes was 4.2 per million person-years. The incidence of TEN alone due to all causes was 0.5 per million person-years. The incidence of EM, SJS, or TEN associated with drug use were 7.0, 1.8, and 9.0 per million person-years, respectively, for persons younger than 20 years of age, 20 to 64 years of age, and 65 years of age and older.

Strom et al. (1991) conducted a descriptive epidemiology study to determine the incidence of SJS using computerized Medicaid billing data from 1980 to 1984 from the states of Michigan, Minnesota, and Florida. They described the incidence rates of SJS as 7.1 (6.1 to 8.2), 2.6 (1.6 to 4.0), and 6.8 (4.3 to 10.3) per million per year in each state, respectively. The authors concluded that SJS is an uncommon condition. The excess risk of Stevens-Johnson syndrome due to any drug is regarded as being very low.

2.5.5.6 Competitor Labels and Potential Class Effects

Undesirable skin effects listed for other products in class are:

Gemfibrozil (Lopid, http://www:medicines.org.uk/EMC, accessed 20 Oct 2011):
Common: eczema, rash
Rare: angioedema, dermatitis exfoliative, urticaria, dermatitis, pruritus

Bezafibrate (Calberzol, http://www:medicines.org.uk/EMC, accessed 20 Oct 2011):
Very rare: erythema multiforme, SJS, TEN
Uncommon: pruritus, urticaria

2.5.5.7 Postmarketing Information

2.5.5.7.1 Postmarketing Exposure

Fenofibrate has been marketed since 1974, the estimated patient exposure for fenofibrate based on available sales data since 01 November 2000 is 34.35 million patient years. The estimated cumulative fenofibric acid patient exposure from the International Birth Date (15 December 2008) through 31 July 2011 were approximately 965,000 PTY from 15 December based on internal sales data.

2.5.5.7.2 Methods/Search Strategy

The Abbott global postmarketing safety database was searched for all reports of TEN or SJS coincident with fenofibrate that were received from 01 January 1900 through 31 August 2011.

For the search all broad terms from the SMQ Severe cutaneous reactions (MedDRA v.14.1) were used to ensure adequate sensitivity. Upon checking all PTs retrieved for fenofibrate belonging to the broad SMQ it was decided that none of them showed enough specificity to describe SJS or TEN. Therefore the further analysis was done based on the narrow search (see below).

2.5.5.7.3 Results

A total of 262 reports with 931 events were retrieved by the broad search criteria. Of the 262 reports, only 114 reports with 116 events were considered relevant for the topic as they mention events belonging to the narrow SMQ Severe cutaneous reactions. Of these 114 reports, 9 reports were solicited, and considered unrelated as already described in section 3.0 Clinical Trials Safety Data. The remaining 105 unsolicited reports were mentioned 107 events. Of these 105 reports, 89 reports were considered serious, 7 of them resulting in death.

The table below provides the list of reported events (PT level) with reporter causality for the 105 unsolicited reports.

Preferred Term	Number of Events	Number of Serious Events	"unlikely" or "probably not"
pustulosis	0	0	0

All of these reports were analyzed individually. Of these reports, 8 specifically mention SJS and 9 mention TEN.

Of the 8 reports of Stevens-Johnson Syndrome one report was with fatal outcome [redacted] which is described below, one has unknown outcome [redacted]) and 6 recovered. All of them were confounded by other medication ([redacted] with seven concomitant medications, [redacted] with allopurinol, [redacted] with carbamazepine, [redacted] with amlodipine and 10 other concomitant medications, [redacted] with Hepatitis A vaccine, [redacted] with amlodipine, [redacted] with nicotinic acid, and [redacted] with paroxetine, acetylsalicylic acid, desloratadine and levothyroxine.

Of the 9 reports of Toxic Epidermal Necrolysis five had fatal outcome and are described below ([redacted], [redacted], [redacted], [redacted] and [redacted]), three reports with recovery and one with

unkown outcome. Of these four non-fatal reports two were confounded by medication (celecoxib and with sulfamethoxazole and trimethoprim and with simvastatin). The remaining report (had too little information (no medical history, information on concomitant medication, skin diagnosis or action taken on diagnosis); in case the narrative is indicative of phototoxicity which is labeled for fenofibrate.

The 7 reports with fatal outcome are discussed further in section 0.

All but 19 reports are confounded by concomitant medication. Five of the 19 reports without concomitant medication do not include a narrative which would help to put the mentioned terms in perspective and were therefore are not analyzed further: , , , and . Of the remaining 14 reports, one pair most likely concerns a duplicate report. Thus 13 remaining unconfounded reports (with 14 report identification numbers) are evaluated in more detail below, even though 10 reports (including the duplicate report) contain too little information for adequate assessment.

	gender			**Information/Confounders**
(most likely duplicate reports)		fenofibrate therapy for hypertriglyceridemia. One day the patient experienced exfoliative dermatitis. Fenofibrate was discontinued on an unknown date and the patient recovered from the exfoliative dermatitis.		onset, concomitant medication, medical history or actions taken to treat condition.
		The patient experienced an upper respiratory infection, two days later erythema multiforme. The treatment was discontinued the same day. On an unreported date, the event of upper respiratory infection resolved. The event of erythema multiforme was resolving. It is unclear whether the respiratory infection is a confounder.	34 days	No information on concomitant medication, medical history, skin testing or actions taken to treat condition was provided.
		erythroderma-like eruption and hepatic function test level abnormal (AST, ALT and gamma-GT). Fenofibrate was discontinued that same day. The patient recovered. The reporter confirmed that the events were considered non-serious events. No skin biopsy was taken.	days	concomitant medications, medical history, skin testing or actions taken was reported.

	gender			information/Confounders
		exfoliation. The rash was described as an intense spotty rash over the entire body, especially on the face, lips and upper extremities. The rash lead to intense "apolepsis". The rash was treated with an unknown medication. Thirty one days later fenofibrate was discontinued, and the symptoms subsequently resolved.		onset, medical history, concomitant medication and or skin testing. Continuation of fenofibrate for 31 days after start of the rash does not strongly support a fenofibrate induced TEN even though the subsequent improvement might support a less severe fenofibrate induced skin :action.
		experienced severe dermatitis exfoliation, especially in the hands, intertrigo, palms, and lips and later, on the whole body (however milder). Fenofibrate was stopped and the symptoms resolved subsequently. No concomitant medication was taken. The patient was not hospitalized.		onset, medical history, concomitant medication, or skin testing. The fact that patient was not hospitalized does not lend support to a diagnosis of TEN.
		pigmented erythema, pruritus, burning sensation and arthralgia while being treated with fenofibrate for hypercholesterolemia. Fenofibrate was stopped and the symptoms resolved subsequently. A few days after stopping the medication, laboratory results revealed hypereosinophilia (15%). No other laboratory results were provided.		history, skin testing or co-prescription were reported.
		dermatitis (localized or[redacted] hands) during last summer.[redacted] has been treated with Fenofibrate for approximately 10 days, and 8 days after start of the treatment,[redacted] experienced the first symptoms. No other clinical signs were found (such as adenopathy or ocular conjunctivitis). Biological results showed a slight anemia and leucocytosis. Liver and renal functions were both normal. The treatment consisted in local treatment (no detail provided).		on outcome, concomitant medication, skin testing or medical history.
		multiforme. The event did not require hospitalization. Dechallenge was negative.		on concomitant medication, relevant history, skin testing or data concerning alternate :iologies.

	gender			information/Confounders
		fenofibrate for an unknown indication. On an unknown date in 2002, the patient, who was hospitalized in a rehabilitation department, experienced bullous dermatosis. The bullous dermatosis was reported to have involved or prolonged inpatient hospitalization and was medically significant.		therapy continues. No information was provided on time to onset, dechallenge, medical history, concomitant medication, skin testing or outcome.
		eczematoid dermatitis.		therapy continues. No information was provided on time to onset, dechallenge, medical history, concomitant medication, skin testing or utcome.

The remaining 3 reports are analyzed below:

[redacted] A report of photosensitivity after sun exposure (erythema multiforme-like eruption) was observed in a [redacted] patient, treated with fenofibrate micronized. Skin biopsy showed the typical characteristics of acute eczematous skin rash. A mild eosinophilia was observed on biological examination (1700/mm3). Fenofibrate was stopped and a treatment with antihistaminic and corticosteroids was begun. The skin rash rapidly disappeared.
Comment: Photosensitivity is considered labeled.

[redacted] A report of a [redacted] treated for 5 years with fenofibrate, without noticeable side effects, who suddenly developed a severely itching dermatosis which spread over her entire body within two weeks. Fenofibrate was discontinued, and the patient was treated with corticosteroids, followed by PUVA, resulting in resolution of the clinical presentation as well as the laboratory abnormalities. Laboratory testing suggested the presence of a lymphoma (elevated LDH and beta microglobin), which could also be causal in this syndrome, although no other evidence to support this diagnosis was found.
Comment: This case described a generalized itching dermatosis with relatively slow progression, does not seem to reflect a case of SJS or TEN.

[redacted]: This report describes the occurrence of erythema multiforme in a [redacted] treated since two months with fenofibrate. Since the beginning of the treatment, progressive appearance of cutaneous lesions starting on the back of hands, extending over the sides of the limbs (forearm, legs and knees), the face and the neck developed. The patient was hospitalized. The dermatological examination including laboratory testing confirmed the diagnosis of erythema multiforme. Fenofibrate was stopped and steroid therapy was started. Rapidly favorable evolution was reported.
Comment: A causal role of fenofibrate cannot be ruled out.

Of the 19 reports without known concomitant medication 18 reports had confounding factors specifically mentioned or too little information for assessment.

2.5.5.8 Reports with fatal outcome

There were no fenofibric acid reports of interest with fatal outcome. Seven fenofibrate reports with fatal outcome are described below.

		papular eruption of the face that extended to the trunk with appearance of cheilitis. Then, skin detachment. Skin biopsy showed a characteristic aspect of TEN. Patient experienced cardiocirculatory arrest and septic shock leading to death. The reporter stated that the death was not related to TEN; and that TEN was unlikely related to fenofibrate. ***Comment***: Patient had a liver transplantation (treated with immunosuppressant) for a year. Treatment for CMV infection had already resulted in pancytopenia and was resumed prior to the events. CMV treatment led to pancytopenia. This could explain the sepsis and the later death. In addition, cotrimoxazol is known to cause TEN.			esomeprazol, ganciclovir, nicardipine, tacrolimus.
		fever about a month after starting fenofibrate and atorvastatin. She then experienced TEN and abdominal compartment syndrome, anaemia, intestinal perforation, malaise, pyrexia, multi-organ failure, acute pancreatitis, renal failure acute, sepsis, tachypnoea, blister, Unresponsive to stimuli, white blood cell count increased, Acute respiratory failure, Thrombocytopenia. ***Comment:*** For atorvastatin TEN is a rare listed undesirable effect.	month		

	gender			causality	Medication
		by skin biopsy. Fenofibrate, allopurinol, gliclazide and furosemide were considered suspect drugs. ***Comment:*** TEN is listed as rare event for allopurinol and furosemide.			galantamine hydrobromide, panadeine, acetylsalicylate lysine
		for many years then switched to bezafibrate, then back to fenofibrate. 35 days later he experienced Erythema multiforme. [redacted] also experienced pulmonary alveolar haemorrhage which was the reported cause of death. It is unclear if the latter event preceded or followed EM. Patient history included angina pectoris, atrial fibrillation, hypertension, hypothyroidism, congestive heart failure and obstructive atherosclerosis of lower limbs. ***Comment:*** Multiple concomitant medications are confounders. The fact that the patient had fenofibrate for many years prior to the occurrence make an association unlikely.		unrelated	acid ethyl ester, warfarin, levothyroxine, cilnidipine, beraprost, acetylsalicylic acid, indapamide, allopurinol, nicorandil, estazolam, ubidecarenone, mecobalamin, spironolactone, diazepam,
		TEN reports attributed to all type of drugs between 1995 and 2009 at a local hospital. 20 reports are disclosed, one of which (TEN) with fenofibrate and metformin as suspect drugs. ***Comment:*** There is too little information to assess the case. SJS or TEN are not labeled for metformin.			

	gender			causality	Medication
		[redacted] experienced SJS 4 days after the re-introduction of tiopronine (received for RA) [redacted] then experienced Gastrointestinal haemorrhage suspected to be due to prednisone (administered for SJS). [redacted] ater died from Septic shock. ***Comment:*** The course of events is compatible with a fatal SJS, however causality seems more plausibly related to tiopronine.			tiopronin, amineptine hydrochloride, iskedyl, rilmenidine phosphate, flunitrazepam, piracetam
	unk	literature article without narrative just listing a number of PTs: **Death,** Alopecia, Blood disorder, Cholelithiasis, Nervous system disorder, Oedema, Face oedema, Eosinophilia, **Toxic epidermal necrolysis**, Pulmonary fibrosis, Gastrointestinal disorder, Hepatitis, Ichthyosis, Renal impairment, Leukopenia, Libido decreased, Liver injury, Myalgia, Myopathy, Neuropathy peripheral, Photosensitivity reaction, Pancreatitis, Eosinophilic pneumonia acute, Aspartate aminotransferase increased, Alanine aminotransferase increased, Skin disorder, Somnolence, Thrombocytopenia, Vertigo, Weight decreased. ***Comment:*** This report provides too little information for any assessment.			

All reports with adequate information mention other suspect medication, so that no index case can be identified. However, in two of the reports there are just two drugs described (Fenofibrate and atorvastatin, fenofibrate and metformin).

2.5.5.9 Consumer Reports

There were no non-medically-confirmed consumer reports including terms of interest received during the current review period.

2.5.5.10 Discussion

The investigation was undertaken to evaluate whether to include severe cutaneous reactions like TEN and SJS into the CCDS.

Epidemiological data indicates that TEN, SJS or EM is seen very rarely (1.8 to 9.0 per million patient-years depending upon geographic area and population studied). Both TEN and SJS are often attributed to the medication taken at the time of the event but can also occur as spontaneously.

Clinical study data did not indicate a risk for TEN or SJS. However the number of patients evaluated in clinical studies is not adequate to exclude these rare events.

The literature search did not identify publications providing strong support for and association of SJS or TEN with use of fenofibrate or fenofibric acid.

Fenofibrate and fenofibric acid have been marketed since 1972. Sales data available for the period November 2000 to August 2011 leads to an exposure estimate of 34.35 million patient-years. If all 114 reports identified through use of the MedDRA SMQ Serious cutaneous reactions (narrow) actually represented reports of SJS; TEN or EM, then the estimated rate would be 3.33 reports per million patient years. However, review of all reports identified only 1 case which might be an index case, and in 1 or 2 reports with fatal outcome causal association also cannot be completely excluded. This would result in an estimated reporting rate of 0.03 to 0.09 per million patient-years. This is far below the incidence rate expected in the population as a whole.

Severe cutaneous skin reaction like SJS and TEN occur as serious, rapidly progressive and potentially fatal drug associated reactions or idiopathic diseases. If a case is suspected all non-vital medications which have been associated with case reports should be immediately discontinued. The decision by treating physicians to discontinue a specific medication immediately and early in the reaction, and thus potentially prevent serious outcomes, might be influenced by the information in the label. Current labeling for fenofibrate and fenofibric acid in the USA does mention TEN, but the SmPCs in Europe do not. Even though the current analysis could only identify one non-fatal outcome case for which a causal association could not be excluded, and 2 fatal outcome reports which were also exposed to an additional suspect drug, given the serious nature of these events and the fact that early discontinuation is crucial for beneficial outcome it seems sensible to add appropriate wording into the CCDS (for wording see below in section 2.5.5.11).

2.5.5.11 Benefits and Risk Conclusions

Based on the analysis of reports describing severe cutaneous reactions like TEN and SJS coincident with fenofibrate or fenofibric acid therapy, the following wording for the CCDS is recommended (bold, Italic):

Undesirable Effects

…
In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of >tradename<. A precise frequency cannot be estimated from the available data and is therefore classified as "not known".
…
Skin and Subcutaneous Tissue Disorders: severe cutaneous reactions (e.g erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.)

2.5.6 OTHER CHANGES

2.5.6.1 Proposed update to Section Fertility, Pregnancy and Lactation

Current wording:

Lactation: It is unknown whether fenofibrate is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore fenofibrate should not be used during breast-feeding.

Proposed wording:

Lactation: It is unknown whether fenofibrate *and/or its metabolites* ~~is~~ *are* excreted in human milk. A risk to the ~~newborns/infants~~ *suckling child* cannot be excluded. Therefore fenofibrate should not be used during breast-feeding.

Justification for the change:

These changes are proposed to comply with the QRD template; wording of lactation has been updated.

2.5.7 BENEFIT AND RISK CONCLUSION

The changes as proposed in the SmPC do not modify the profile of fenofibrate and, therefore, its benefit/risk ratio remains positive.

2.5.8 REFERENCES

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